

STUDIES RELATED TO SYNTHESIS OF TETRACYCLINE

a thesis submitted by

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for the award of the

Ph.D. DEGREE

(UNIVERSITY OF LONDON)

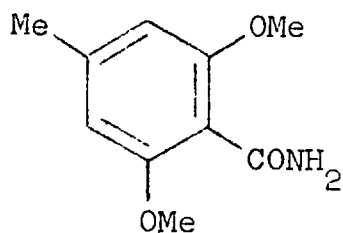
Abstract.

This thesis describes three aspects of tetracycline chemistry:

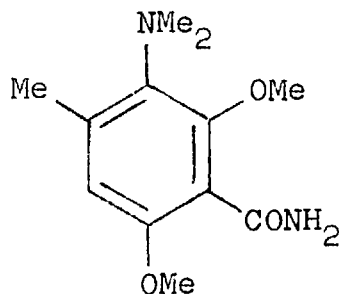
1. Reactions of the tetracyclines and their derivatives.
2. Published achievements in the field of tetracycline synthesis.
3. Advances made by chemists of this laboratory towards total synthesis of a natural tetracycline.

The author's work on this project involved:

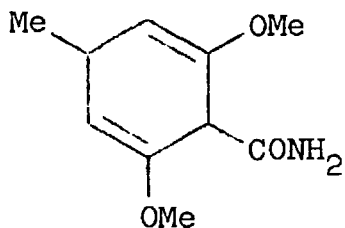
- a. An examination of the suitability of metal-ammonia solutions for reduction of the amides A and B to the corresponding dihydro-compounds C and D.



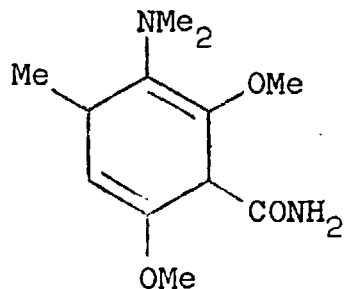
A.



B.



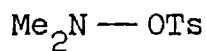
C.



D.

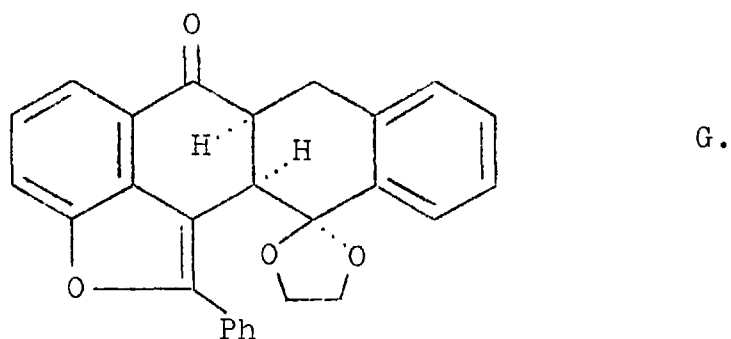
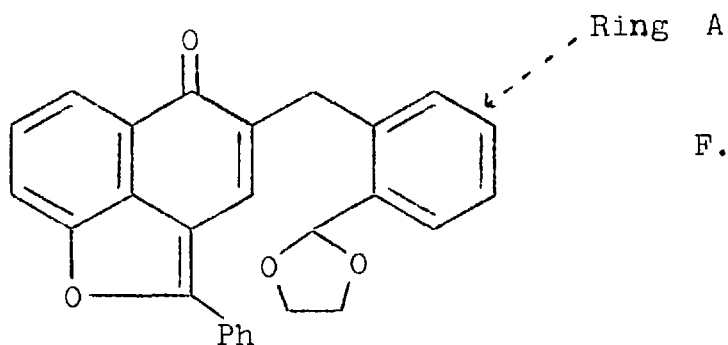
Only the simpler dihydro-amide C could be obtained.

b. An unsuccessful search for methods of inserting nitrogen into the double bond of an enol ether. During this work a new type of hydroxylamine derivative E was synthesised and its reactions were studied.



E.

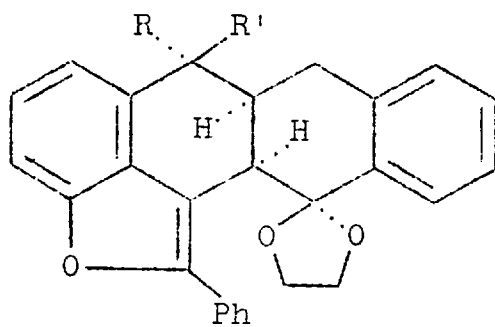
c. Discovery of a photolytic method for converting the acetal F into the ketal G.



Certain aspects of this cyclisation were examined and the technique was extended to the parent aldehyde and other of its derivatives.

Evidence was obtained that cyclisation of the acetal is also possible when ring A is substituted.

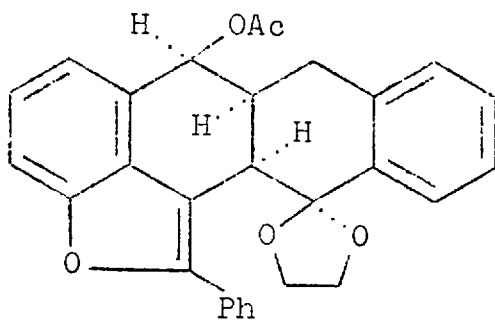
d. Establishment of methods for reducing the ketal G to the compounds defined by formula H.



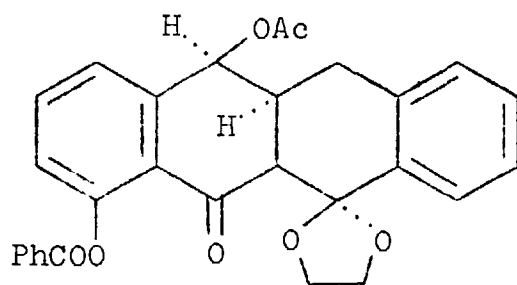
- i. $R=H, R'=H$
- ii. $R=H, R'=OH$
- iii. $R, R'=Me, OH$

H.

e. Development of a method for cleavage of certain furans
(e.g., I $\rightarrow$ J).



I.



J.

f. Preliminary studies aimed at hydrolysis of both ester groups of compound J.

Acknowledgements

I want to thank my supervisor, Professor D. H. R. Barton, F.R.S., for allowing me to work in his research group and for providing inspiration and guidance at all times.

It is a pleasure to acknowledge the contribution of Dr. J. E. Baldwin, who read parts of the manuscript and made many useful suggestions during the course of the experimental work.

My gratitude also extends to the Scholarships Committee of the University of London and to Imperial College for financial support.

Technical assistance was given skilfully by Dennis R. Aldrich and Ian C. Scobbie. N.m.r. and mass spectra were measured by the staff of the Spectroscopy Department, and combustion analyses were performed in the Analytical Laboratory.

Derrick L. J. Clive,
Whiffen Laboratory.
July, 1966.

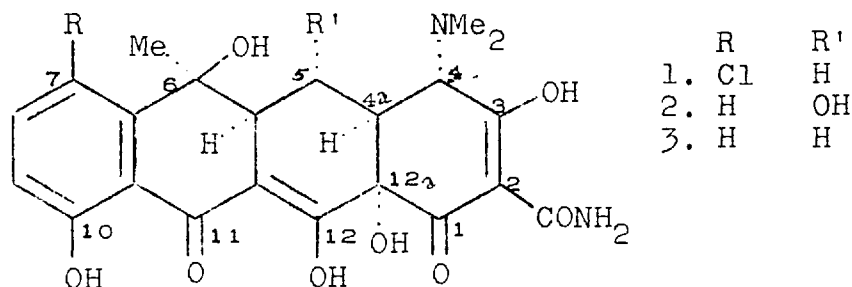
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INTRODUCTION.

The tetracyclines, mould metabolites produced by various forms of Streptomyces, are a group of poly-functional compounds based upon a hydronaphthacene skeleton.

Aureomycin, or 7-chlorotetracycline (1), was the first of these substances to be discovered,¹ and its pronounced antimicrobial activity quickly gained for



it an important place in medicinal practice. Shortly afterwards, Terramycin, or 5-oxytetracycline (2), was isolated² and this substance also, was recognised as a valuable antibiotic, as later still, was its 5-deoxy-analogue, Tetracycline (3).³ The latter may be regarded as the parent system not only for the two metabolites already discovered but also for a number

of related materials subsequently isolated. These include 7-bromotetracycline⁴, 6-demethyltetracycline⁵, 6-demethyl-7-chlorotetracycline⁵, several 2-acetyl-2-decarboxamidotetracyclines⁶, and a 7-chlorodehydrotetracycline.⁷ The position of the extra double bond in the last substance has not been settled, the problem being made difficult by the existence of two tautomeric forms.

A comparison of chemical, physical, and biological data for terramycin and aureomycin indicated a close similarity between the two substances. The structure of terramycin was determined⁸ by chemical methods, and, once its constitution was known, it was possible to deduce,⁹ within a short time, the structure of aureomycin. At this stage the structure of tetracycline became apparent because of its simple relationship to aureomycin,^{10,3} from which it may be obtained by hydrogenolysis.

With the chemical and spectral attributes of the tetracyclines properly defined, structural assignments could be made easily to other members of the group.^{4,5,6,7}

An examination¹¹ of aureomycin hydrochloride by X-ray techniques confirmed the chemical assignment (1) and established the relative configuration at each of

the asymmetric centres. The results are expressed by the formula which also shows the absolute configuration.¹²

In the case of terramycin, an X-ray study¹³ again confirmed the gross structure but did not define properly the relative stereochemistry at C-5. The formulation given (2), in which the hydroxyl group at C-5 is trans to that at C-6 is supported by evidence obtained¹⁴ by n.m.r. spectroscopy. The same technique has furnished data on the conformation of 5-oxytetracycline and some of its derivatives.¹⁵

The absolute configuration of tetracycline is defined by formula 3 since, when tetracycline is obtained from aureomycin, the only indicated molecular change is replacement of chlorine by hydrogen.^{12,3e}

Chemistry of tetracyclines and their derivatives[#].

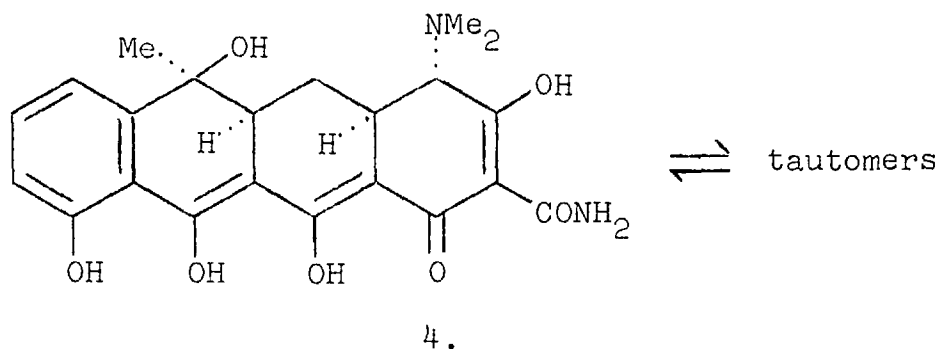
The oxygenation pattern of the tetracyclines renders these materials sensitive to acids and to bases. Consequently, reaction conditions that may be used during synthesis are limited and the restrictions will become increasingly severe in the last steps as the natural product is approached.

In this section we shall examine the response of the tetracyclines and their derivatives to a number of reagents. Such a study will indicate conditions that are best avoided in the last stages of synthetic work and will serve to screen the reactions for their potential use in such projects.

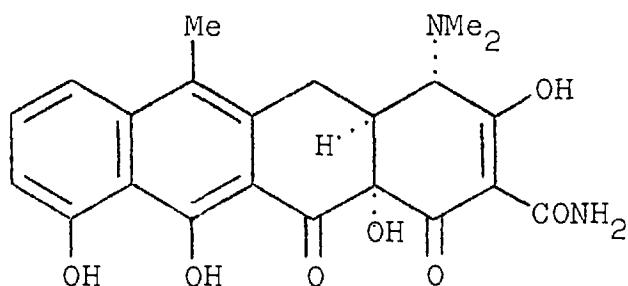
At the outset, we may note two simplifications. The hydroxyl group at the 12a-position of the tetracyclines can be replaced by hydrogen and the site may be rehydroxylated in the correct stereochemical sense by procedures to be specified later. Secondly, it is known that the asymmetric centre at C-4 is readily

[#]In some cases stereochemistry is not defined in the original literature. We have made assignments on this point that are compatible with present knowledge.

epimerized within the pH range 2 to 6. The carboxamide group must be intact, but the change is controllable and both epimers can be isolated.^{16,17,18,19} Since no other alterations take place during these two processes, synthesis of tetracycline actually involves preparation of compound 4.



The status of the hydroxyl group at C-6 in the natural tetracyclines is secondary or tertiary. The position is benzylic and the function bears a trans relation to the adjacent hydrogen atom (see 4). This situation accounts for the acid lability of the C-6 hydroxyl group. The aromatic nature of ring B in the resulting anhydrotetracyclines (e.g., 5) makes the dehydration process an especially facile one.



5.

(5a,6-anhydrotetracycline)

Warm mineral acids are usually employed for the preparation of anhydrotetracyclines²⁰ but strong organic acids are also suitable.²⁰

Tetracycline itself is stable for 'long periods' in 0.03 N hydrochloric acid¹⁶ but further increases in acid strength bring about dehydration. Data relevant to our interests are summarised in the table.

Compound	Conditions	Half-life	Reference
7-chloro TC [‡]	Aq. solution of hydrochloride (pH 2.5-2.8), room temp.	14 days	21
5-oxy TC	37°, pH 1	114 hr.	22
	37°, pH 2.5	134 hr.	22
	37°, pH 4.6	45 hr.	22
	37°, pH 5.5	45 hr.	22
	37°, pH 7.0	26 hr.	22
TC	100°, 1N sulphuric acid	✓ 1 min.	7a, 5a
5a- <u>epi</u> -TC	100°, 1N sulphuric acid	67 min.	7a
7-chloro TC	100°, 1N sulphuric acid	2.1 min.	5a
5-oxy TC	100°, 1N sulphuric acid	4.5 min.	5a
6-demethyl TC	100°, 1N sulphuric acid	24.8 min.	5a
7-chloro-6-demethyl TC	100°, 1N sulphuric acid	445 min.	5a

[‡]In full: 7-chlorotetracycline. Abbreviated names are used in all tables.

The enhanced acid stability of 6-demethyltetracycline and 5a-epi-tetracycline, the latter obtainable by hydrogenation of the natural 7-chlorodehydrotetracycline,⁷ is not unexpected. In one case the hydroxyl group is secondary and in the other it is cis to the adjacent hydrogen atom. What is surprising is the dramatic influence of chlorine at C-7 in the case of the 6-demethyltetracyclines. The effect is probably a

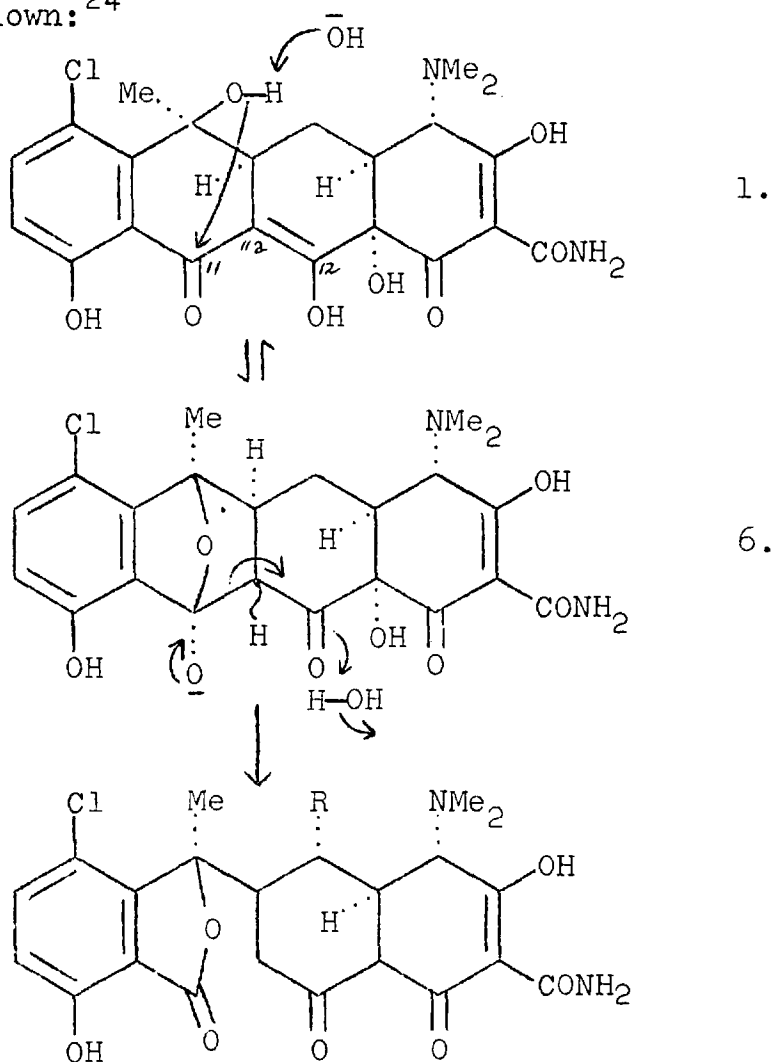
steric one but it is difficult to see how it operates. As the last entry shows, 7-chloro-6-demethyltetracycline may be expected to survive acid conditions of comparative severity and it is conceivable that the same will be true of immediate precursors in synthesis. This exception apart, it is clear that only very mild acid conditions can be tolerated for any length of time by the natural tetracyclines. Unfortunately, the compounds are also very sensitive to bases. We have collected in the table representative data on this point.

Compound	Conditions	Half-life	Reference
TC	0.1N sodium hydroxide, 100°	6.8 min.	5a, 23
5-oxy TC	0.1N sodium hydroxide, 100°	2.2 min.	5a, 23
7-chloro TC	0.1N sodium hydroxide, 100°	<0.3 min.	5a
6-demethyl TC	0.1N sodium hydroxide, 100°	31.5 min.	5a, 23
7-chloro-6-demethyl TC	0.1N sodium hydroxide, 100°	40 min.	5a
7-chloro TC	5% aq. sodium bicarbonate, room temp.	1-3 hr.	9a
TC	5% aq. sodium bicarbonate, room temp.	24-30 hr.	9a
5-oxy TC	37°, pH 7	26 hr.	22
5-oxy TC	37°, pH 8.5	33 hr.	22
5-oxy TC	37°, pH 10	14 hr.	22
TC	pH 8.85, room temp.	12 hr.	3d

Again, the presence of a 7-chloro-substituent affects the stability. Tetracycline is more base

resistant than aureomycin while, in the 6-demethyl-series, the chlorinated compound is the more stable.

The initial products formed in basic media are the iso-tetracyclines (e.g., 7) and they are produced in the manner shown:²⁴



7. R=H (Iso-aureomycin)
8. R=OH (Iso-terramycin)

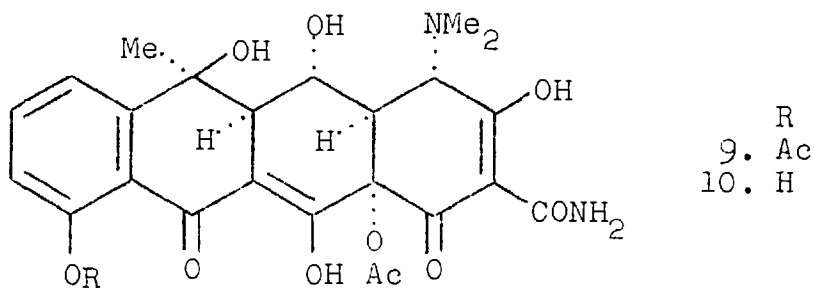
In the case of iso-terramycin (8; R = OH) the hydroxyl group on ring B permits further base degradation and, in fact, iso-terramycin has not been isolated. Fission of the skeletal bond between C-11 and C-11a requires ketonisation of the C-12 carbonyl group, which is initially present as an enol (see 1). It is to be expected, therefore, that any device for stabilising the C-11-C-12 dicarbonyl system in an enolised form would protect the antibiotic against base degradation. It is well known that the tetracyclines form complexes with many metal cations but the site of binding is still a matter of dispute. There is evidence²⁵ to support the belief that in solid complexes binding takes place through two of the oxygen atoms of ring A. Other evidence, which refers to complexes in solution, favours the enolised β -dicarbonyl system at C-11-C-12.²⁶ The second assignment would account for the observed enhancement of base stability. A number of complexes of general formula (tetracycline-group antibiotic) (aluminium)_a (calcium)_b (gluconic acid)_c have been made²⁷ where a, b, and c are the molar ratios of the respective constituents. Greatly enhanced alkaline stability occurs when a and b have certain values:

Compound	Conditions	Half-life
6-demethyl-7-chloro TC.HCl	0.1N sodium	40 min.
6-demethyl-7-chloro TC:Al:Ca:Gl [⌘]	hydroxide ₈	3000 min.
1: 4: 2:12	90-100°	

[⌘]Gl = gluconic acid

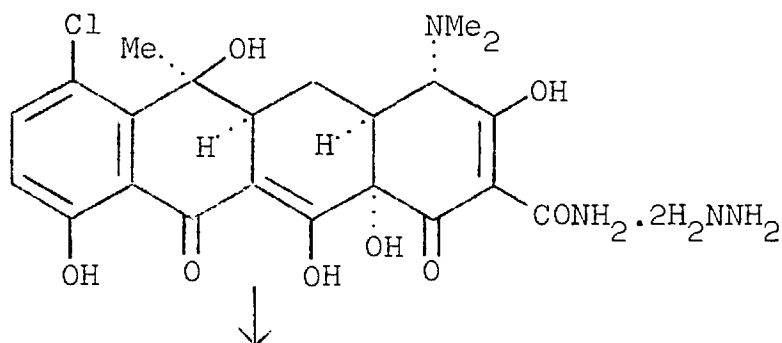
The molar ratio of gluconic acid appears to play an important part only in solubilising the derivative. The acid stability is little affected.

Of greater interest is the use²⁸ of concentrated aqueous ammonia, in the presence of magnesium chloride, to hydrolyse the diester 9 to the monoester 10.

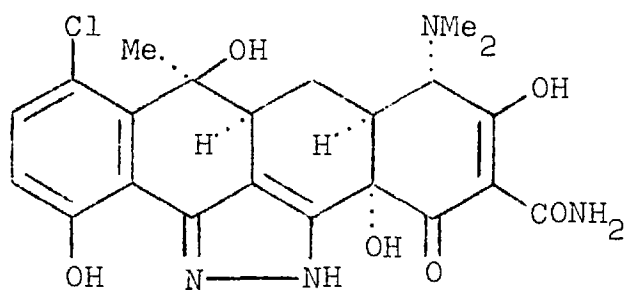


Degradation occurs in the absence of the metal cation unless the reaction time is very short.

Finally, it is relevant to note that tetracycline forms addition products with hydrazine²⁹ and can be recovered by the action of water. Aureomycin, however, cannot be regenerated from its addition compound since the substance readily forms a pyrazoline (11→12).



11.



12.

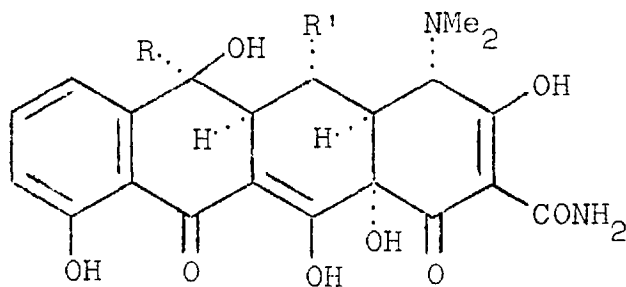
(more probable tautomer
than that given in ref.
29)

There exists in certain circumstances, therefore, the opportunity of removing ester groups from synthetic tetracycline precursors by treatment with hydrazine or with ammonia-metal ion combinations.

Although the C-6 hydroxyl group plays a central rôle in reactions brought about by acids and bases it also participates in a number of non-degradative transformations which temporarily modify its own chemical activity as well as that of other positions on the tetracycline skeleton. These reactions suggest techniques that might profitably be used in synthesis and we shall examine them here.

When the compounds specified by formula 13, as well as several others of lesser interest, are treated

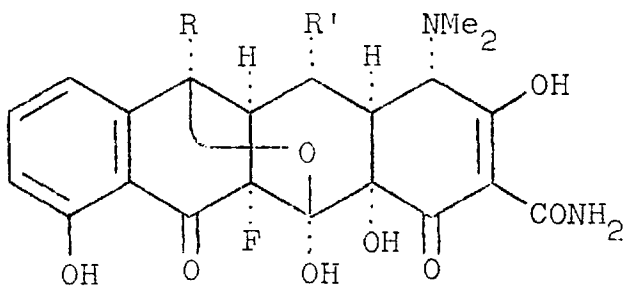
with perchloryl fluoride in the presence of a base there are obtained^{30,31,32} pure, crystalline substances



	R	R'
a.	Me	H
b.	Me	OH
c.	H	H

13.

in yields of 15 to 83% for which the 11a-fluoro-6,12-hemiketal structures (14) have been established,



	R	R'
a.	Me	H
b.	Me	OH
c.	H	H

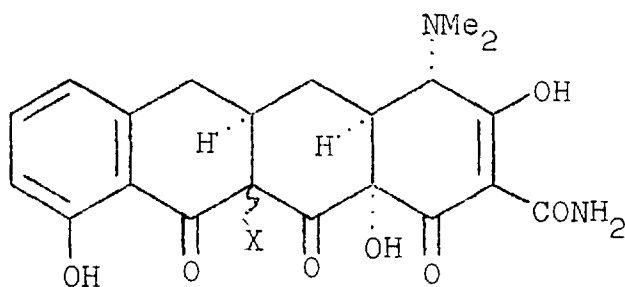
14.

Since formation of 6,12-hemiketals is sterically possible only if the C-5a hydrogen atom and the C-6 hydroxyl group are trans, isolation of compound 14c proves that the C-6 hydroxyl function in 6-demethyl-

tetracyclines has the same stereochemistry as in the parent series.

The 11a-fluorine atom in the hemiketals can be removed to regenerate the antibiotic. For compound 14a, one procedure involves catalytic hydrogenolysis at 5000 p.s.i. and at 30-100°. An alternative employs zinc in hydrochloric acid.

When the C-6 hydroxyl group is absent a hemiketal cannot be formed. Instead, compounds such as 15 (X = F) are produced,^{30,31,32} and from these, the 11a-fluorine atom is easily removed by hydrogenolysis under mild conditions or simply by treatment with methanolic hydrogen chloride.

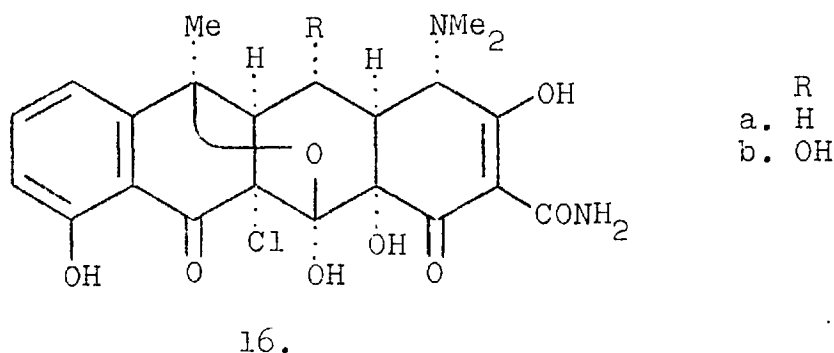


15.

Of particular relevance is the observation that the 11a-fluoro-compounds 14 resist the dehydrating action of acids and can even survive treatment with boiling

methanolic hydrogen chloride.³² This stability is attributed to the fluorine atom which, in its position at the ring junction, is able to prevent enolisation of the C-11 carbonyl group.

Treatment of amphoteric tetracycline or terramycin with N-chlorosuccinimide in glyme affords the analogous chloro-hemiketals³² 16a and 16b.

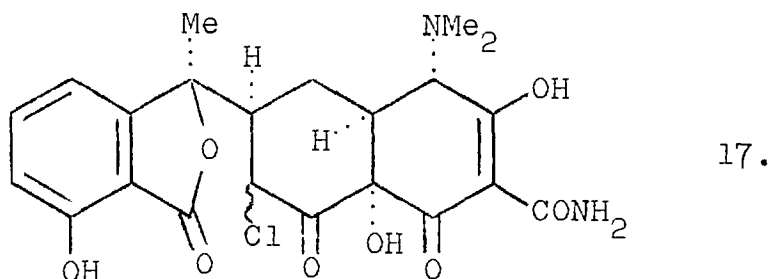


Again, in the 6-deoxy-series, hemiketal formation is impossible and the product (e.g., 15; X = Cl) is easily reconverted to starting material by mild reduction.³⁰

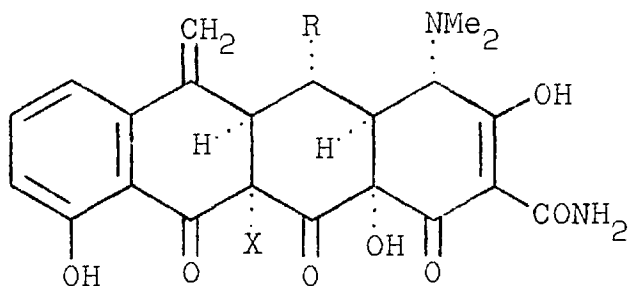
Unlike its fluoro-analogue, compound 16a dissociates in solution to the C-12 ketonic form. In this tautomer, the halogen atom is activated and, therefore, removable under mild conditions such as hydrogenation at room

temperature or treatment with sodium hydrosulphite.

When the hemiketal 16a is heated in methanolic hydrogen chloride it is converted to 11a-chloro-iso-tetracycline (17), the 5a,6-elimination reaction, so characteristic of normal tetracyclines, not occurring in the present case.



In liquid hydrogen fluoride the substance is degraded in a different way. Exocyclic dehydration occurs to yield the 11a-chloro-6-methylene derivative 18a.

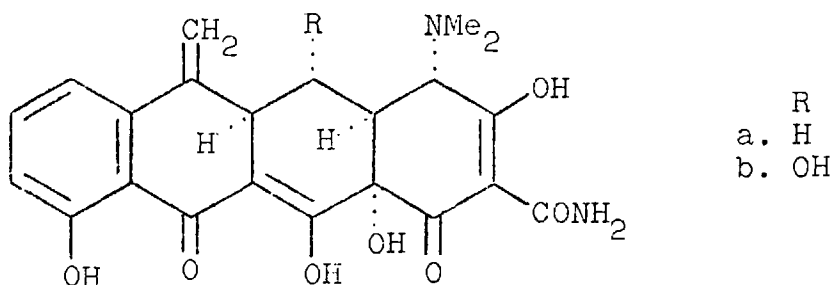


	R	X
a.	H	Cl
b.	OH	Cl
c.	H	F
d.	OH	F

18.

Compounds 18b-18d are formed in the same manner from the corresponding hemiketals. All these derivatives have a much greater acid stability than the natural tetracyclines.^{32,33,34}

Compounds 18a and 18b are readily reduced to the corresponding 6-methylene-tetracyclines 19a and 19b, respectively.

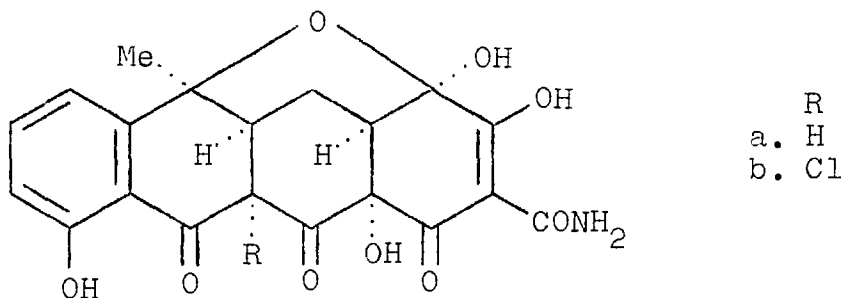


19.

The course of the dehydration has been attributed³² to the presence of the C-11a substituent. This removes a powerful driving force for 5a,6-dehydration by preventing aromatisation of ring C. The acid stability of the 11a-halo-6-methylene-compounds 18 is understandable on this basis, but the explanation is incomplete since the halogen-free compounds 19 also have enhanced acid stability. They are intermediate in this respect³² between tetracycline and the 6-deoxytetracyclines. They

do not serve as good precursors for the 6-deoxy-compounds since saturation of the methylene group by catalytic hydrogenation gives products epimeric at C-6.³⁵

11a-Chlorotetracycline-6,12-hemiketal (16a) is prepared from amphoteric tetracycline. If tetracycline hydrochloride is used instead and is treated, in water, with N-chlorosuccinimide, 4-oxo-4-dedimethylaminotetracycline-4,6-hemiketal (20a) is precipitated.³⁶ The gross structure deduced from chemical experiments demands the stereochemistry shown, and this assignment has been proved by X-ray crystallography.³⁷

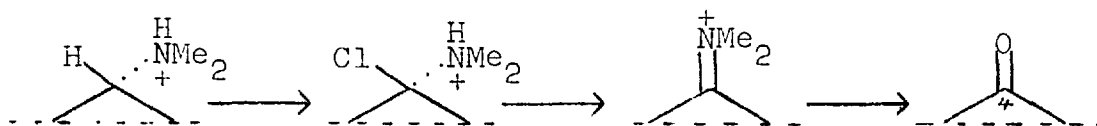


20.

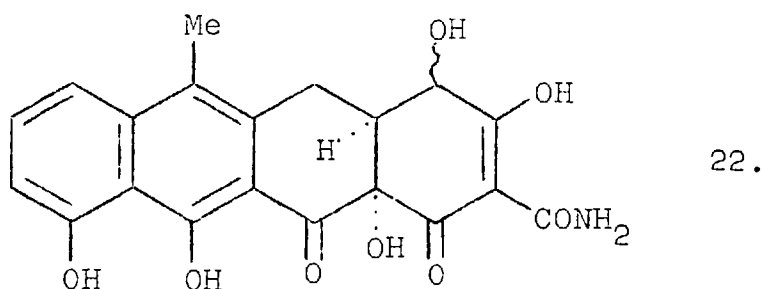
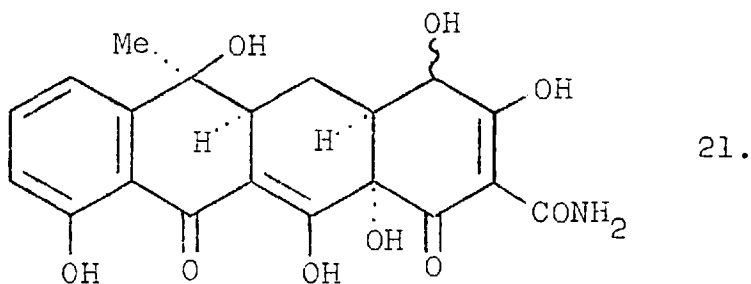
The 11a-chloro-analogue (20b) is obtained by treating the 11a-chloro-6-12-hemiketal 16a, in dilute hydrochloric acid, with N-chlorosuccinimide.

It is considered that formation of the 4-oxo-

derivative occurs in the manner illustrated: cf. 38



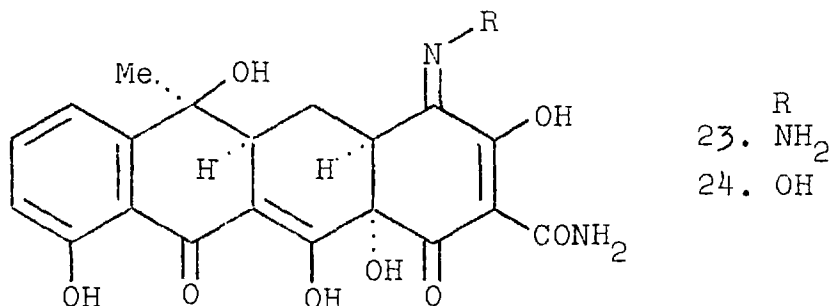
The hemiketal 20a is reduced to the alcohol 21 by sodium hydrosulphite, catalytic hydrogenation, or by zinc and acid.



The alcohol, in turn, is converted by acid degradation (p-toluenesulphonic acid in refluxing acetone) into its 5a,6-anhydro-derivative 22.

Hydrazine and hydroxylamine react at room temperature

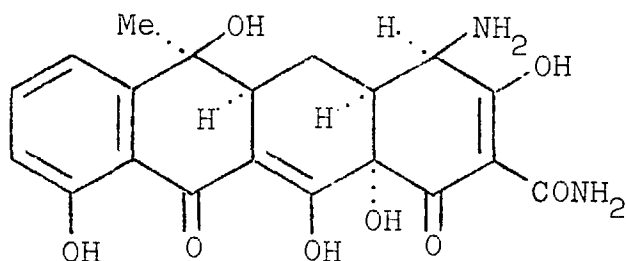
with the hemiketal 20a to produce the hydrazone 23 and the oxime 24, respectively.



Similar transformations at the C-4 position, using ammonia and a number of primary amines, have been carried out in the 6-demethyl-series.³⁸

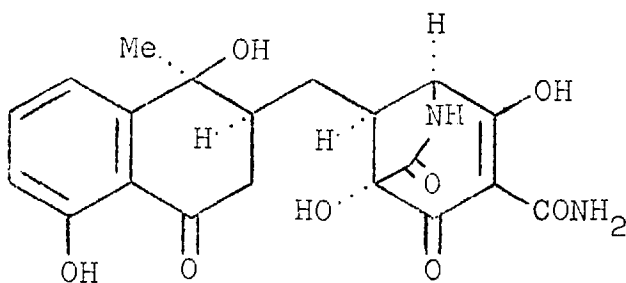
Formation of all these derivatives is significant not only because it represents a method for introducing nitrogen at C-4 but also because it suggests that tetracycline-like molecules can be treated with weakly basic but strongly nucleophilic reagents in order to effect removal of protecting groups.

Both imino-compounds 23 and 24 are reduced catalytically or by sodium hydrosulphite or zinc-acetic acid. It is believed that the first step is hydrogenolysis to an imine which is further reduced to the 4-epi-compound 25. The same compound is formed directly from the hemiketal 20a by hydrogenation in dimethylformamide containing ammonium hydroxide and magnesium chloride. The



25.

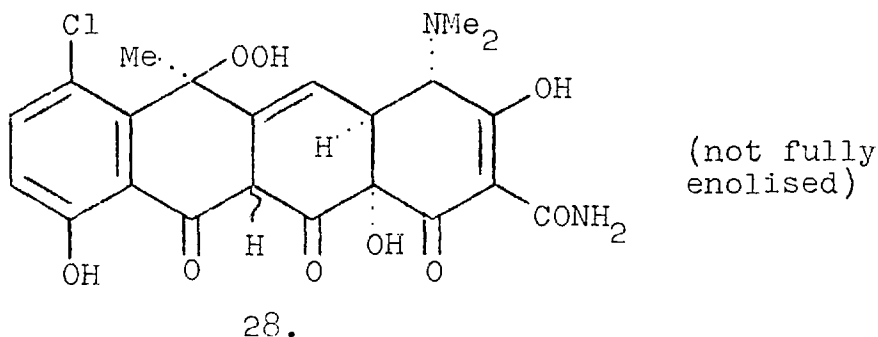
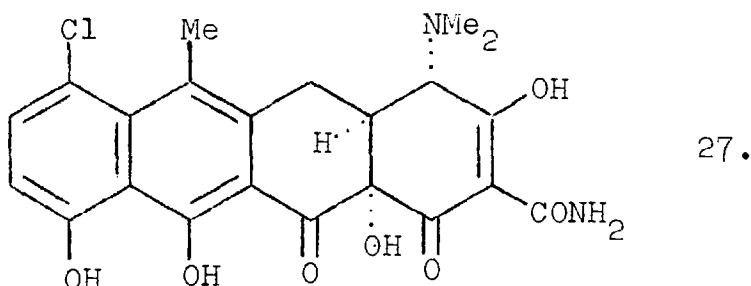
primary amine 25 is degraded by hot aqueous sodium bicarbonate in a manner reminiscent of that leading to iso-tetracyclines. In the present case, rings A and B are involved. The imino-function attacks the C-12 carbonyl group and the lactam 26 is formed.³⁹



26.

The survey of reactions involving the C-6 hydroxyl group is now complete except for the observation that this group can be introduced in the final stage of

synthesis. Such a possibility arises from the discovery^{7c} that 7-chloroanhydrotetracycline (27) can be oxygenated photolytically to give the hydroperoxide 28. Catalytic reduction converts this substance to the natural

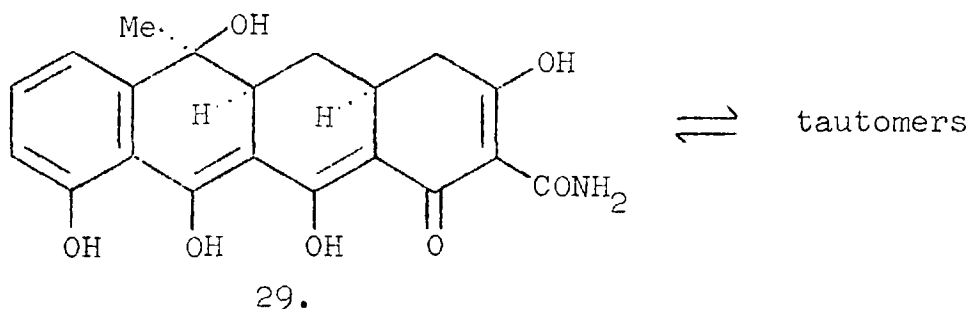


7-chlorodehydrotetracycline and then to tetracycline itself. The oxygenation procedure has been studied in detail⁴⁰ and is of interest for two reasons. It is considered to simulate part of tetracycline biogenesis, and it provides an alternative synthetic route to the antibiotic.

Ring A of the tetracyclines survives the reactions that have been discussed so far. It is possible, however,

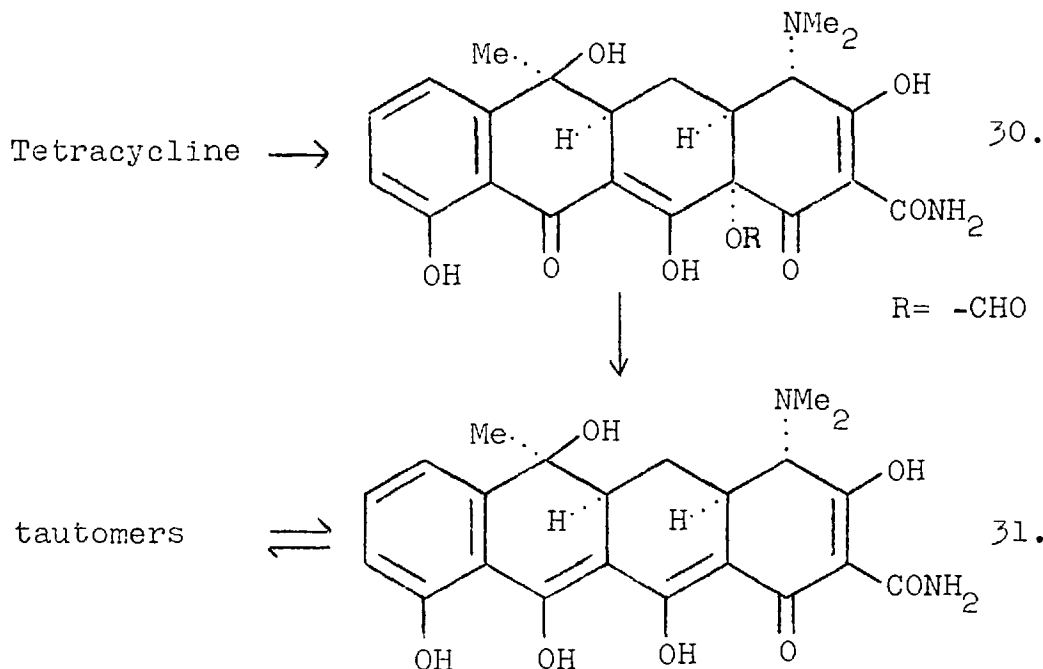
to modify this part of the molecule and some of the products may be useful as relay-compounds in synthesis.

Epimerisation at C-4 has already been described, and removal of the C-12a hydroxyl group was mentioned. The process is carried out in two ways. One procedure involves^{41,42} treatment of the tetracycline with zinc dust in 15% aqueous ammonium hydroxide. 12a-Deoxytetracycline, for example, may be isolated in 42% yield by this method after a two-hour reaction period at room temperature. Use of zinc dust in acetic acid results in an additional change, for the amino-group is removed,⁴³ and 12a-deoxydedimethylaminotetracycline (29) can be prepared in this way.



The other procedure requires preparation of a 12a-O-acyl derivative.^{44,45,46} Usually, the O-formate is used. The substance is obtained readily by the action

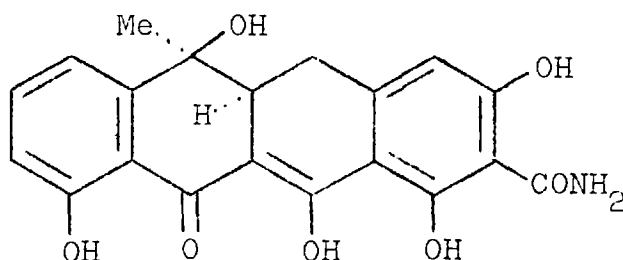
of acetoformic acid and is hydrogenolised in a dry, inert solvent.⁴⁵ The two-step method is illustrated for tetracycline:



The 12a-position in the deoxygenated compounds is an activated site. Thus, treatment of 12a-deoxydedimethylaminotetracycline (29) with one equivalent of N-bromosuccinimide in chloroform affords 12a-bromo-12a-deoxydedimethylaminotetracycline.⁴³ More significantly, the α -oriented hydroxyl group at C-12a can be replaced. 12a-Deoxytetracycline can be hydroxylated microbiologically⁴⁷ but this substance, as well as certain of its

derivatives that still possess the β -dicarbonyl system at C-12—C-1—C-3, are more conveniently hydroxylated by the use of chemical oxidants. Sodium nitrite, potassium permanganate, iodine, potassium dichromate, potassium ferricyanide and potassium peroxydisulphate are the reagents most commonly employed^{48,49,50,51} but there are also reports on the use of peracids,⁵² and of oxygen in the presence of noble metals.^{53,42}

12a-Deoxytetracycline (31), on treatment⁴⁴ with methyl iodide in tetrahydrofuran containing an acid scavenger (propylene oxide), affords compound 32.

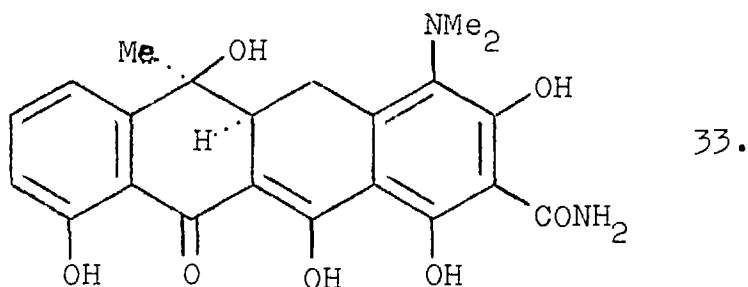


32.

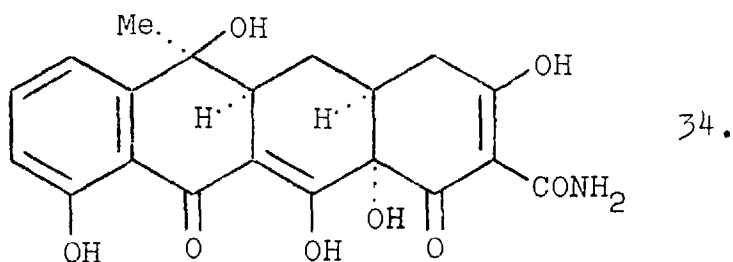
This substance is available⁴¹ from the same starting material by the action of perbenzoic acid or, in increased yield, by treating 12a-bromo-12a-deoxydimethylaminotetracycline with pyridine.^{43a} The first technique probably involves quaternisation and epimerisation of the C-4 substituent while the second is believed to proceed

by Cope elimination of an N-oxide.

Pyrolysis of the ester 30 also effects aromatisation of ring A.⁴⁴ Formic acid is eliminated but the amino-group is retained and the product is the compound 33.

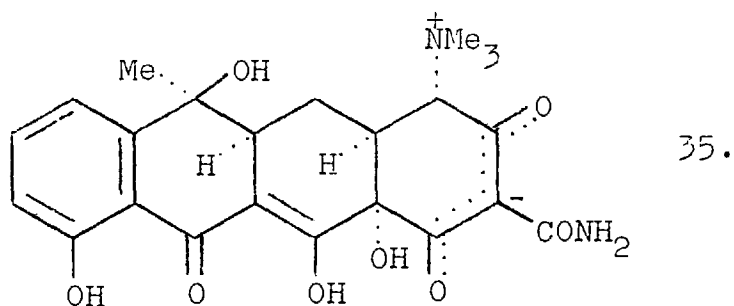


When tetracycline and aureomycin are treated with methyl iodide at room temperature the amino-function is quaternised.⁵⁴ The product from terramycin undergoes further modification but in the case of the other two antibiotics the quaternised derivatives can be isolated and they are useful for the preparation of 4-dedimethylaminotetracyclines (e.g., 34) which they yield on brief treatment with zinc in acetic acid.⁵⁵ Dedimethylaminotetracycline (34) has been brominated at the 11a-position^{43a} by treatment with one equivalent of N-bromosuccinimide in chloroform. The halogen is labile and is easily removed by reduction.

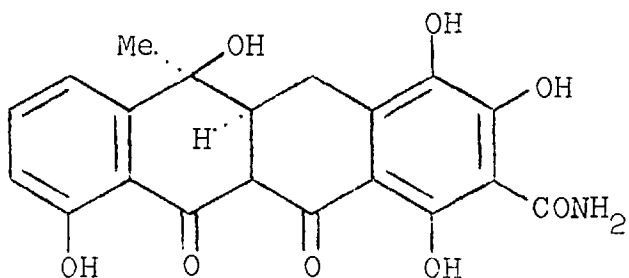


Direct halogenation at C-11a has also been reported⁵⁶ for some natural 7-halotetracyclines (in which the dimethylamino-function is present). The method calls for the use of N-chlorosuccinimide or N-bromosuccinimide in acetic acid, the product being obtained after very brief (4 min.) exposure to the reagent.

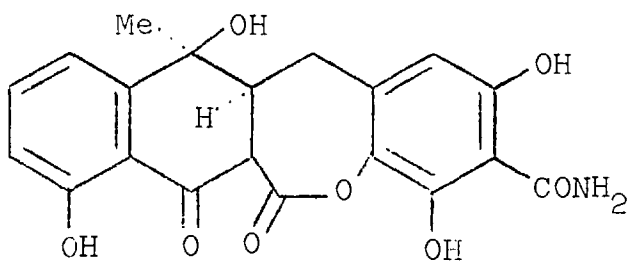
When tetracycline is quaternised with methyl iodide, the product dissolved in water, and the solution adjusted to pH 4-5, the betaine 35 separates as a crystalline



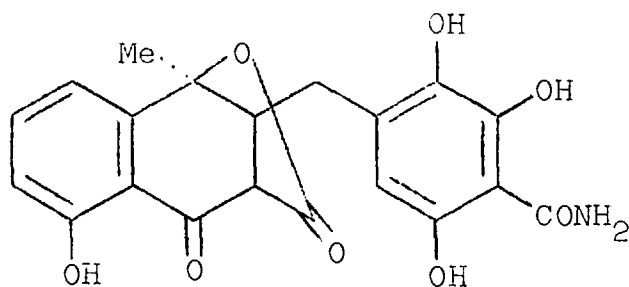
solid.⁵⁴ On pyrolysis⁵⁷ in acetonitrile, this substance is converted to the phenolic diketone 36. When methanol is the solvent the lactones 37 and 38 are formed. Both



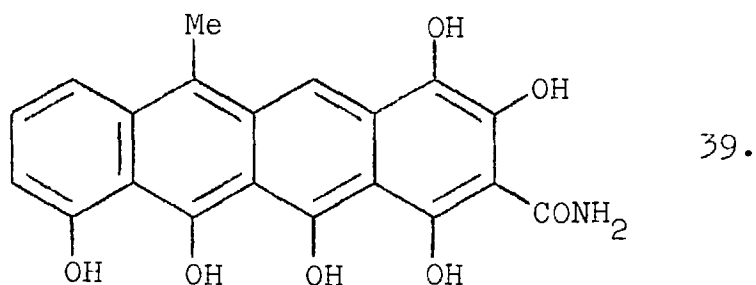
36.



37.

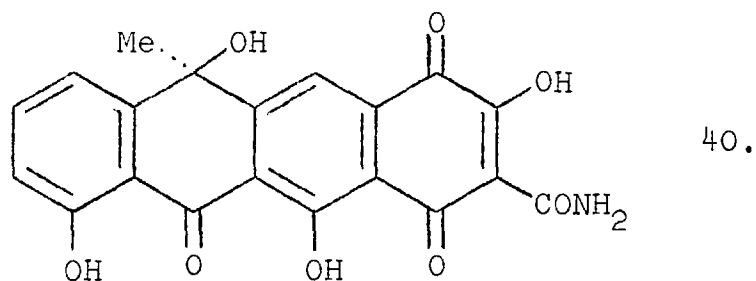


38.



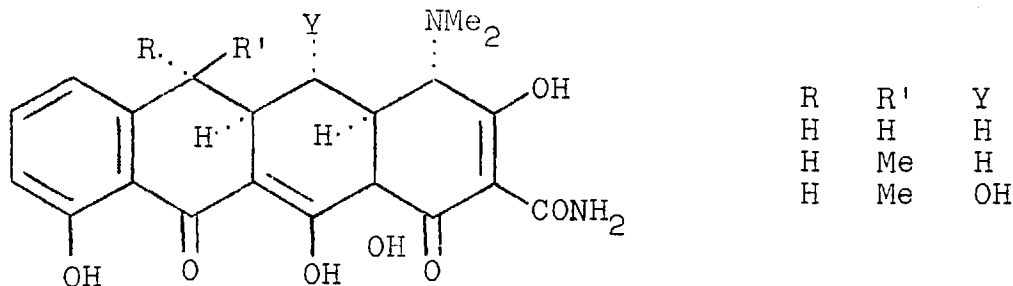
the diketone and the γ -lactone are transformed by strong acids into 4-hydroxy-6-methylpretetramid (39). This fully aromatic compound has been isolated⁵⁸ from the mash of a *Streptomyces aureofaciens* mutant and is regarded as a biogenetic precursor of aureomycin. 7-Chloro-4-hydroxy-6-methylpretetramid is available by a similar route.⁵⁷

Aerial oxidation⁵⁹ of the pretetramid 39 converts it to the ketonic substance 40. The change can be reversed by use of hydrogen iodide.



There are two final points that are of experimental interest. The solubility of tetracyclines can be altered by modifying the carboxamide group.⁶⁰ This function, which can be dehydrated to a nitrile,⁶¹ enters into Mannich reactions.^{60,62,63,64,65,66} For example, tetracycline, on treatment with morpholine and formalin, yields N-(morpholinomethyl)-tetracycline in 88% yield.⁶⁰ The substance is extremely soluble in water and can be degraded to tetracycline by hydrogenolysis in methanol with Raney nickel (43% yield) or, by treatment in water with sodium bisulphite (96% yield).

The second point is concerned with the sensitivity of tetracyclines to hydrogenation conditions. In neutral or basic solution the halogen at C-7 is replaced by hydrogen.⁶⁷ Under acidic conditions (e.g., pH 1.8) with a noble metal catalyst (usually palladium), 6-deoxy-tetracyclines are formed along with a number of byproducts.^{68,35,23} Often a chelating agent such as boric acid is added to protect the C-11—C-12 dicarbonyl group.^{69,23} Typical 6-deoxytetracyclines are collected in the table:



The C-7 chlorine atom is hydrogenolysed except under special conditions,⁷⁰ and epimerisation takes place at C-6.^{71,35} It is relevant to recall here that the presence of a halogen atom at C-7 can be useful during certain stages of synthetic work.

Hydrogenolysis of the C-6 hydroxyl group results in a dramatic increase in acid and base stability. The change is illustrated in a quantitative manner by the tabulated data²³ and has permitted a series of reactions to be carried out in strongly acid media.³⁵

Compound	Conditions and Half-life	
	3N hydrochloric acid 100°	0.1N sodium hydroxide 100°
6-deoxy TC	1600 min.	570 min.
TC	<<1 min.	6.8 min.

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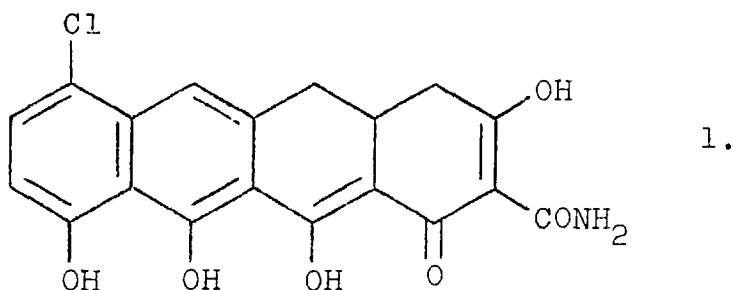
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Achievements in the field of tetracycline synthesis.¹

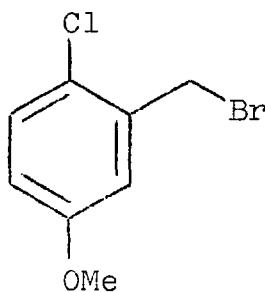
Total synthesis of a natural tetracycline is a problem which many have appreciated but which none has been able to solve. Major achievements in this field are summarised by the present review, in which compounds for examination are chosen from totally synthetic hydronaphthacenes with ring D aromatic and ring A oxygenated in the pattern of a dihydroresorcinol system. The substances are classified according to the status of ring C.

The first compound to be discussed in this scheme is ($\pm$)-dedimethylamino-12a-deoxy-6-demethylanhydrochloro-tetracycline (1). Preparation of this substance is a

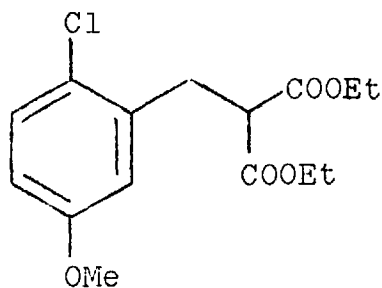


much less difficult synthetic task than that posed by one of the natural antibiotics: there is but one asymmetric centre, the 6-position is unsubstituted, and the material is not degraded by acids.

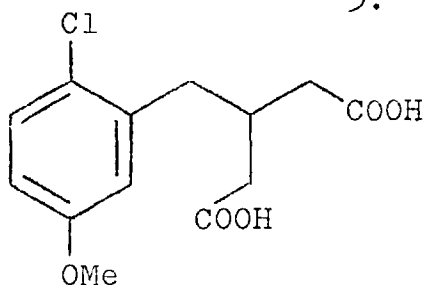
The aromatic halide 2, destined to provide ring D of the final product, was selected^{2,3} as the foundation on which to build the rest of the molecule. Condensation



2.

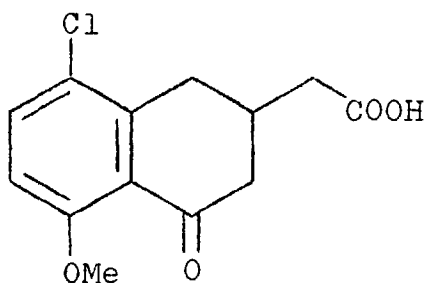


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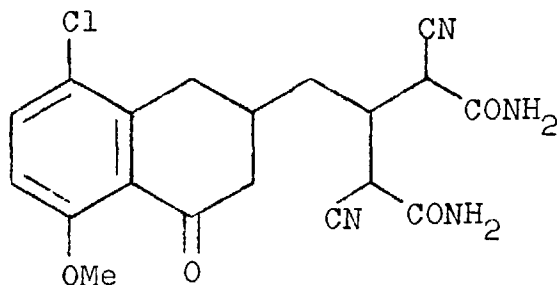


4.

with diethylsodiummalonate gave the diester 3 which was converted by standard methods to the glutaric acid 4. The chlorine atom in the starting material (2) had not yet served any purpose, but in the next step, which involved treatment with polyphosphoric acid, it limited the direction of ring closure so that the tetralone 5 was formed. The carboxyl group was reduced by the

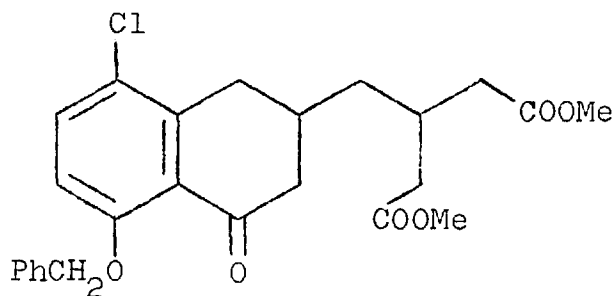


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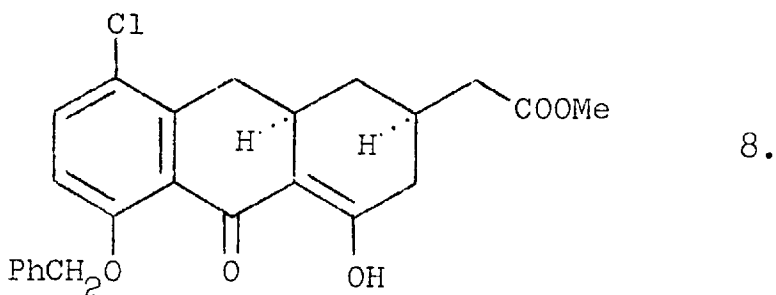


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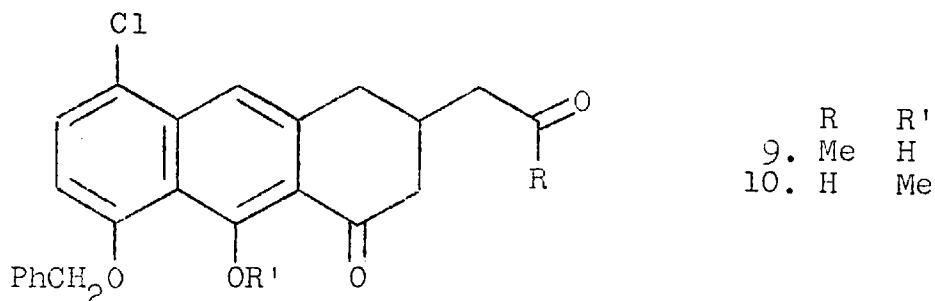
Rosenmund method, and base-catalysed reaction of the substance with cyanoacetamide gave compound 6. When this was heated in a mixture of hydrochloric and acetic acids, demethylation occurred; the nitrogen functions were hydrolysed and the resulting acids suffered decarboxylation. The free hydroxyl groups in the product were protected by converting the substance to the benzyl-diester 7. At this stage ring B was formed



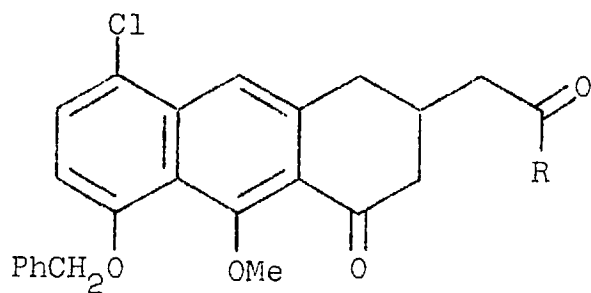
7.



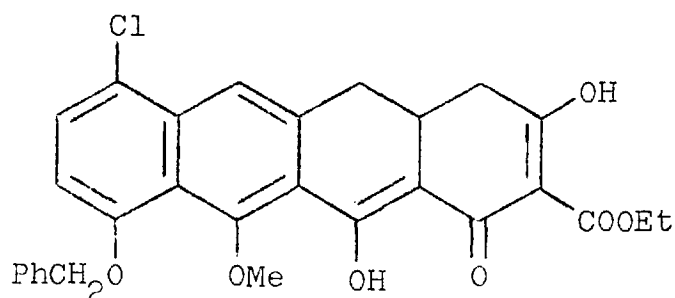
by treating the diester with sodium hydride in boiling toluene. The resulting tricyclic compound (8) was brominated at the ring junction between the β -dicarbonyl groups and heated with collidine to obtain compound 9. After protecting the phenolic hydroxyl group by methylation



and hydrolysing the ester the process of side-chain extension and ring closure was repeated ($10 \rightarrow 11 \rightarrow 12 \rightarrow 13$). Fusion of the tetracyclic ester 13 with ammonium formate and treatment of the product with acid completed the synthesis ($13 \rightarrow 1$). The results were published early in 1959.

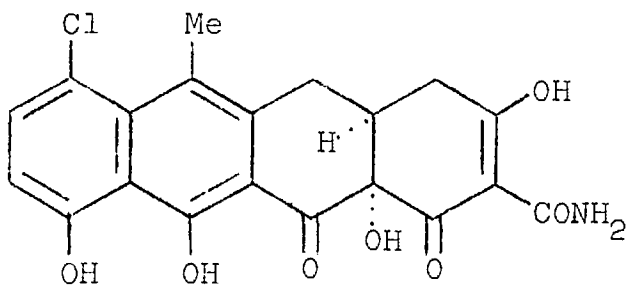


- R
 11. OCOOEt
 12. $\text{CH}(\text{COOEt})_2$

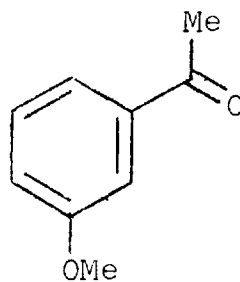


13.

A few months later synthesis of (+)-dedimethyl-aminoanhydrochlorotetracycline (14) was announced⁴ by Muxfeldt. He also began with an aromatic ring D and

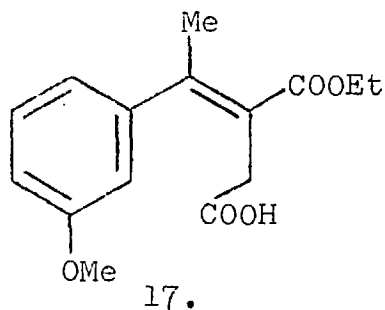
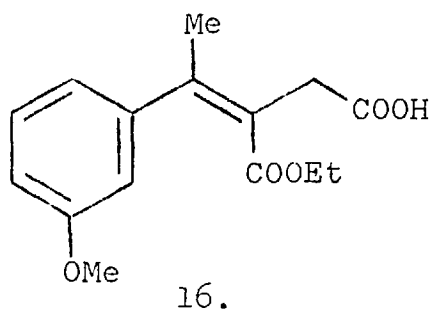


14.

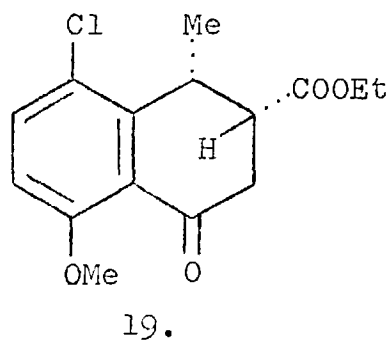
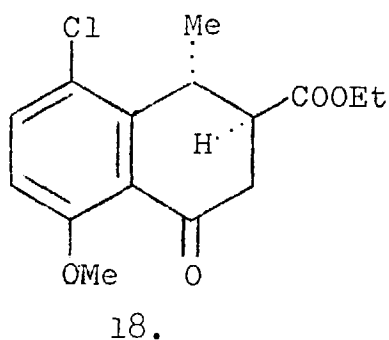


15.

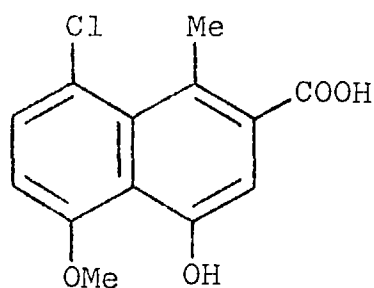
condensed the acetophenone 15 with diethylsuccinate.⁵
The resulting isomers, 16 and 17, were separated and



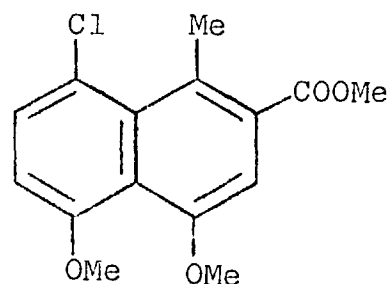
reduced catalytically. The position para to the methoxy-group was blocked by chlorination, and the tetralones 18 and 19 were obtained by dehydration with polyphosphoric acid. Muxfeldt later used the separate isomers 18 and



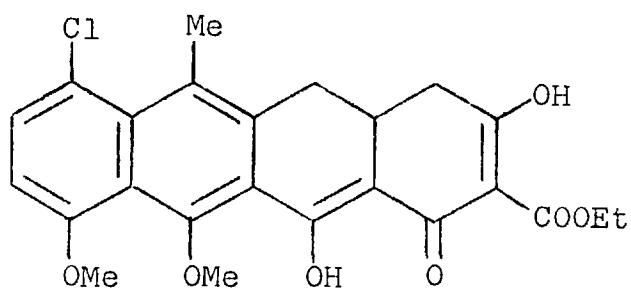
19 in other projects, but at this time he converted both of them to the substituted naphthalene 20, using a bromination-dehydrobromination sequence. The compound was methylated (20→21) and converted,^{5b} by a method similar to that already described, into the tetracyclic compound 22.



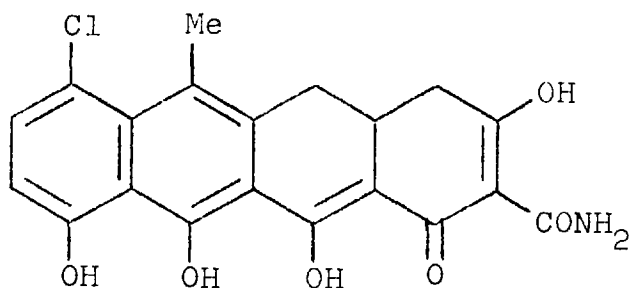
20.



21.



22.

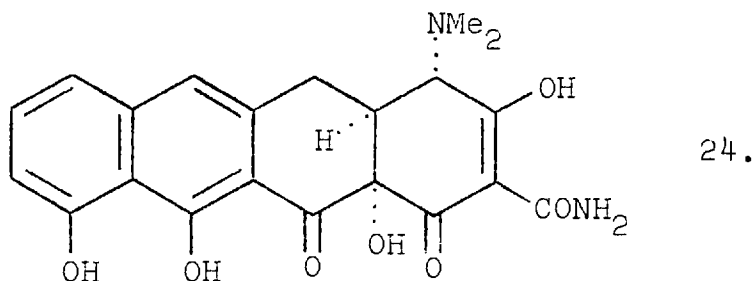


23.

Ammonolysis of the ester group was achieved in only 6% yield but sufficient material was obtained to carry out the next step (demethylation to 23) and to prove the structure of the product by comparison with an authentic

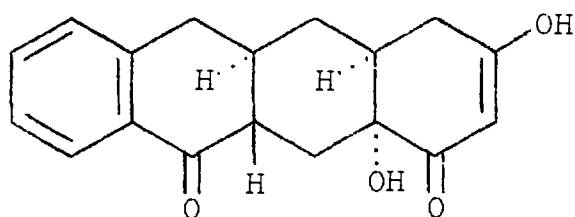
sample of dedimethylamino-12a-deoxy-anhydrochlorotetracycline. The work was carried a stage further by methylation of the hydroxyl group at C-10 and oxidation^{5c,5d} at C-12a with perbenzoic acid. Demethylation of the product afforded (+)-dedimethylaminoanhydrochlorotetracycline (14) in low yield.

No anhydrotetracycline with a dimethylamino-function at C-4 has been made by a direct route, but Muxfeldt has dehydrogenated⁶ 6-demethyl-6-deoxytetracycline, whose total synthesis we shall soon describe, to 6-demethyl-anhydrotetracycline (24). Probably, he plans⁶ to

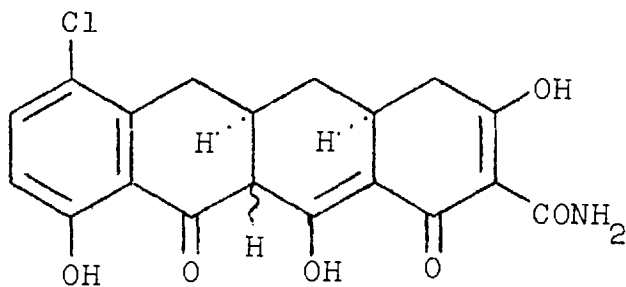


synthesise 6-deoxy-7-chlorotetracycline in the hope that ring C can be aromatised so that the product could be converted to tetracycline by the photo-oxygenation procedure of Scott and Bedford.⁷

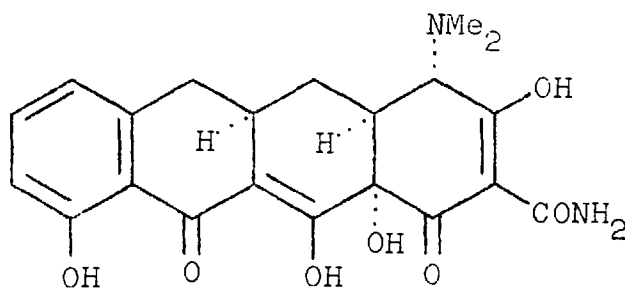
The 6-demethyl-6-deoxy-compounds 25, 26, and 27 constitute the next group in our classification. The simplest of these, 25, was made by Shemyakin and his



25.



26.

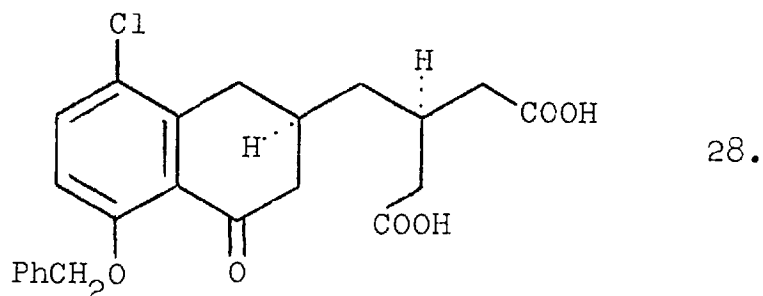


27.

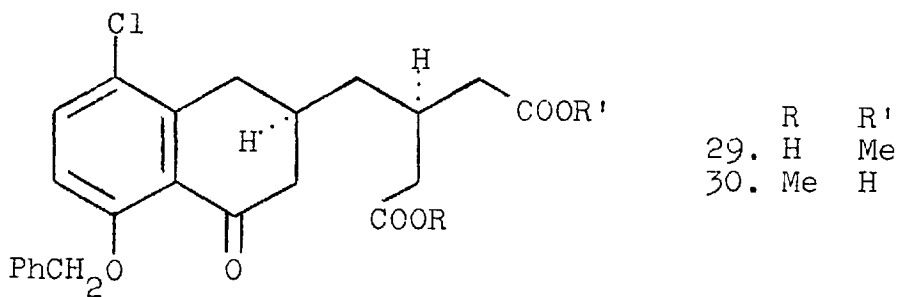
colleagues.⁸ The approach of these chemists will be illustrated later, when their more advanced results are presented; here we shall examine further only

compounds 26 and 27.

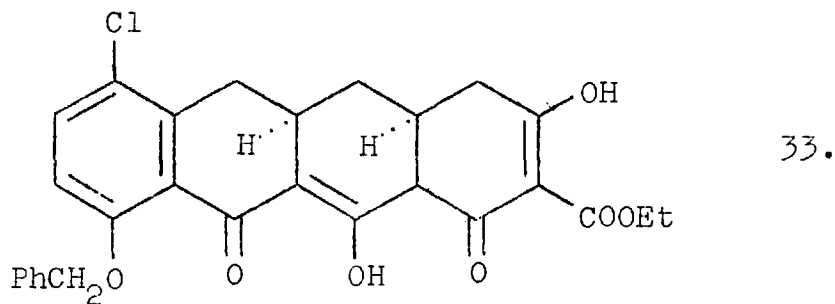
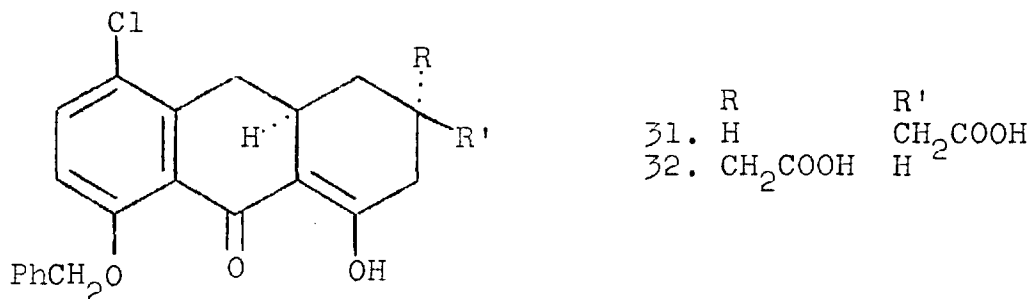
(+)-Dedimethylamino-6-demethyl-6,12a-dideoxy-chlorotetracycline (26) was synthesised⁹ in the same laboratory where the anhydro-compound (1) had been made. The glutaric acid 28, an intermediate from the earlier work, was converted to its anhydride and thence to a



mixture of the esters 29 and 30. These were cyclised



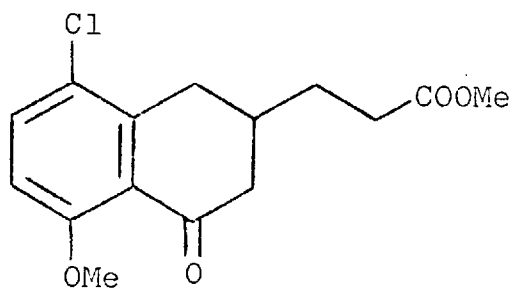
in the usual way and the resulting diastereoisomeric acids 31 and 32 were separated. The syn-acid 31 was converted, by the route that the group had used previously into the tetracyclic ester 33. Hydrogenolysis



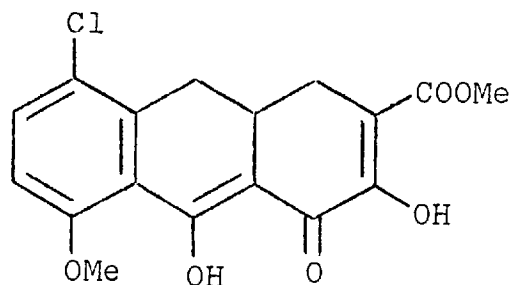
of the benzyl-ether and introduction of the carboxamide group completed the synthesis.

The product (26) lacks a dimethylamino-function at C-4. Incorporation of this unit into a 6-demethyl-6-deoxytetracycline was first achieved by Woodward in collaboration with a team working for Chas. Pfizer and Co.

Their initial experiments¹⁰ followed principles already exemplified and led to the tetralone 34.

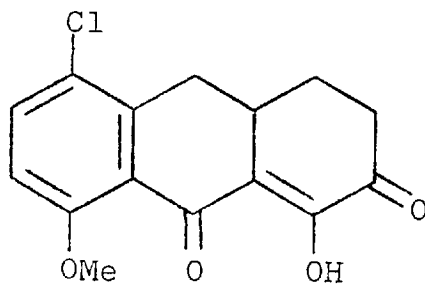


34.

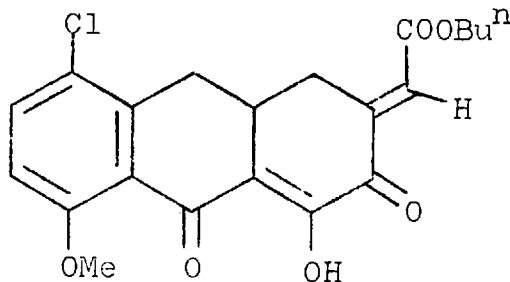


35.

Condensation with dimethyloxalate yielded the tricyclic substance 35 which was hydrolysed and decarboxylated to the triketone 36.

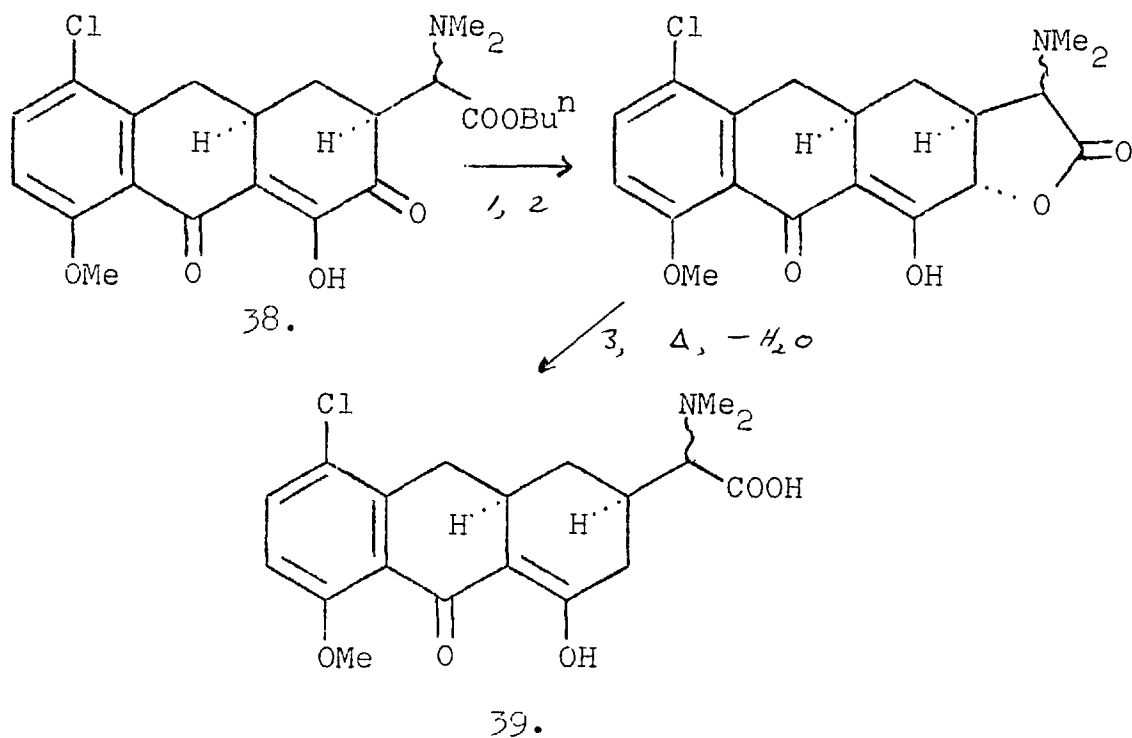


36.



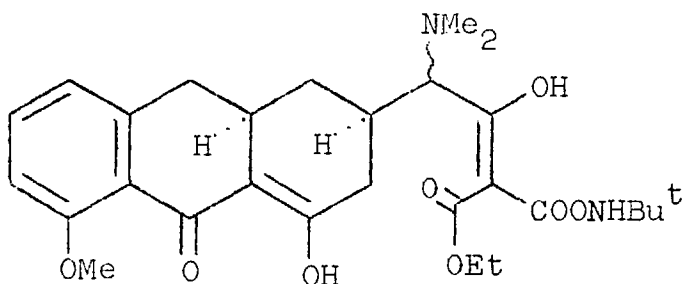
37.

Base-catalysed combination with n-butylglyoxalate gave the glyoxylidene derivative 37 in which the newly-formed double bond was readily attacked by dimethylamine ($37 \rightarrow 38$). The product was converted, by the method shown, into the amino-acid 39 from which the chlorine atom was removed by hydrogenolysis.



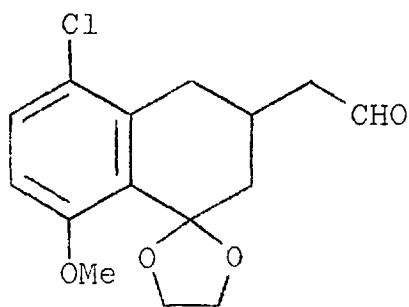
Reagents: 1, $NaBH_4$; 2, $TsOH$; 3, $Zn-HCOOH$.

The free carboxyl group was acylated to form a mixed anhydride which was condensed with the ethoxymagnesium-derivative of ethyl N-t-butylmalonamate. Compound 40 was formed and ring A was closed by using sodium hydride. Acid treatment effected removal of protecting groups and the molecule was hydroxylated at C-12a. Finally, the C-4 position was epimerised since the α -epimer had been obtained.

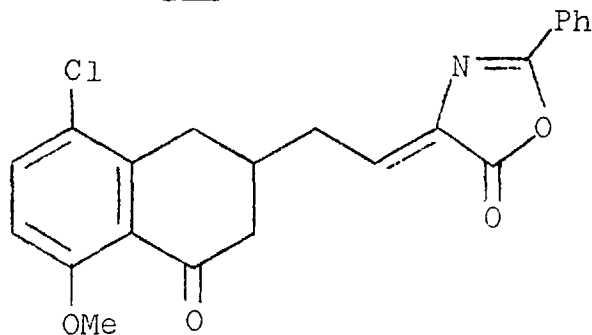


40.

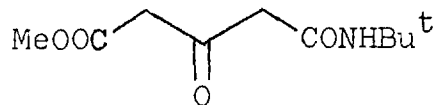
Another, and quite different synthesis of 6-demethyl-6-deoxytetracycline was achieved by Muxfeldt.¹¹ Starting with the aldehyde 41, which was obtained by the now standard methods, he prepared the azlactone 42 by condensation with hippuric acid followed by hydrolysis. When



41.

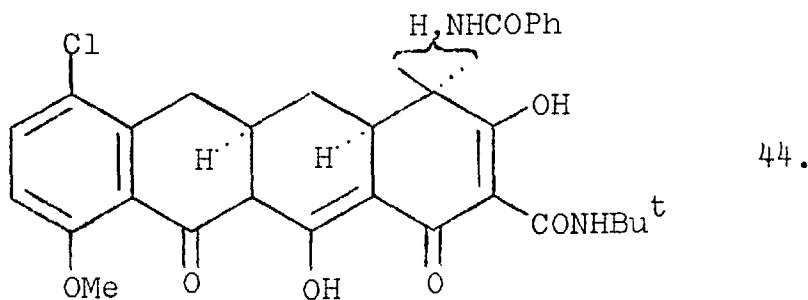


42.



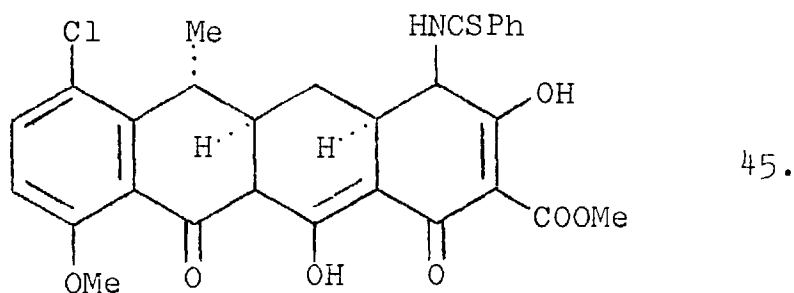
43.

this substance was treated with the glutaramate 43 in the presence of two equivalents of sodium hydride the epimers 44 were obtained. The halogen and the protecting

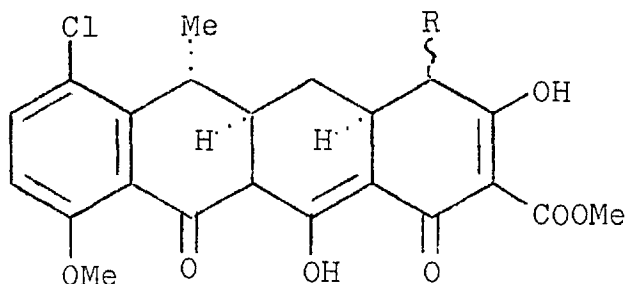


groups were removed and the amino-function at C-4 methylated. These operations completed, formally, the second total synthesis of 6-demethyl-6-deoxytetracycline.

A number of tetracycline-like molecules have been synthesised by Muxfeldt in which C-6 bears a methyl group. Preparation of compound 45 represents a

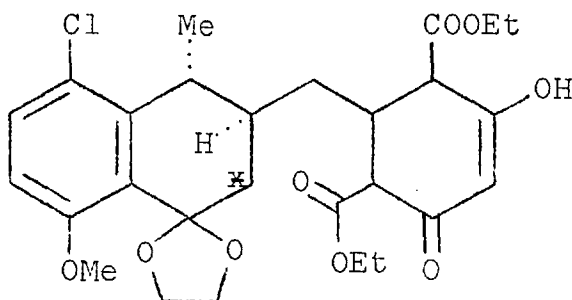


variation of the azlactone route¹² but the examples 46 and 47 illustrate a procedure not described so far.



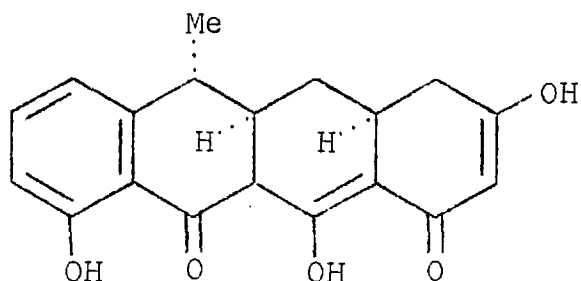
R
46. H
47. COOEt

Aldehyde 41 was converted^{5c,13} into the ACD-tricyclic compound 48 by condensation successively with diethylmalonate and acetoacetic ester. Hydrolysis of the ketal



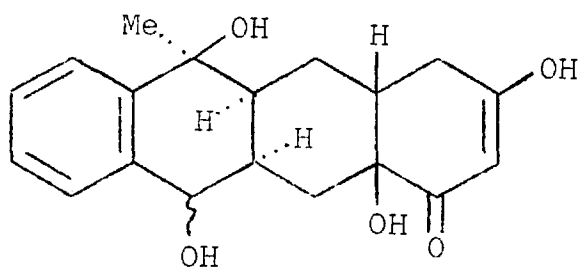
48.

generated an active methylene group (starred) and cyclisation with sodium hydride gave compounds 46 and 47. The route was easily modified to yield compound 49.



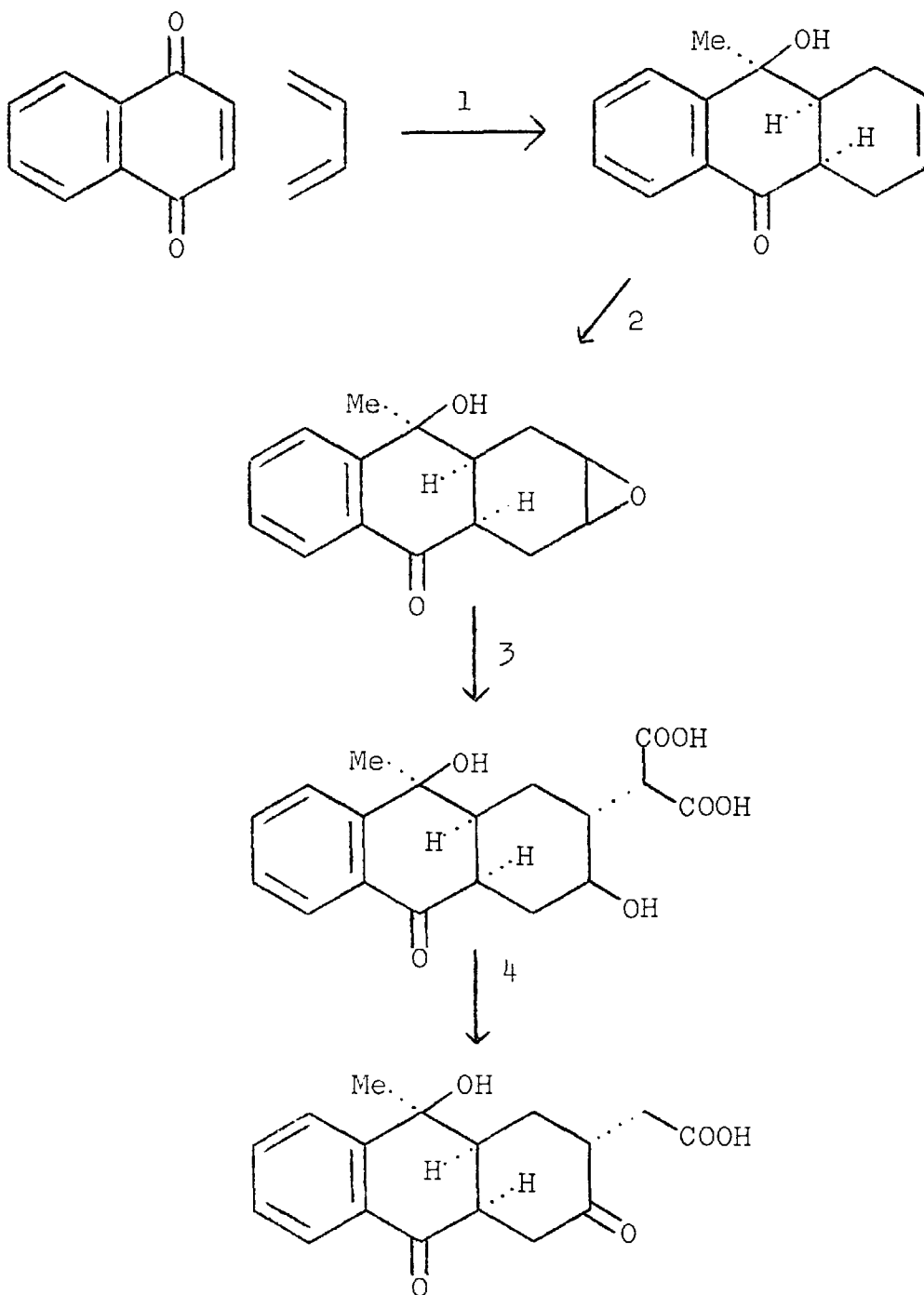
49.

The next, and last, stage of substitution at C-6 is represented by the model compound 50. This substance

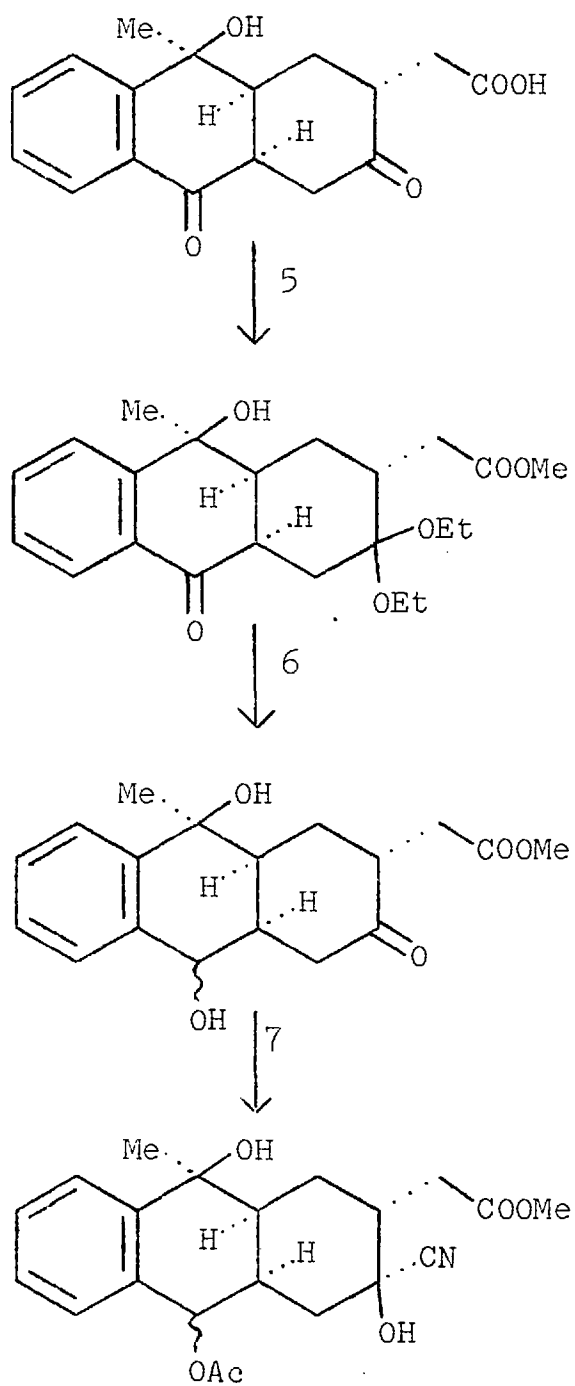


50.

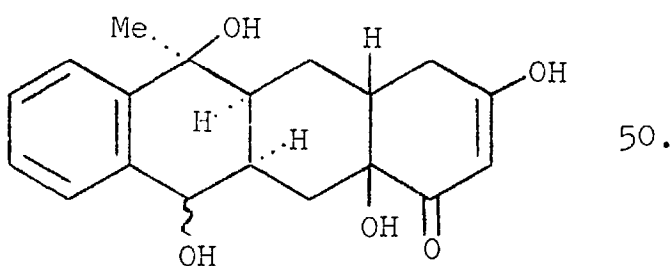
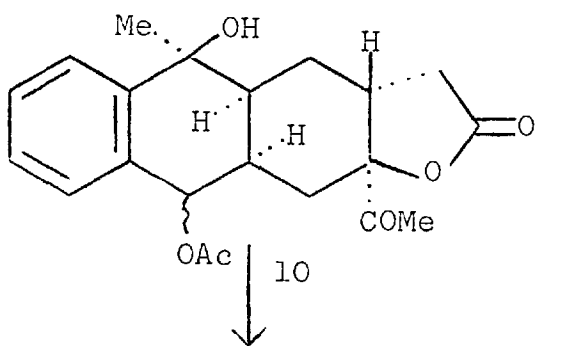
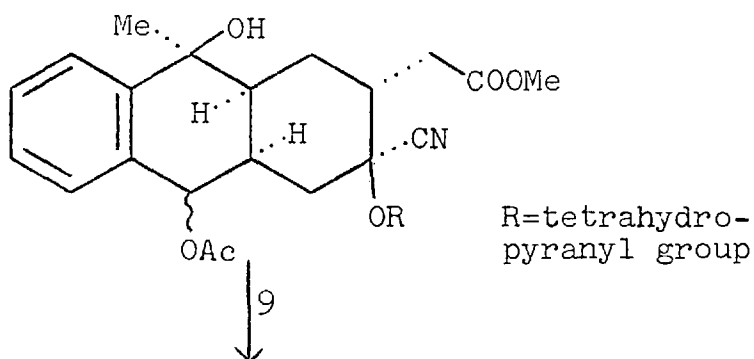
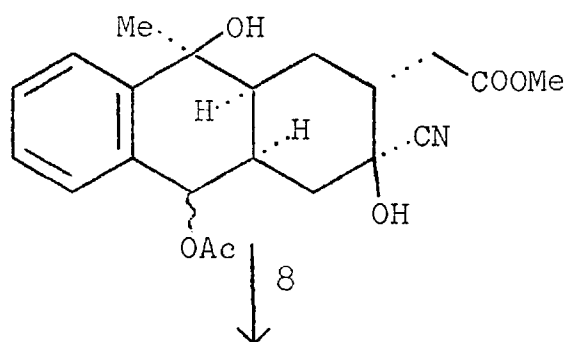
was prepared in Shemyakin's laboratory and the route is summarised in the chart.¹⁴ The stereochemistry shown for the end product (50) is that given in the original literature but it appears that definitive evidence for this assignment has not yet been published.



1. Heat, MeMgI ; 2. Bu^tOCl , KOH ; 3. $\text{NaCH}(\text{COOEt})_2$, KOH ;
 4. Heat, $\text{CrO}_3 + \text{AcOH}$.



5. CH_2N_2 , $\text{CH}(\text{OEt})_3$; 6. NaBH_4 , H_3O^+ ; 7. Ac_2O + pyridine, $\text{Me}_2\text{C}(\text{OH})\text{CN}$ + K_2CO_3 .



8. Dihydropyran + POCl_3 ; 9. MeMgI , H_3O^+ ; 10. EtOH + NaOEt .

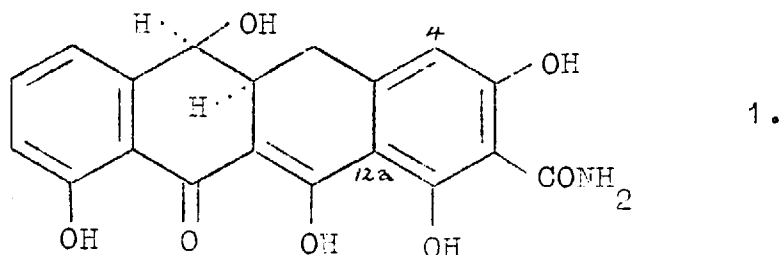
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Discussion.

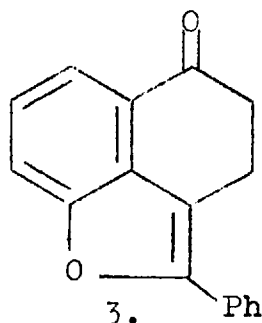
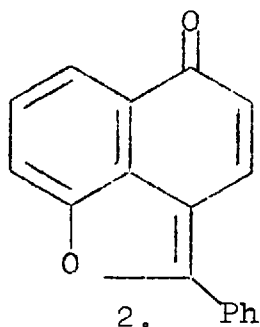
When the work described in this thesis was begun the tetracycline project had been under way for some time. The initial objective was total synthesis of 4a,12a-anhydro-4-dedimethylamino-6-demethyltetracycline 1. It was hoped to obtain this relay from 6-demethyltetracycline and to reconvert it into the



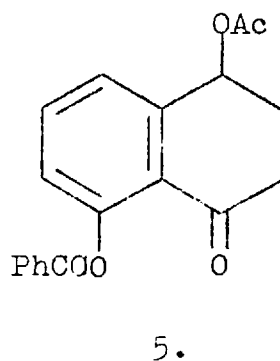
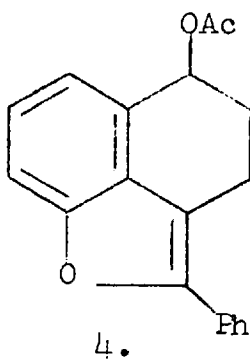
natural antibiotic in three stages: attachment of a dimethylamino-group at C-4, partial reduction of ring A, and hydroxylation at C-12a.

Many preliminary studies had been carried out and these have already been described.¹ Those that are relevant to the present work are discussed here.

The naphthofuran 2, obtained by condensation of benzoic acid with 1,5-dihydroxynaphthalene in the presence of zinc chloride, and destined to provide rings C and D of the antibiotic, was selected as the starting point for the synthesis. Hydrogenation

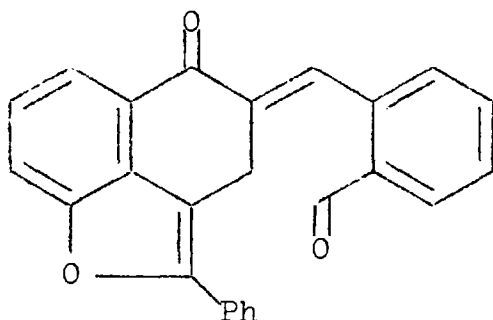


over Raney nickel afforded the dihydronaphthofuran 3 which was reduced with potassium borohydride and treated with acetic anhydride in pyridine. The product, a non-crystalline acetate 4 gave, on ozonolysis, an oily tetralone 5 which resembles the C and D rings of 6-demethyltetracycline.

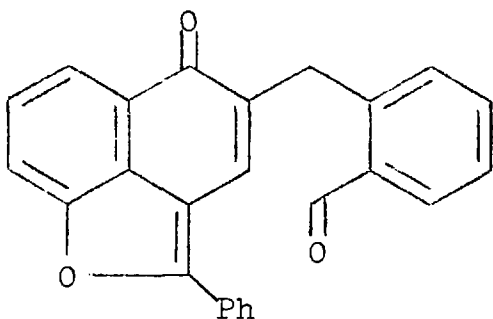


With a method for cleaving the furan ring established, work was begun on the construction of rings A and B. The dihydronaphthofuran 3 was condensed with o-phthalaldehyde in the presence of

triethylamine. Under these conditions the initial product 6 isomerised, so that the ACD-tricyclic compound 7 was obtained directly. The latter was

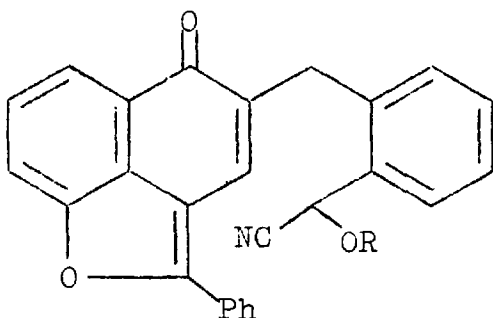


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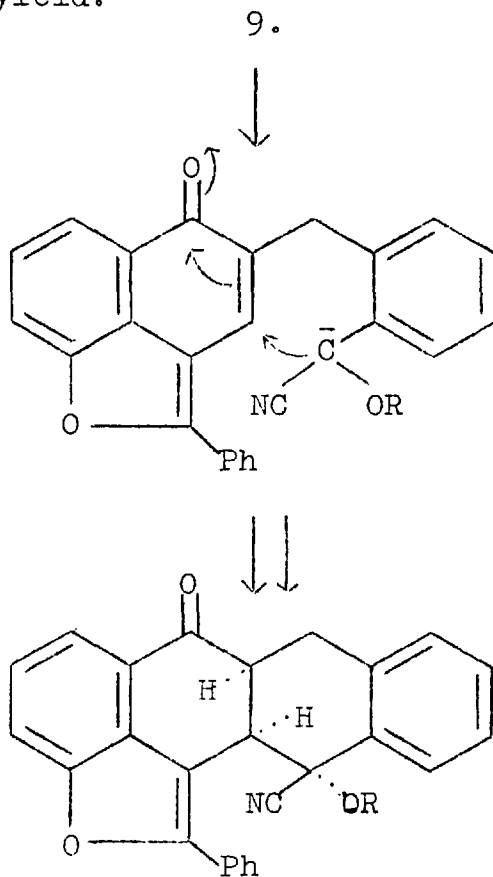
7.

converted to the cyanohydrin 8, and the hydroxyl group protected by treatment with dihydropyran in the presence of acid (8→9).

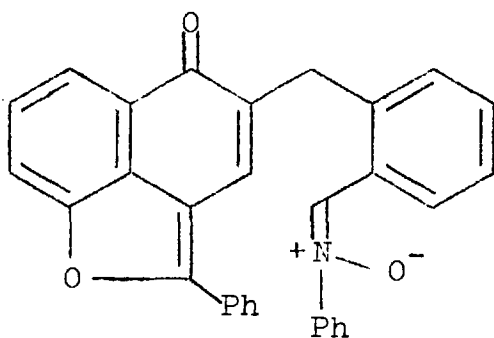


8. H
9. 2-tetrahy-
dropyranyl group

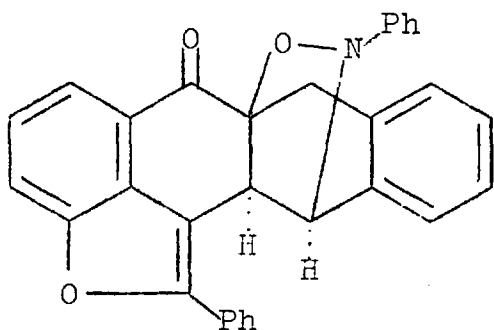
The action of potassium t-butoxide on the protected cyanohydrin 9 brought about ring closure, the ABCD-tetracyclic compound 10 being formed in good yield:



An alternative method for cyclisation was found in the action of phenylhydroxylamine on the model aldehyde 7. The intermediate nitron 11 cyclised spontaneously to form the isoxazolidine 12. This compound was studied further at a later date; in

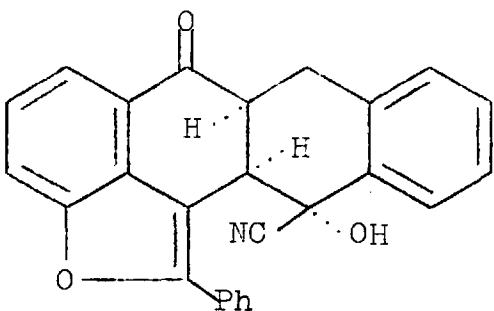


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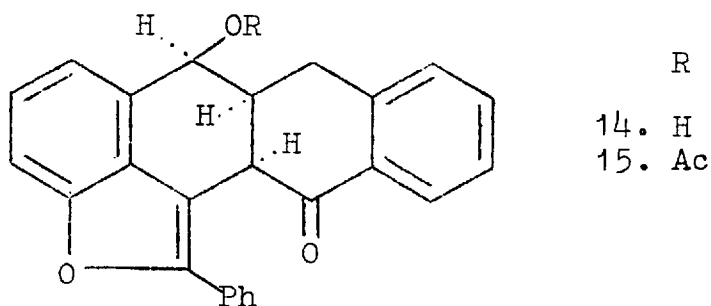
12.

the meantime, the acid-sensitive tetrahydropyranyl-ether 10 was hydrolysed to the cyanohydrin 13 and

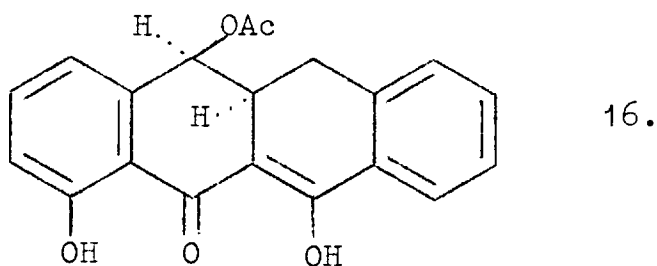


13.

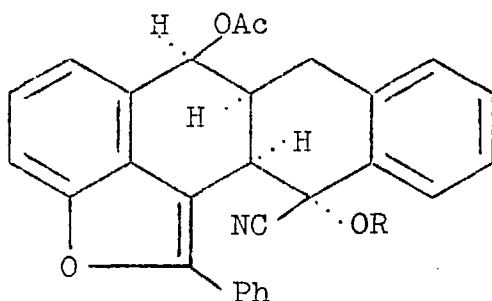
reduced by the Meerwein-Ponndorf method to the ketol 14.



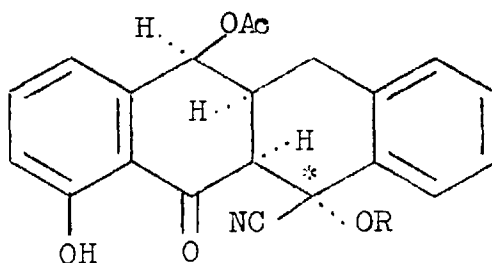
Ozonolysis of the derived acetate gave the required β -diketone (15 $\rightarrow$ 16). The yield, however was very low.



The same compound could also be obtained by changing the sequence of operations. The tetrahydropyranyl-ether 10 was treated with tri-*t*-butoxy-aluminium hydride and the product was acetylated. Ozonolysis then afforded a phenolic-ketone in good yield (17 $\rightarrow$ 18).



17. R=2-tetrahydro-
pyranyl group



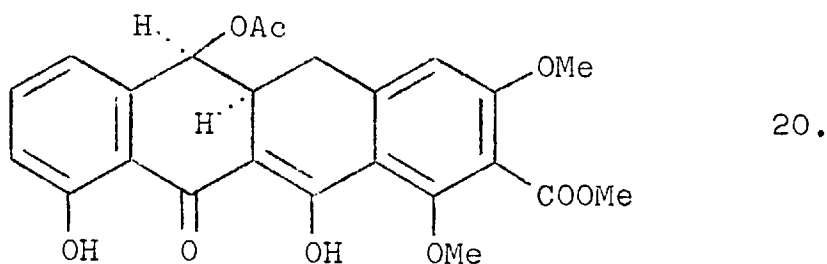
18. R=2-tetrahydro-
pyranyl group

19. R=H

Although hydrolysis to the cyanohydrin 19 was easily carried out, the next step — regeneration of the carbonyl group (see 19, starred) — could not be accomplished in a satisfactory manner.

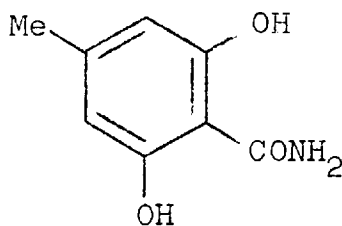
It was clear that a few of the stages in the scheme would require considerable improvement; nevertheless, the experiments had served as a useful test of the approach to tetracycline synthesis.

Work was then started on compounds with substituents attached to ring A. The details will be given later; here it is necessary only to note that, when our own investigation was begun, it seemed likely that the β -diketone 20 would soon become available.

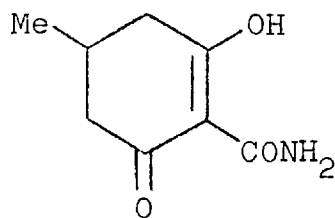


Ring A would then have to be modified, and we began our studies on this aspect of the synthesis.

During preliminary work the tetracycline group had investigated ¹ the possibility of catalytic reduction.² By this technique the amide 21 was easily converted to the cyclic β -diketone 22, but

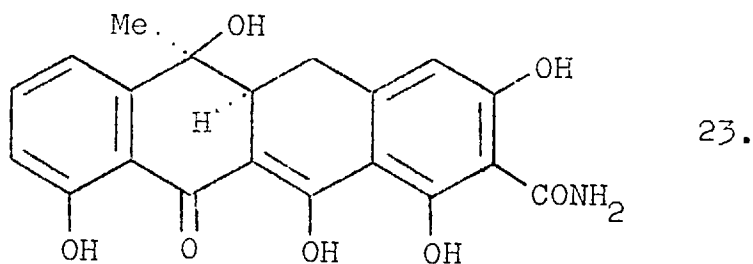


21.

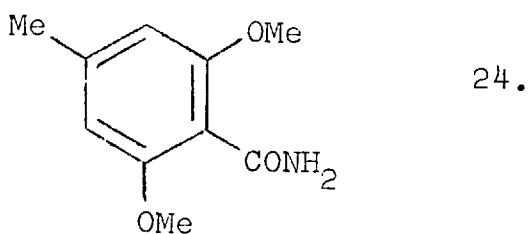


22.

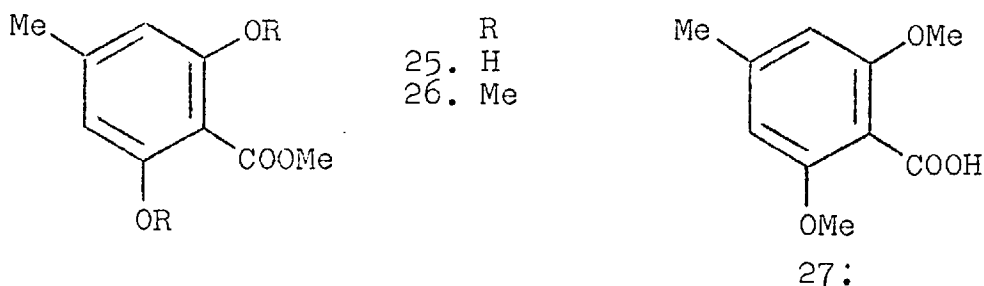
more advanced compounds, in particular 23, ³ could not be so hydrogenated. It was decided to investigate the technique of Birch reduction.



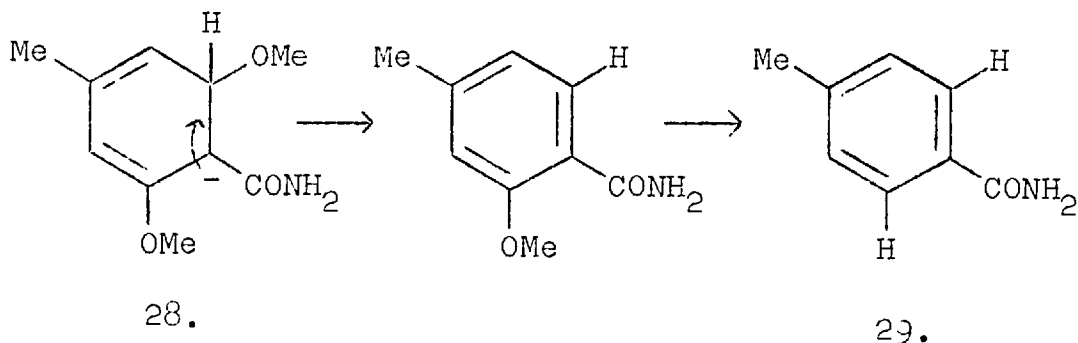
The sensitivity of esters to solutions of alkali metals in liquid ammonia is well known; ^{4a} therefore an amide (24) was selected as a model with which to work. The compound was made by a slight modification



of the published route:⁵ . Methyl p-orsellinate (25) was methylated with dimethyl sulphate in the presence of aqueous sodium hydroxide, and the resultant dimethoxy-ester 26 was saponified. The acid 27,



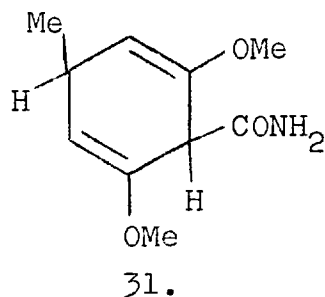
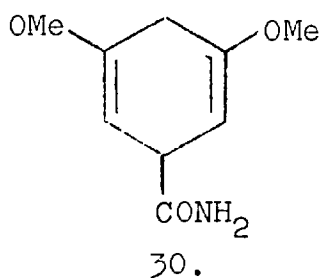
obtained in this way, was converted to the required amide (24) by the action, first of thionyl chloride, and then of ammonia. It was now possible to try the reduction and to determine whether the methoxyl groups would be lost ($28 \rightarrow 29$):^{4b}



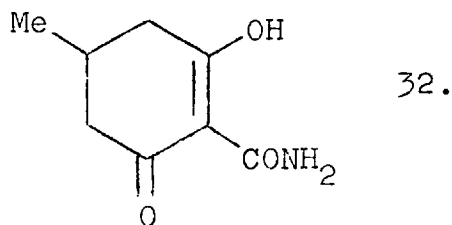
Use of the procedure described⁶ by Kuehne and Lambert for the preparation of compound 30, afforded the required dihydro-compound^{*} 31 from the model

*The relative configuration at the two asymmetric centres was not established.

amide. As expected, the C-methyl group (see 31) gave rise to a doublet in the n.m.r. spectrum and the presence of another doublet at 5.22τ with a

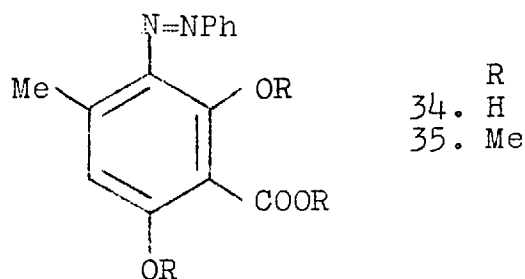
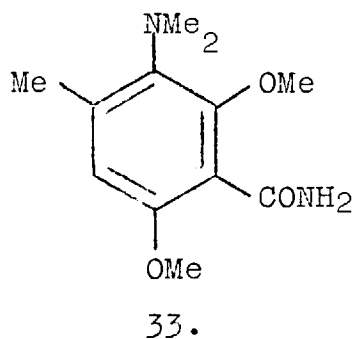


relative integrated-intensity of 2 hydrogen atoms proved that the double bonds were not conjugated. Treatment with mineral acid afforded the cyclic

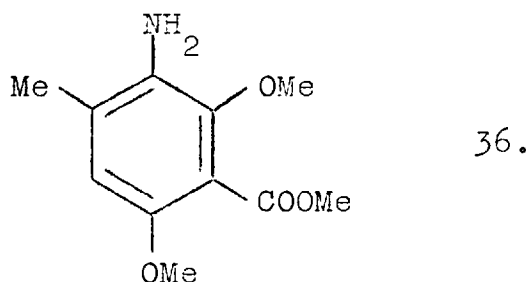


β -diketone 32 which was compared with an authentic sample made by catalytic reduction (pH 7.5-8) of p-orsellinamide. ¹, ²

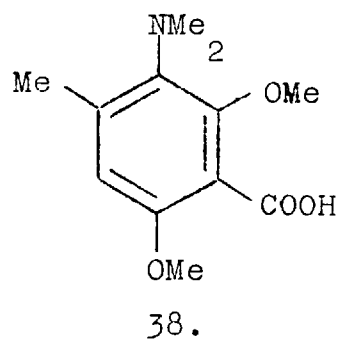
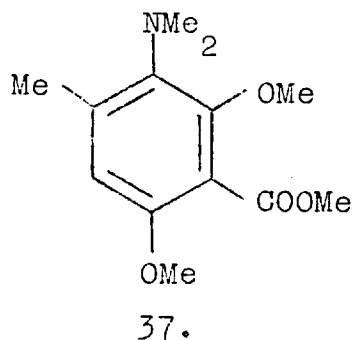
The next step was to investigate a more advanced model, and the amino-amide 33 was selected for this purpose.



This compound, which is not described in the literature, was made in the following way: the known⁷ azo-dye 34 was methylated completely ($34 \rightarrow 35$) by prolonged treatment with potassium carbonate and dimethyl sulphate in refluxing acetone. Hydrogenolysis then gave the amine 36 which was not purified but used directly in the next stage. This again involved treatment in refluxing acetone with potassium



carbonate and dimethyl sulphate, and afforded the dimethylamino-ester 37 in high yield. The structure



of this compound, as of the methylated dye 35, was indicated clearly by its simple n.m.r. spectrum although the origin of the individual O-methyl signals could not be specified. Hydrolysis to the amino-acid 38 was easily achieved, and the crude product was converted to its acid chloride and thence to the amide 33. A correct carbon analysis was not obtained for this amide, but its composition, $C_{12}H_{18}N_2O_3$, was established unequivocally by mass measurement of its molecular ion (which was also the base peak in the mass spectrum). The n.m.r. spectrum was compatible in every detail with the required structure. It was now possible to attempt the reduction step.

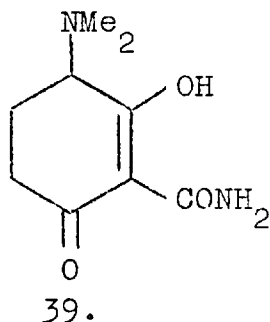
The amide was subjected first to the conditions that had been successful in the case of the simpler model. The method involved rapid addition of sodium (5 mole/mole amide) to a solution of the amide in liquid

ammonia containing ethanol (50 mole/mole amide). The partially crystalline product consisted mainly of starting material but contained a small amount of a ketonic component ($\nu_{\text{max.}}$ 1705 cm.^{-1}). The n.m.r. spectrum showed a weak doublet centred at 9τ .

When a larger proportion of sodium was used the starting material was destroyed and the infrared spectrum of the total product showed strong carbonyl-absorption at 1705 cm.^{-1} . A high-field doublet and a broad methylene envelope were present in the n.m.r. spectrum.

In an effort to avoid destruction of the carboxamide group the system ammonia — t-butanol — lithium⁸ was used but a similar result was obtained. (t-Butanol is a weaker acid than ethanol so that the opportunity for stabilisation of the carboxamide group as an anion is increased. Lithium ethoxide is less effective than sodium ethoxide in conjugating double bonds and thereby permitting further reduction.^{4c} It is possible that the same is true of other lithium alkoxides.)

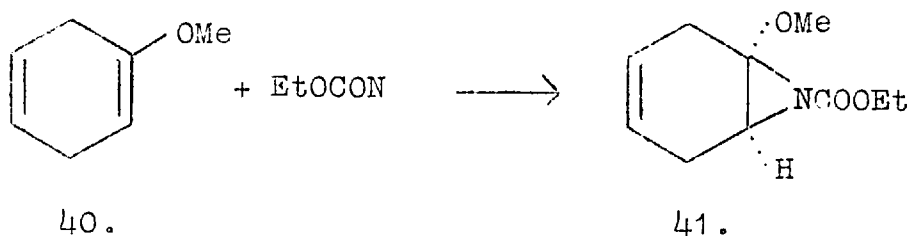
In each experiment the change in the ultraviolet spectrum brought about by acid treatment of the product was observed. In no case did a band develop at 261 $\text{m}\mu$, the absorption maximum reported⁹ for compound 39.



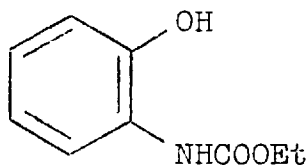
Clearly, the amino-group would have to be introduced after reduction, so that we were now faced with the problem of inserting nitrogen into the double bond of an enol ether:¹⁰



The initial experiments were based on 2,5-dihydroanisole (40). This compound was exposed to the action of ethoxycarbonylnitrene (generated photolytically¹¹) in the hope that the more nucleophilic double bond would be attacked preferentially (40 → 41) as occurs with dichlorocarbene.¹² However, complex



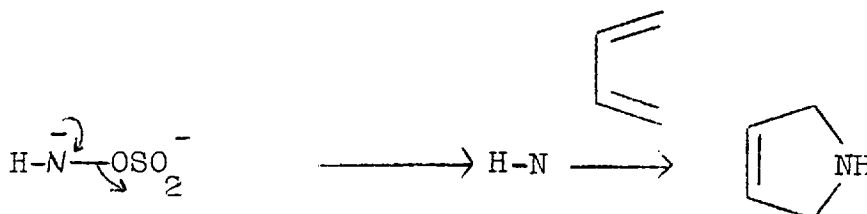
mixtures were obtained, both in the presence and absence of solvent (cyclohexane). In the latter case ten major products were detected by g.l.c., but treatment of a portion of the total product with *o*-chloranil in boiling xylene afforded a small quantity of oily crystals ($\nu_{\text{max.}}$ 3510; 3420, 1720 cm^{-1}) that may be the phenol 42.¹³ Because of the multiplicity of products the reaction was of no synthetic value and was not investigated further.



42.

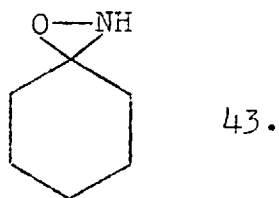
An alternative method for generating nitrenes was examined next. It is reported¹⁴ that butadiene affords 2,5-dihydropyrrole when treated with hydroxylamine-O-

sulphonic acid and sodium methoxide. The process was interpreted as shown but the mechanism was not proved:

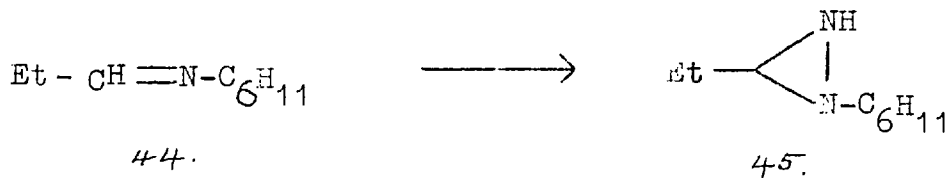


Although the reagent reacts with butadiene it did not attack 2,5-dihydroanisole appreciably: very little acid-soluble material was formed.

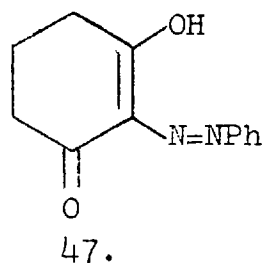
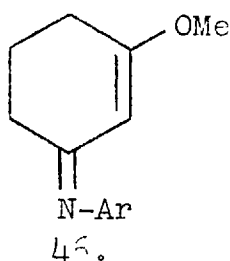
We next attempted to transfer nitrogen from the oxaziridine 43¹⁵ to the enol ether but the result was equally disappointing. Certain oxaziridines are known¹⁵



to aminate Schiff bases (e.g., 44 $\rightarrow$ 45) but compound 43 failed to react with the enol ether.



On examining the action between the enol ether and picryl azide,¹⁶ however, a crystalline compound was isolated. The reaction could be carried out in the absence of solvent at room temperature, or in boiling chloroform. In the second method the (participating) stabilizer had to be removed. The n.m.r. spectrum of the product suggested structure 46 and this assignment

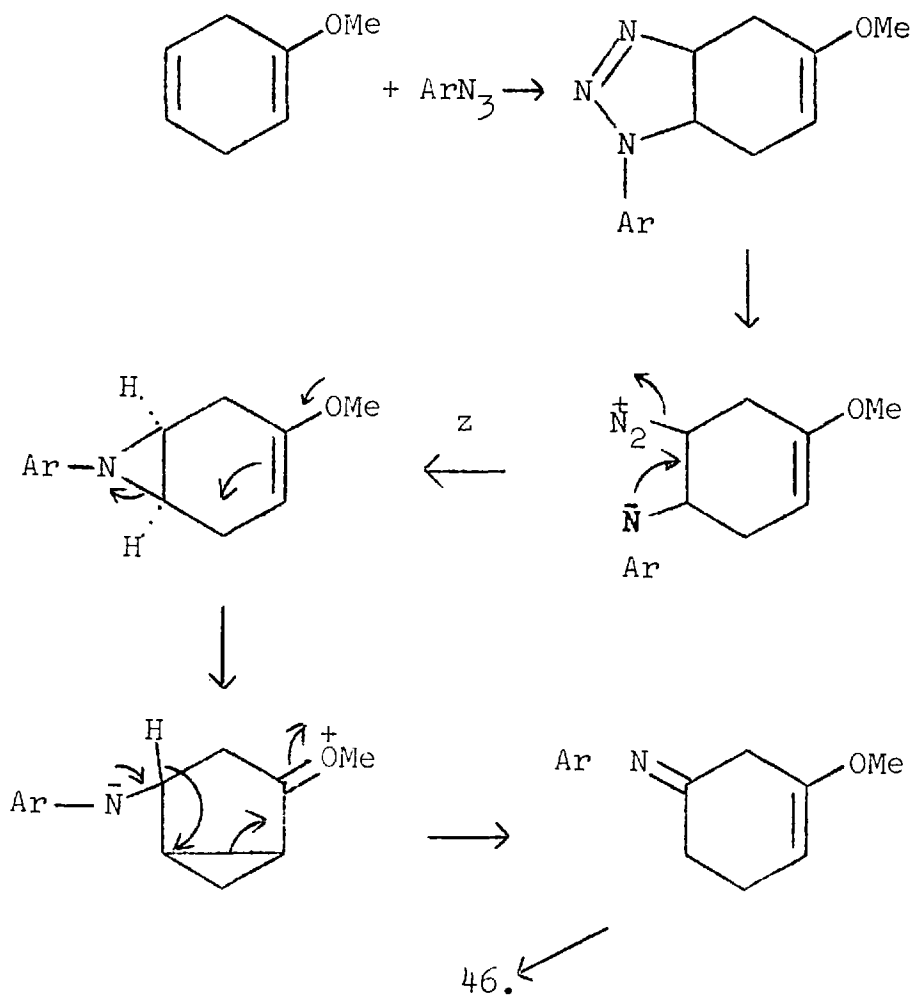


Ar=2,4,6-trinitrophenyl group

was confirmed by chemical experiments. Acid-catalysed hydrolysis gave picramide and dihydroresorcinol. The former was compared directly with an authentic sample but the latter was first coupled with benzenediazonium chloride to afford the known¹⁷ dye 47. It is possible

that the Schiff base was formed in the following way and

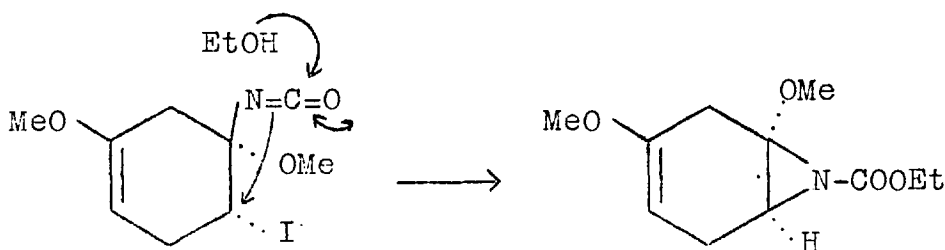
Ar=2,4,6-trinitrophenyl group



this view indicated the advisability of using a more symmetrical enol ether.

When a solution of 2,5-dihydroresorcinol dimethyl ether and N-iododimethylamine ($\lambda_{\text{max.}}$ 368 m μ) in tetrahydrofuran was irradiated with a tungsten lamp heterolysis of the nitrogen — iodine bond did not take place and no reaction occurred. The halo-amine did not attack cyclohexene under these conditions, or when a high-pressure mercury lamp was employed.

It was hoped that 2,5-dihydroresorcinol dimethyl ether, on treatment with iodine isocyanate and then with ethanol, would give an aziridine:¹⁸



However, no pure compound could be isolated when the reaction was tried.

The utility of nitrenium ions was examined next.¹⁹ Olefinic substrates were treated with a halo-amine and silver oxide or silver trifluoroacetate. The results are summarised in the table.

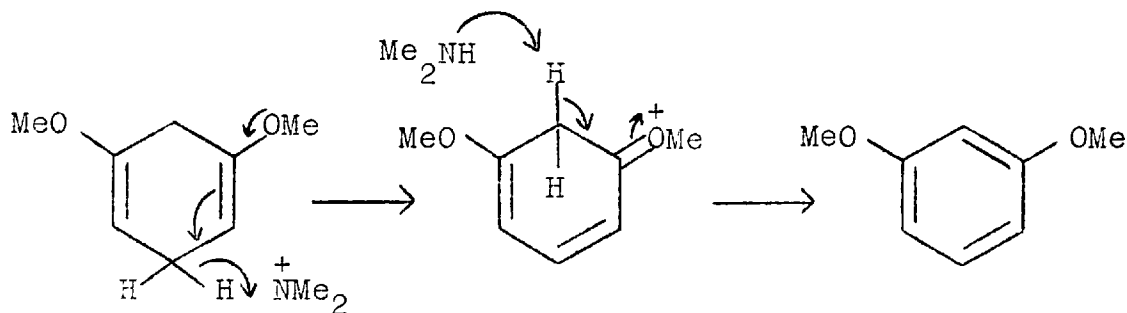
Substrate	Halo-amine	Silver compound	Solvent	Products
AH ₂	Me ₂ NI	Ag ₂ O	Et ₂ O	AH ₂ +aromatic material
AH ₂	Me ₂ ^N Cl	Ag ₂ O	Et ₂ O	AH ₂
AH ₂	Me ₂ NCI	AgOCOCF ₃	Et ₂ O	AH ₂ +A
AH ₂	Me ₂ NCI	AgOCOCF ₃	aq. thf.	aromatic material
AH ₂	Me ₂ NI	AgOCOCF ₃	thf.	aromatic material
Cyclohexene	Me ₂ NCI	AgOCOCF ₃	Et ₂ O	no cyclohexyl amine

thf. = tetrahydrofuran

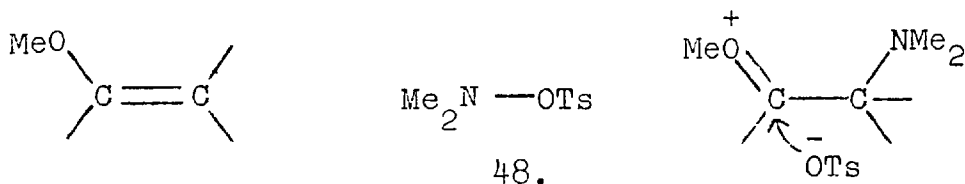
A = resorcinol dimethyl ether

AH₂ = dihydroresorcinol dimethyl ether.

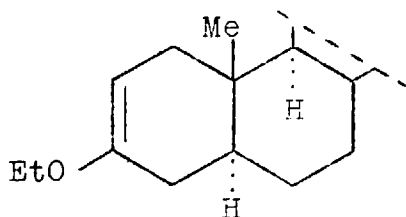
N-Chlorodimethylamine did not react with silver trifluoroacetate in the absence of the enol ether. It is possible that the latter formed a reactive complex with silver ions²⁰ but the following mechanism also accounts for the aromatisation process.



By analogy to epoxidation of double bonds with peracids it was considered that enol ethers would be attacked by the tosylate 48:



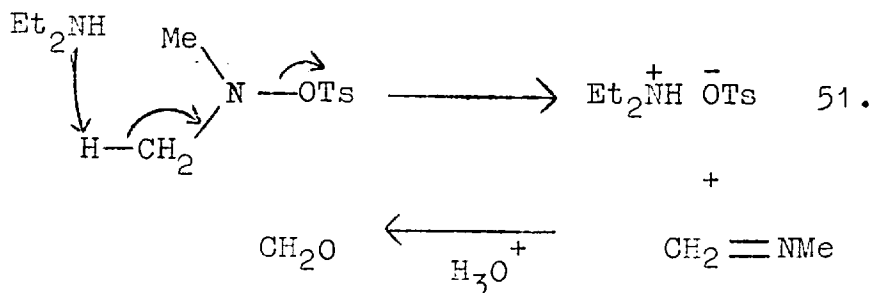
This substituted hydroxylamine was of a type that had never been prepared,²¹ and although a method for making it was discovered, the compound turned out to be of little value. When it was allowed to act on 2,5-dihydroresorcinol dimethyl ether, or on 3-ethoxy-5 α -cholest-2-ene (49) under a variety of conditions, no useful result was obtained.



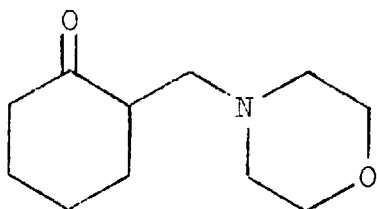
The corresponding mesylate 50 was also prepared though its structure was not rigorously established because the

substance was very unstable. Like the tosylate, it did not insert nitrogen into the steroidal enol-ether.

The chemistry of the tosylate was studied further. With diethylamine, it gave the amine salt 51 and, after acidification of the reaction mixture, formaldehyde was obtained. These changes are understandable in terms of an E2 mechanism.



When diethylamine was replaced by the morpholine enamine of cyclohexanone the ketone 52 was formed; a Mannich reaction had taken place between cyclohexanone, formaldehyde, and morpholine.

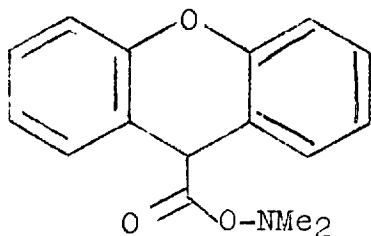


52.

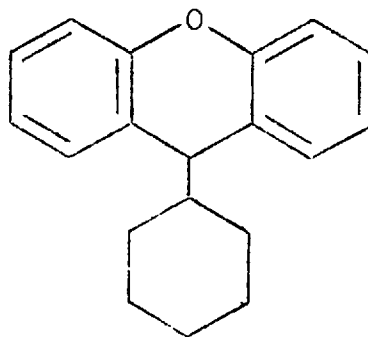
During treatment of the tosylate with phenylmagnesium bromide, elimination of *p*-toluenesulphonic acid was not observed. Instead, *N,N*-dimethylaniline was isolated in nearly 60% yield. A similar result was obtained with cyclohexylmagnesium bromide. The yield was lower in this case but the result was still superior to that normally obtained in the comparable reaction between Grignard reagents and the *N*-chloro-derivatives of secondary amines.²²

When sodium 2,6-di-*t*-butylphenol was treated with the tosylate, the phenol was largely recovered.

We next prepared the ester 53 from xanthen-9-carboxylic acid chloride and *N,N*-dimethyl hydroxylamine.



53.



54.

On irradiation in cyclohexane with a high-pressure mercury lamp, carbon dioxide and the hydrocarbon 54 were formed. Presumably, dimethylamino-radicals were also produced but these were not detected. Repetition of

the photolysis in carbon tetrachloride in the presence of the steroidal enol-ether 49 gave a ketone, believed to be 5 α -cholest-1-ene-3-one.²³

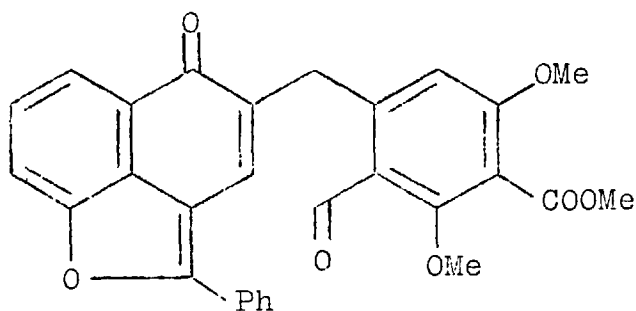
Photolysis in the melt (80-90°) afforded a substance whose constitution was, surprisingly, that of a dimethylamino-xanthone.

Finally, we returned to ethoxycarbonylnitrene and generated this as before, but in the presence of the steroidal enol-ether. A small amount of an essentially-pure oil was isolated from the reaction mixture. The mass spectrum contained a peak corresponding to loss of C₂H₅O from the molecular ion (m/e 516) and the infrared spectrum showed absorption maxima at 3380, 2940, 1720, 1677 cm⁻¹. On this evidence the substance must be a urethan but no further work on its structure was carried out.

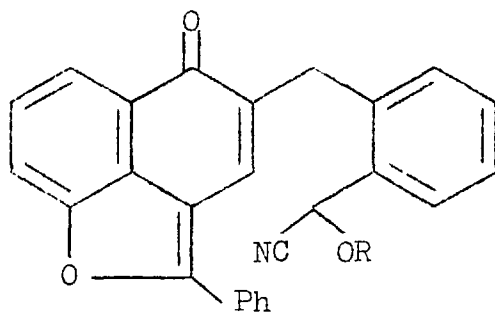
By this stage many attempts had been made to insert nitrogen into the double bond of an enol ether. None of the experiments had given a result of any use in the main synthesis; moreover, the facile aromatisation of dihydroresorcinol dimethyl ether demonstrated the inadvisability of using Birch reduction in our synthetic scheme. It was decided to abandon the enol-ether project.

Lack of success was not the only motivation behind this step, for any work on ring-A models anticipates the availability of properly substituted tetracyclic compounds: these had not yet been made. In fact, the tetracycline group now faced a serious obstacle because ACD-tricyclic compounds, substituted in ring A, could not be cyclised in a satisfactory manner.¹

The aldehyde 55 had been prepared and converted into the protected cyanohydrin 56. Unfortunately, the next stage, which worked so well in the model series (ring A unsubstituted), could not now be accomplished.

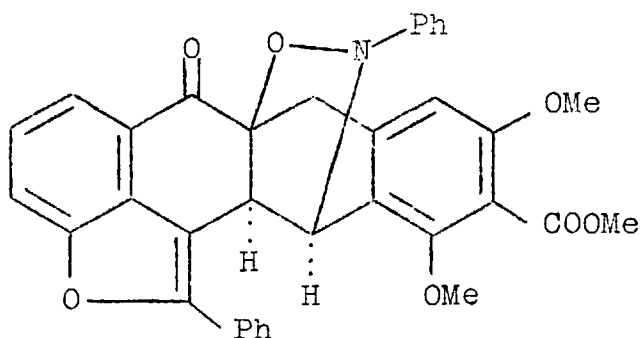


55.



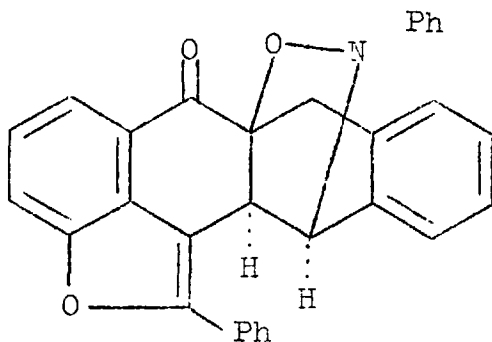
56. R=2-tetrahydropyranyl group

Treatment of the aldehyde 55 with phenylhydroxylamine, however, did afford a substance with the required carbon skeleton. This compound, the isoxazolidine 57, was



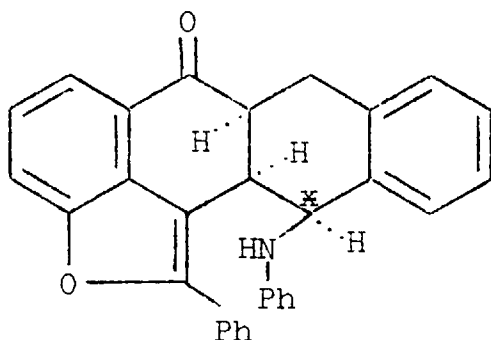
57.

obtained in almost the same high yield as was achieved in the model series. Unfortunately, it possesses a number of undesirable features which were exemplified by the model 12. It was experimentally



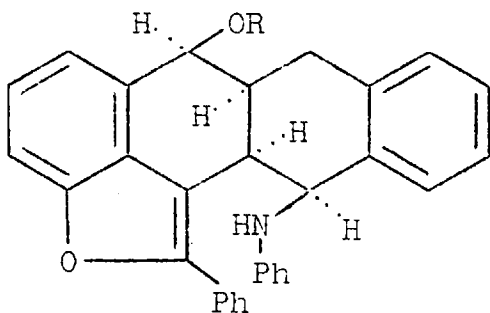
12.

difficult to reduce the latter to the amino-ketone 58, and once this transformation had been achieved, and the



58.

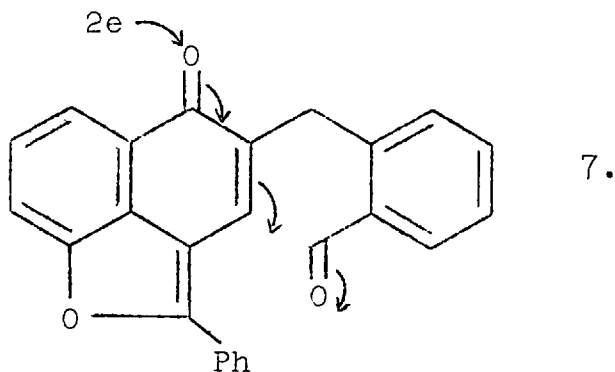
substance converted to the alcohol 59 or the acetate 60, it was impossible to oxidise the eventual C-12 position (see 58, starred) to a carbonyl group.



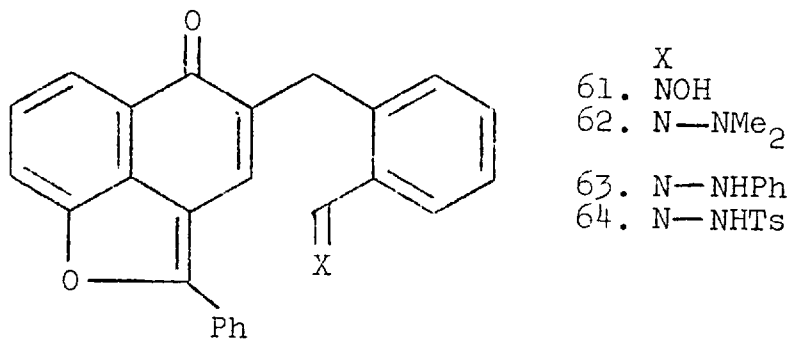
R
59. H
60. Ac

Oxidation could have been left till after ozonolysis, but the amino-function probably would not have survived contact with ozone and it seemed inadvisable to introduce complications late in the synthesis.

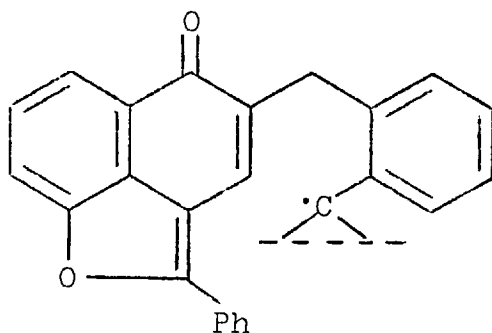
Several other methods for cyclisation had also been investigated. The aldehyde 7 failed to react in



the required way (see arrows) when treated with lithium in liquid ammonia, nor could its derivatives 61, 62, 63 or 64 be cyclised under a variety of conditions.

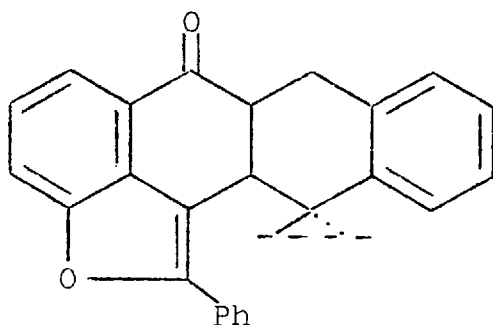


Reflection on further ways of achieving the crucial ring-closure suggested that one technique — the generation of a carbon radical of the type shown (65) — warranted investigation. Conceivably, this species



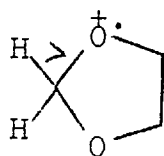
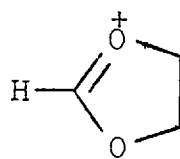
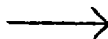
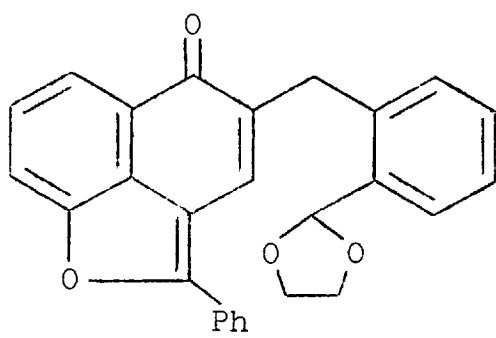
65.

could participate in a chain reaction to give the ABCD-tetracyclic substance 66.

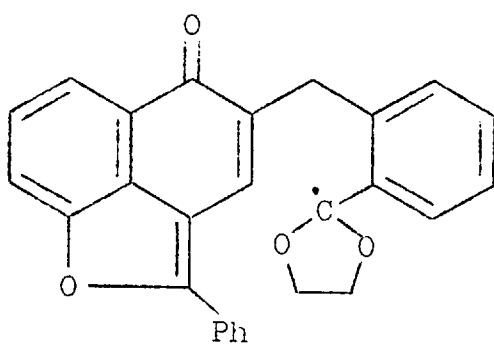


66.

Many acetals give rise to intense (M-1) peaks in their mass spectra (e.g., $67 \rightarrow 68$)²⁴ and it was hoped that loss of hydrogen, brought about by electron bombardment, could also be effected under less drastic conditions. Perhaps the acetal 69, when photolytically energised, would afford radical 70. This idea led to a satisfactory procedure for cyclisation.

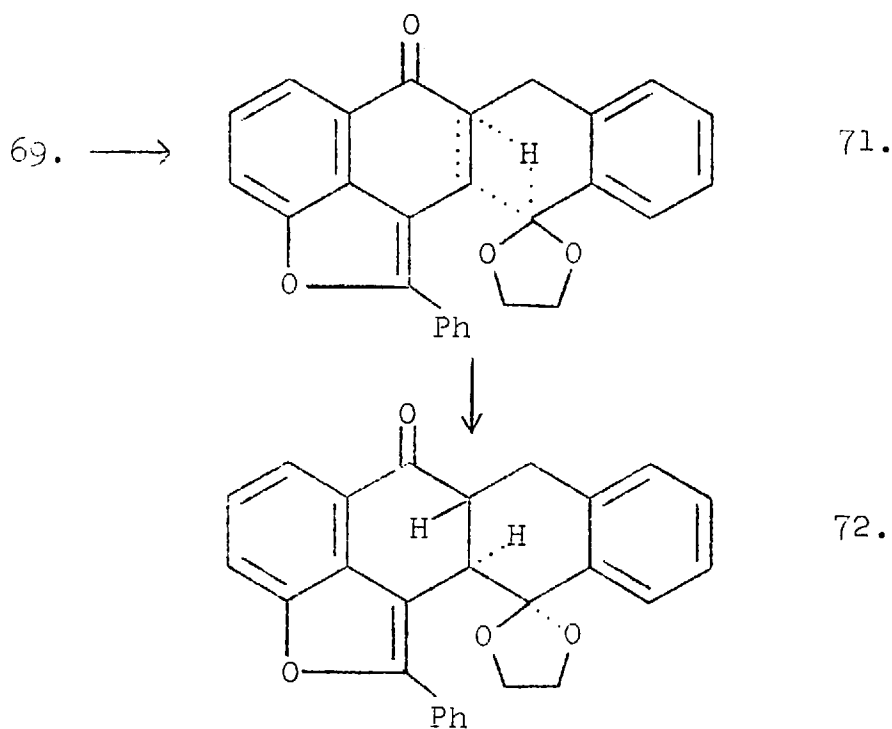
67.
(M)68.
(M-1)

69.

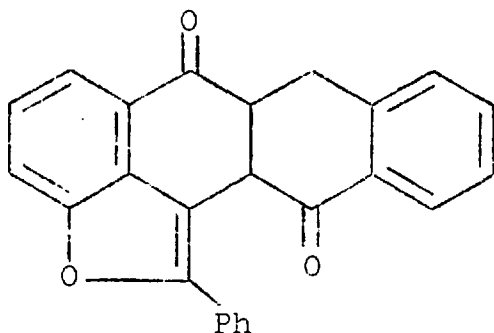


70.

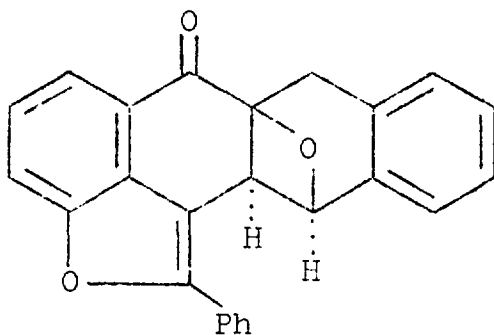
The possibility was appreciated though, that radical 70 might collapse to an ester. A brief examination of of the literature revealed that conversion of acetals to esters is a well-known process,²⁵ but the encouraging observation was made that photolysis of the acetal 69 is a special case in which a free radical need not be produced: cyclisation could take place through a four-centre transition state, the process being initiated by photo-excitation of the naphthofuran (71→72):



It was also considered that use of a derivative of the aldehyde might be unnecessary, for the parent substance itself could afford a valuable compound on photolysis (73 or 74)^{26,27}.



73.



74.

During these speculations we had refluxed a benzene solution of the aldehyde 7 with ethylene glycol and a trace of *p*-toluenesulphonic acid. Continuous removal of water from the mixture afforded the required acetal 69 in high yield. The substance had actually been made

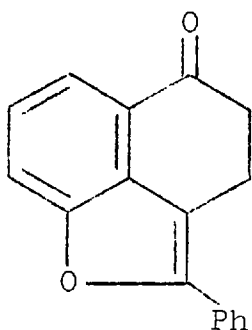
previously but in a different, and less satisfactory, manner.¹ Interestingly, the mass spectrum showed an (M-1) peak with an intensity as high as 14% of the molecular-ion peak.

It was now possible to try the photolysis. In the first experiment a solution of the acetal in anhydrous benzene was irradiated under nitrogen, and in pyrex apparatus, with a high-pressure mercury lamp. Within a short time it became clear that less energetic radiation would have to be used, for a very complex mixture of products was formed.

The ultraviolet spectrum of the acetal shows an absorption maximum at 400 m μ and previous work¹ indicated that the desired product (72) would have $\lambda_{\text{max.}}$ ca. 360 m μ . This information suggested that a tungsten lamp would be more suitable.

Fortunately, the total remaining supply of acetal was first submitted for n.m.r. examination and the sample recovered by evaporation of the solvent chloroform. Traces of chloroform left in the oily compound were responsible for the success of the next photolysis (see later). The experiment was carried out in the same way as before except that a tungsten lamp was used. The acetal slowly disappeared and a new

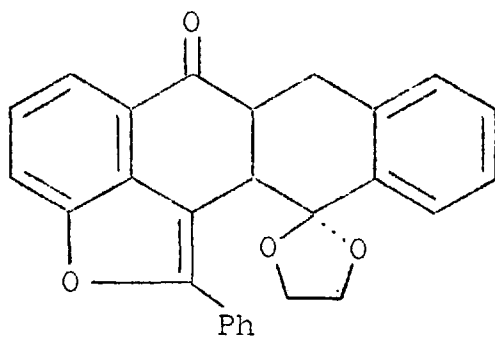
substance was formed. The progress of the reaction was followed by thin-layer chromatography: the starting material is bright yellow, the product fluoresces in ultraviolet light, and both substances are readily detected with hot sulphuric acid. The product was isolated by evaporation of the solvent and chromatography over alumina. The substance was crystalline and its spectral properties $\bar{\nu}_{\text{max.}}$ 1691 cm.^{-1} , $\lambda_{\text{max.}}$ 276, 294, 306, 351 $\text{m}\mu$ were those characteristic of the naphthofuran 3. The mass



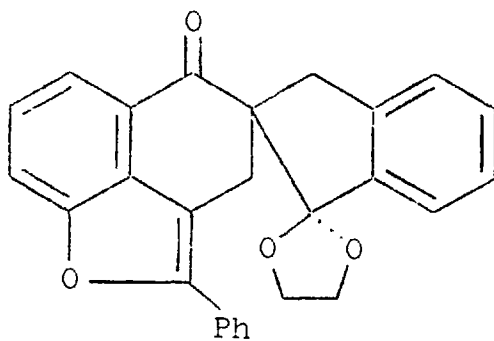
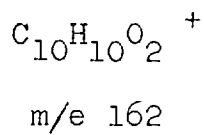
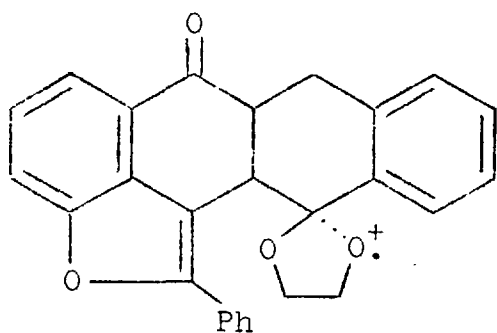
3.

spectrum showed a molecular ion peak with m/e 408. Significantly, the base peak had m/e 162. All the spectral evidence was compatible with the gross structure 75, but the alternative, the spiro-formulation 76, could not be excluded. A reference compound in the form of the diketone 77 was available, and the correctness of structure 75 was established by hydrolysing the photo-

product. Mineral acid at room temperature was quite ineffective for this purpose, but treatment with

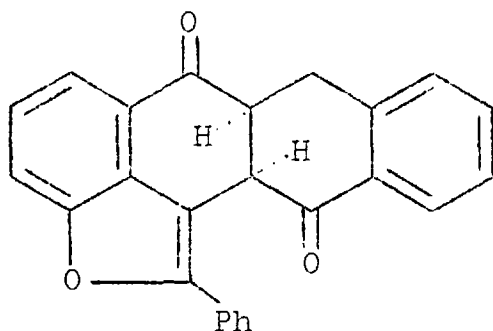


75.



76.

with *p*-toluenesulphonic acid in aqueous acetone at 100° (sealed tube) for 12 hr. proved suitable. The crystalline product was identical to an authentic sample¹ of the diketone 77.



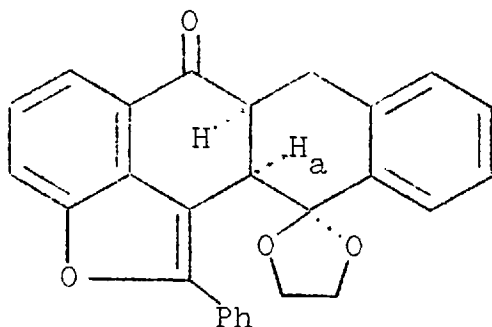
77.

When the photolysis was repeated using the pure acetal, the yield of ketal was variable and low. However, addition of a trace of dibenzoyl peroxide at the beginning of the photolysis and thereafter at 24-hr. intervals resulted in a dramatic improvement. The new procedure was used routinely and it afforded the ketal in yields of 62-71%.^{*}

When sufficient material was available the n.m.r. spectrum was measured. The trace is very complicated but a doublet ($J = 5.5$ c/sec.) at 5.67τ could be

* The ketal was found to be resistant to the photolysis conditions.

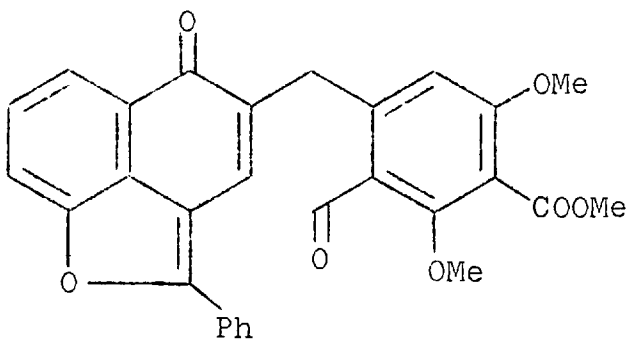
assigned to H_a (see 78) if rings B and C were cis-fused. This interpretation is consistent with extensive n.m.r. data accumulated by the tetracycline group. Definitive evidence will be given later for the stereochemistry



78.

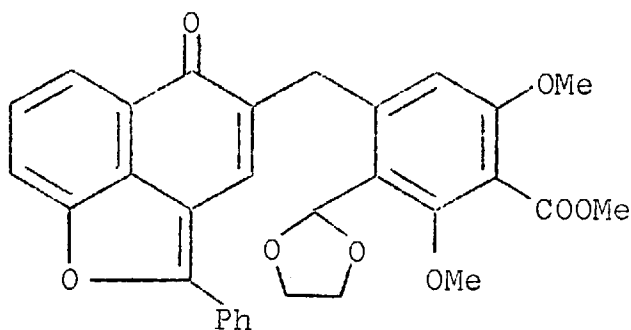
shown but it should be noted here that the ketal was always purified by chromatography; therefore, it is possible that the photo-product is the trans-fused compound 72 and that epimerisation occurs on contact with alumina.

It was now important to determine whether the photolysis would be successful when ring A was substituted.



55.

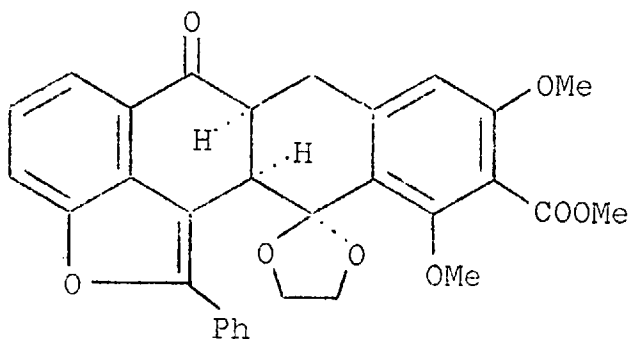
An impure specimen of the aldehyde 55 was available and the substance was converted into the acetal 79. No attempt was made to characterise the crude



79.

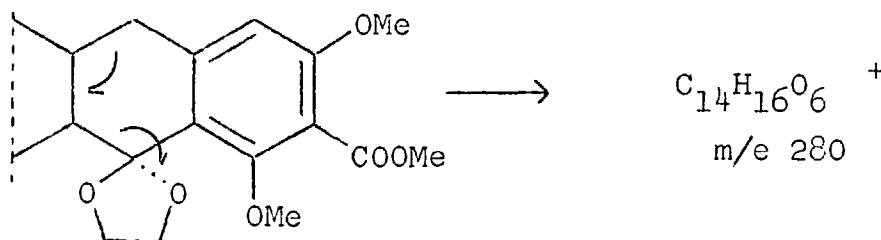
acetal beyond measurement of its infrared spectrum; little had been made for the parent aldehyde was a very precious compound at this time.

When the acetal 79 was photolysed in the normal way a very slow reaction occurred but the photo-product had all the spectral attributes anticipated for compound 80. Infrared absorption at 1695 cm.^{-1}



80.

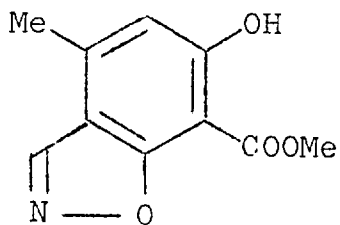
indicated that the unsaturated carbonyl system of the starting material had been reduced and this conclusion was supported by the ultraviolet spectrum which was extremely similar to that of the model ketal 78. The mass spectrum defined the molecular weight, and fragmentation of the molecule was dominated, in this case also, by the ketal group for the base peak occurred at m/e 280:



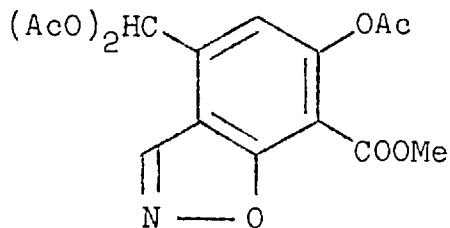
The implications of formula 80 go beyond those permitted by the spectral evidence given here, but the formula is almost certainly correct for several analogous compounds have now been obtained in this laboratory: in all cases ring B is six-membered and is cis-fused to ring C (see Ref. 1 and the following discussion).

By the time the ring-A substituted photo-product was obtained it had become clear that the route to the

starting material, the aldehyde 55, was unsatisfactory. For reasons that have been explained elsewhere¹ a very long and devious method had been used. The procedure started with methyl *p*-orsellinate and involved formylation, production of an oxime, dehydration to the isoxazole 81, acetylation of the remaining hydroxyl group, and oxidation by the method of Thiele and Winter²⁸ to the formyldiacetate 82. The latter was condensed in an acidic medium with

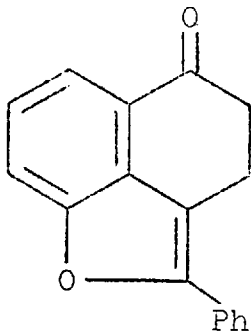


81.



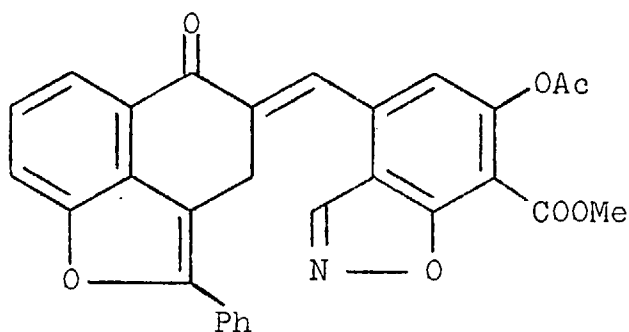
82.

the naphthofuran 3 to obtain the ACD-tricyclic



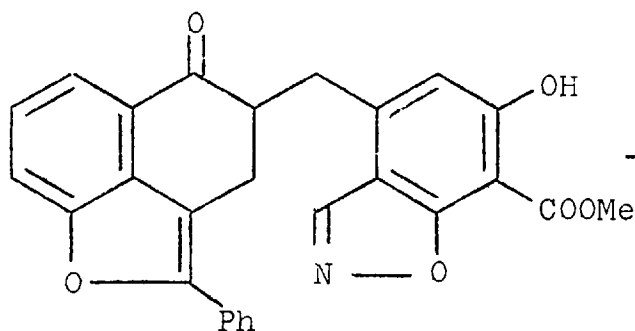
3.

compound 83 in which the double bond could not be isomerised.

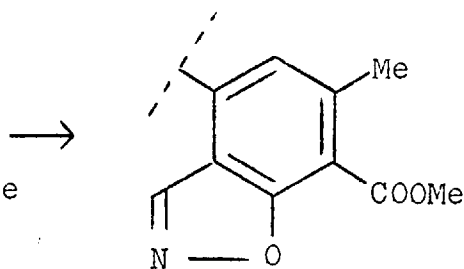


83.

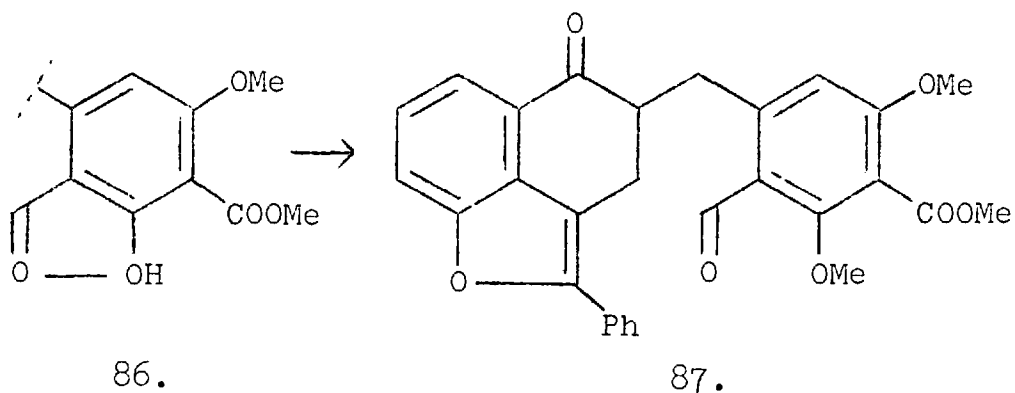
Reduction of the double bond with hydrogen iodide was accompanied by deacetylation, and the product 84 was methylated with methyl iodide — silver oxide, reduced catalytically, and methylated again (84→85→86→87). Dehydrogenation with 2,3-dicyano-5,6-dichloro-1,4-benzoquinone completed the synthesis (87→55).



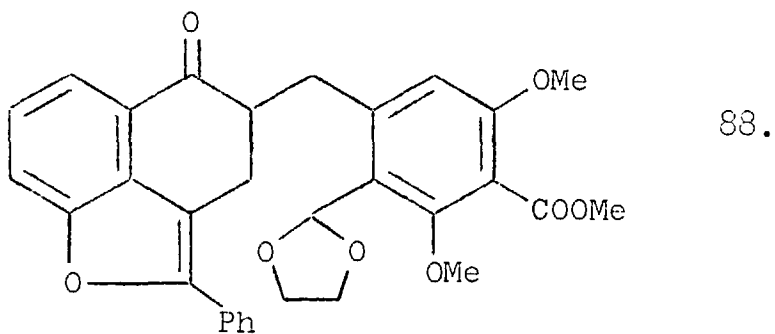
84.



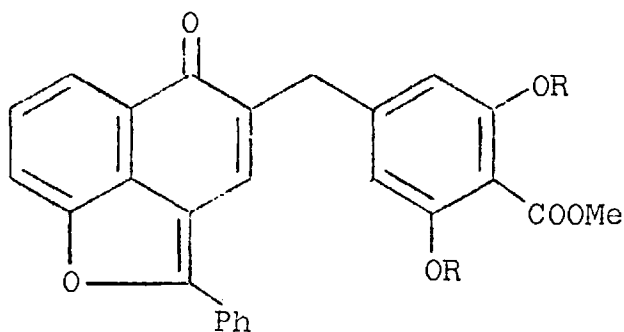
85.



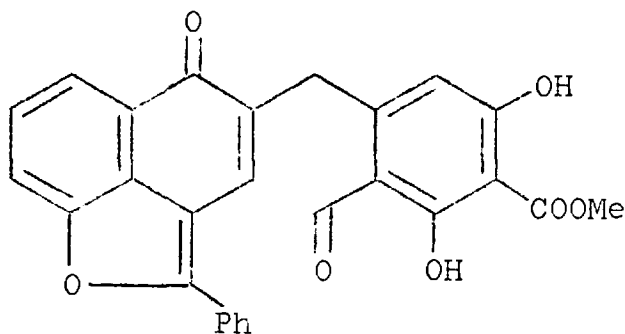
The mass spectrum of the ring-A substituted photo-product 80 showed an (M+2) peak slightly more intense than the (M+1) peak. On the basis of the reactions just described it is very likely that the material was contaminated by a small amount of the acetal 88.



We realised that the isoxazole route could be simplified considerably. It seemed that the diphenol ^(R=H) 89_A should be easy to make and that it would be possible to formylate ring A $\angle 89(R=H) \rightarrow 90$. This transformation was achieved by the tetracycline group, but



89.

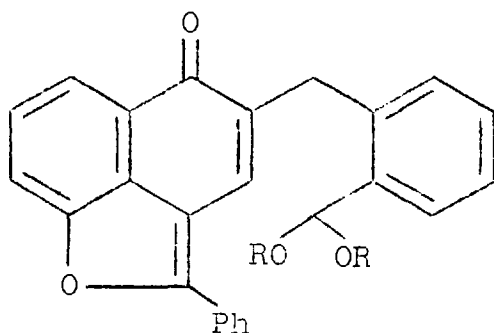


90.

very recently an even better route to the aldehyde 55 was found involving direct formylation of the dimethyl-ether 89 (R=Me).

During the work on ACD-tricyclic compounds we had continued photolysis studies in the model series. A criticism of the new cyclisation method was the very low rate of reaction: in order to process 500 mg. of model acetal an irradiation period of about one week was necessary. An examination of other aldehyde derivatives was undertaken partly for this reason, and partly to define the scope of the reaction.

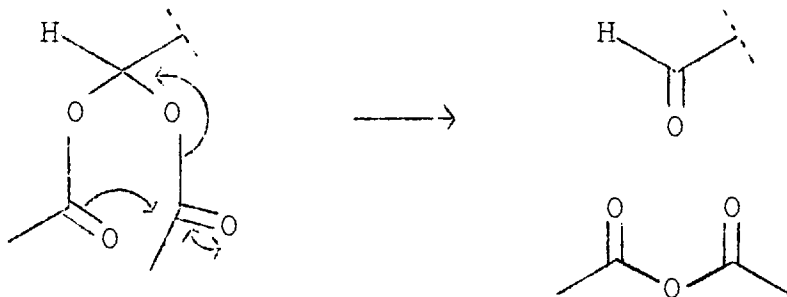
The formyldiacetate 91 was obtained by treating the



91. R=Ac

model aldehyde 7 with acetic anhydride and boron trifluoride etherate. In this, and other aldehyde derivatives, the naphthofuran system was easily

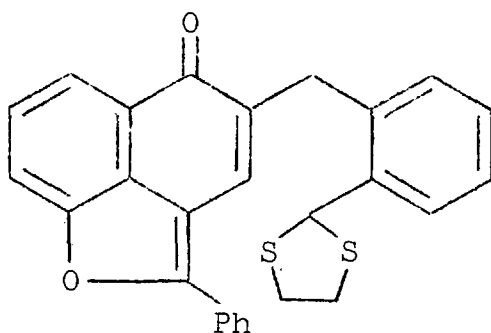
detected by its characteristic infrared and ultra-violet absorption, the values for the present case being $\nu_{\text{max.}}$ (Nujol) 1632 cm.^{-1} and $\lambda_{\text{max.}}$ (chloroform) $267, 397 \text{ m}\mu$ (ϵ 14,470, 28, 050). The n.m.r. spectrum was unexceptional but the mass spectrum showed a molecular ion which corresponded not to the formyldiacetate but to the parent aldehyde which underwent the fragmentation processes typical of benzaldehydes. Clearly, acetic anhydride is first lost in a thermal process:



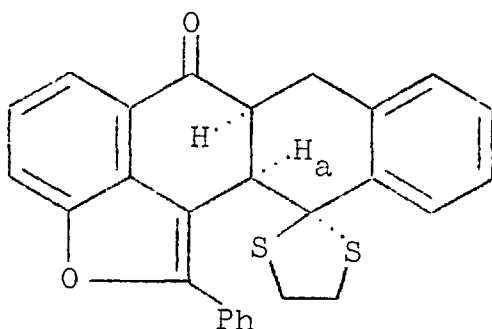
The formyldiacetate was found to be immune to the normal photolysis conditions. It decomposed slightly but a photo-product could not be detected.

The situation was very different in the case of the next derivative to be made, the thioacetal 92. The compound was obtained by Fieser's method,²⁹ and

even during purification, its great sensitivity to light was apparent. On photolysis it was converted rapidly to the thioketal 93. The rate of cyclisation



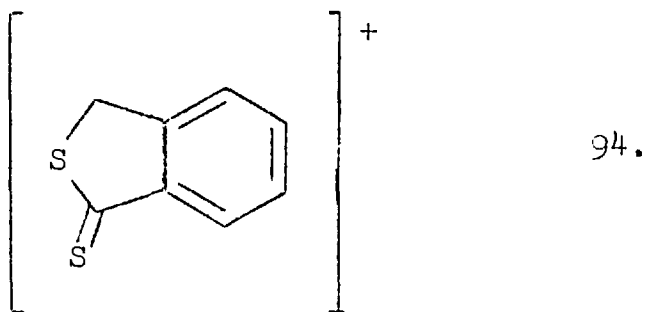
92.



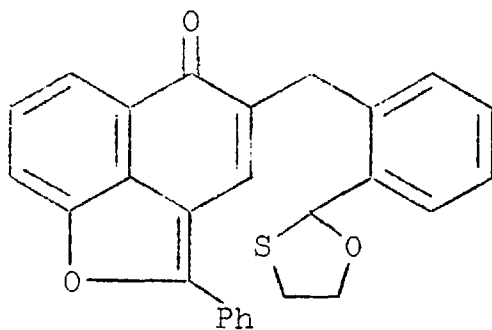
93.

was very much higher than in the case of the corresponding acetal: 415 mg. of thioacetal could be processed in 24 hr. The doublet representing H_a (see 93) in the

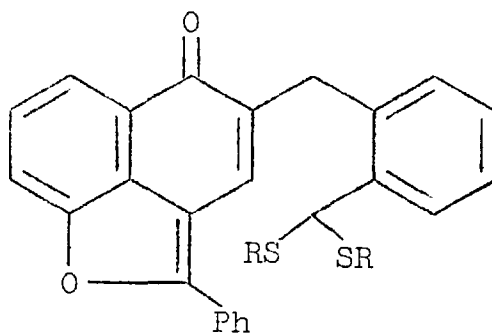
n.m.r. spectrum was well separated from other signals and the coupling constant (5 c/sec.) is compatible with the cis-fusion shown. The ultraviolet spectrum of the thioketal showed none of the fine structure characteristic of its oxygen analogue. Probably, this results from an interaction between the π electrons of the carbonyl group and the vacant d orbitals of one of the sulphur atoms. On electron bombardment, the thioketal underwent fragmentation in a manner very different from that of the ketal 78, for the base peak in the mass spectrum occurred at m/e 166 and might, conceivably, represent the ion 94.



The third derivative to be made was the hemi-thioacetal 95. Use of β -mercapto-ethanol in acetic acid containing boron trifluoride etherate afforded a mixture of products from which the bis-adduct 96 was isolated. Infrared bands at 3480 and



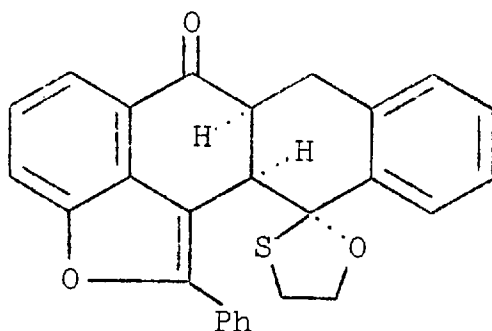
95.

96. $R = \text{CH}_2\text{CH}_2\text{OH}$

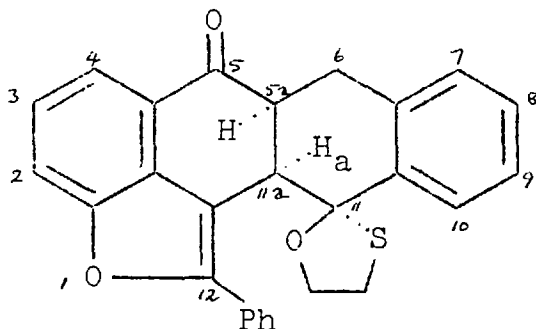
1635 cm^{-1} were consistent with the structure proposed (96) and the mass spectrum revealed the ready loss of $\text{C}_2\text{H}_5\text{O}$ and $\text{C}_2\text{H}_5\text{OS}$ from the molecular ion. This mode of fragmentation was supported by appropriate metastable peaks. It seemed that the compound should

not be formed in an exchange reaction between the model aldehyde 7 and the hemithioketal of acetone. When this method was tried the required compound 95 was obtained in high yield.

It was anticipated that photolysis of the hemithioacetal 95 would effect ring closure at a rate intermediate between the two values already observed, and it was appreciated that two isomers might be formed. Both expectations were realised and a crystalline mixture of diastereoisomeric hemithioketals was isolated in 81% yield. Each isomer was obtained as a pure, crystalline compound. Their mass spectra showed the same cracking patterns and there were minor differences between the infrared spectra. Significantly, one isomer showed no fine structure in its ultraviolet spectrum. If the opinion expressed earlier on this matter is correct then the isomers can be formulated as follows:



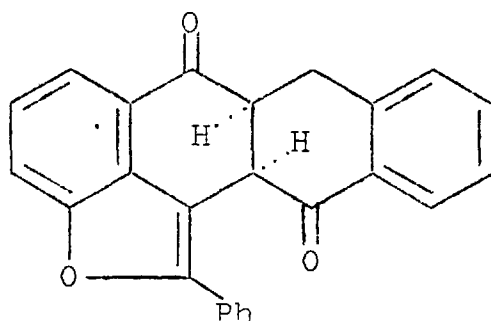
97.
(No fine structure)



98.
(Fine structure)

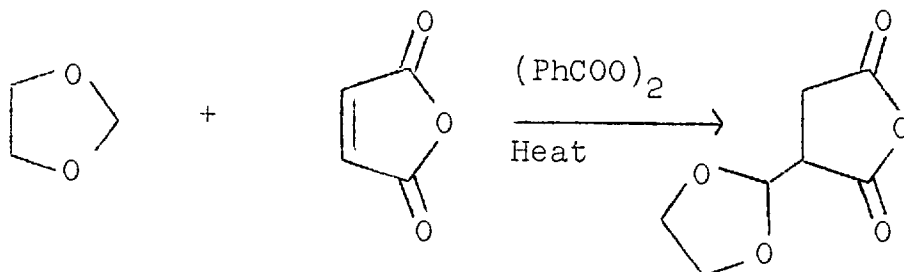
The stereochemical assignments and the size of ring B in formulas 97 and 98 are based only on analogy with the ketal 78 and the thioketal 93. However, the tetracycline group has obtained the photo-product from a hemithioacetal with substituents on ring A, and the n.m.r. spectrum of the material showed the characteristic doublet for the hydrogen atom at C-11a (see 98).

Finally, the model aldehyde itself was photolysed but on this occasion no dibenzoyl peroxide was used. The diketone 77 was produced and was identical with an authentic sample.¹ The yield was low (ca. 28%) but this probably reflects the difficulty of purifying the sensitive compound.



77.

Naturally, during the photochemical studies the question of the reaction mechanism arose. Examination of the literature revealed that formal addition of a 2-(1,3-dioxolanyl) group to an α,β -unsaturated carbonyl system is a known process. A number of simple examples, such as the following one, have been published³⁰ but comparable reactions with 2-(1,3-dithiolanyl) or 2-(1,3-oxathiolanyl) groups do not seem to have been reported. Apparently, the method has never before been exploited for synthetic purposes. On the other hand photo-cyclisation of the aldehyde has many formal analogies, for radical addition of aldehydes to α,β -unsaturated ketones has often been observed.²⁷



Our interests lay in establishing as quickly as possible, reaction conditions that would lead to acceptable yields of ketal^{*}, and a detailed mechanistic study was not undertaken. Nevertheless, several aspects of the reaction were examined and any mechanistic theory will have to accommodate the following observations.

The first point to be made is that the reaction is definitely a photochemical process. When a solution of the model acetal in benzene or toluene was refluxed in the dark in the presence of dibenzoyl peroxide (added in portions) the acetal was unaffected: no ketal was formed. Not only is

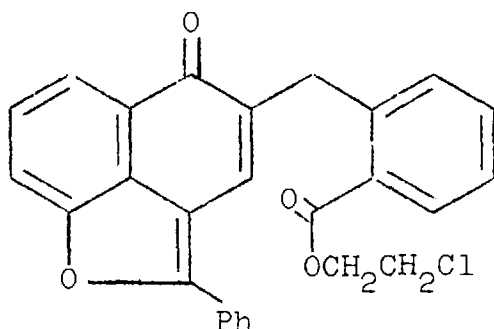
^{*}The following discussion refers to cyclisation only of the acetal 69.

irradiation necessary but the nature of the light is also critical. When pyrex apparatus was used with a high-pressure mercury lamp negligible amounts of ketal were formed; use of a tungsten lamp (weak emission at ca. 400 mμ) led to good yields but the rate was very low; with a mercury discharge lamp (Osram type MB/U) intense emission at approximately 362, 403, 436, 544, 574 mμ a marked rate-enhancement — about twenty-fold — was observed, though the yield was only ca. 39%; but, when a filter was used with the Osram lamp to remove much of the light at 360 mμ the rate was still high and the yield rose to 53%. Presumably, monochromatic light of wavelength ca. 400 mμ would be best.

It has already been mentioned that the presence of a trace of dibenzoyl peroxide is necessary if the photolysis is to be successful, but the optimum concentration was not determined. In the absence of the initiator, at room temperature or at the reflux temperature of the benzene solution, more by-products are formed and the low yield renders the process of little value. Traces of azobisisobutyronitrile or of chloroform appear also to be effective but the rigid

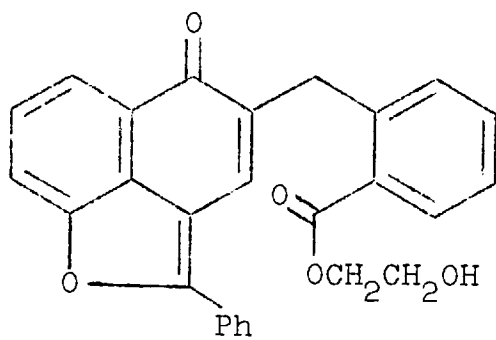
requirement exists that all the initiators be present in only very low concentrations.

When the photolysis was carried out in neat chloroform the chloro-ester 99 was produced. When an

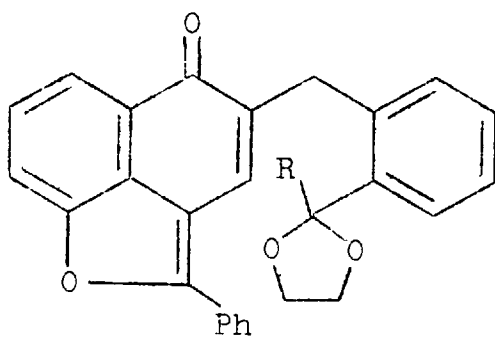


99.

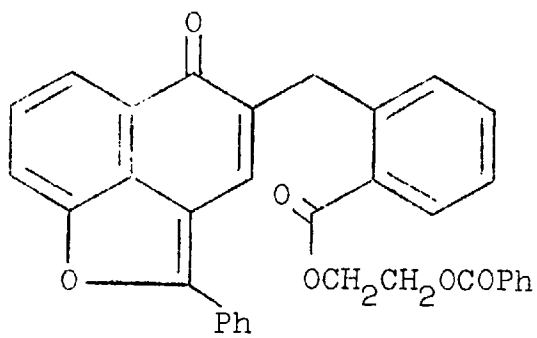
excessive amount of azobisisobutyronitrile was employed, cyclisation appeared to be slower than usual and many by-products were formed. Use of reagent quantities of dibenzoyl peroxide afforded an unstable ester ($\nu_{\text{max.}}$ 1718, 1639 cm^{-1} , $\lambda_{\text{max.}}$ 405m μ). On storage in the presence of traces of chloroform it was converted to a hydroxy-ester, formulated as compound 100 on the basis of its infrared, ultraviolet, and mass spectra. It follows that the original product must have had the constitution 101 or 102.



100.

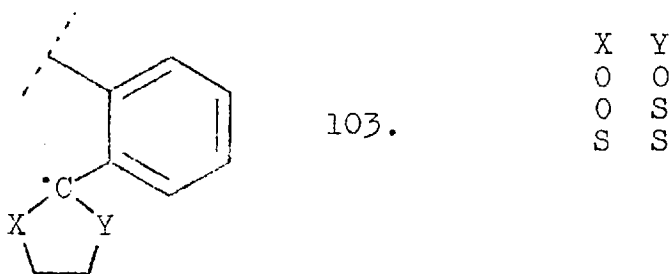


101.
R=OCOPh



102.

Formation of a free or incipient radical 103 is compatible with the evidence collected so far. The fate of this species depends on the prevailing

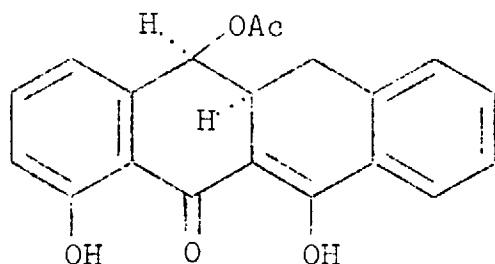


conditions: it can react intramolecularly to give an ABCD-tetracyclic compound, or, in the presence of certain other radicals it can be trapped in an intermolecular process to give (eventually) an ester.

This interpretation makes the observed rate sequence $\text{thioacetal} > \text{hemithioacetal} > \text{acetal}$; formyldiacetate (no reaction) reflect the order of decreasing stabilisation³¹ afforded the radical 103 by the heteroatoms. The necessity for both light and dibenzoyl peroxide remains obscure as do the structures of the ketonic by-products formed in the absence of

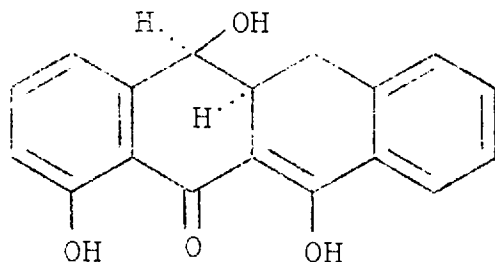
initiator. These observations complete the discussion of our experiments on the photolysis and we can now return to the main synthetic work.

It will be recalled that the acetate 16 had been



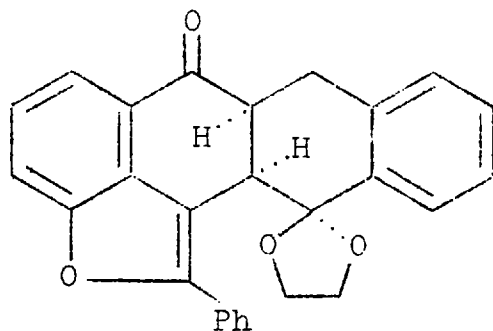
16.

made previously¹ and it was decided to prepare the corresponding alcohol 104.



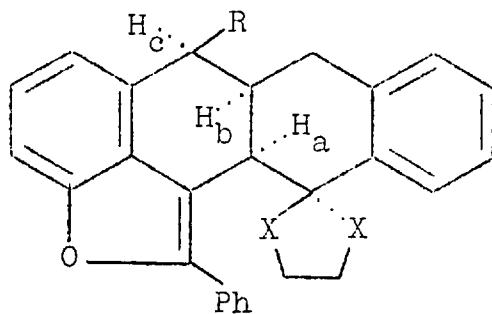
104.

Hydrogenation of the ketal 78 over palladised



78.

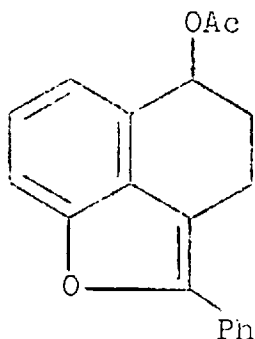
charcoal afforded the deoxy-compound 105. Reduction to the required alcohol 106 was achieved with lithium aluminium hydride but the product was always impure.



	R	X
105.	H	O
106.	OH	O
107.	OH	S
108.	OAc	O
109.	OAc	S

Apparently, some of the starting material was trapped as an enolate and the ketone was regenerated during work-up. Sodium borohydride proved a more satisfactory reagent for the preparation of the alcohol 106 and of the corresponding hydroxy-thioketal 107.

Both alcohols were acetylated by treatment with acetic anhydride in pyridine. In the case of the hydroxy-ketal 106 it was necessary to heat the mixture, but the acetoxy-thioketal 109 could be made at room temperature as could the CD-model 4.



4.

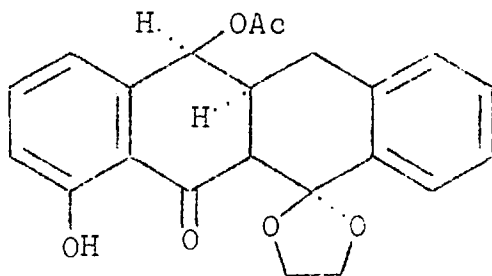
A comparison of the n.m.r. spectra of the three acetates was informative.

	acetoxy-ketal 108	acetoxy-thioketal 109	CD-model 4
H _a	5.72 (centre of doublet) J = 4.7 c./sec.	5.42 (centre of doublet) J = 4.5 c./sec.	
H _c	3.61 (centre of doublet) J = 4 c./sec.	3.60 (centre of doublet) J = 3.5 c./sec.	
CH ₃	8.74 (singlet)	8.73 (singlet)	7.93 (singlet)

The coupling constants suggest³² a cis-relation between the hydrogen atoms H_a, H_b and H_b, H_c (see 106). This tentative assignment is supported by the observed shielding of the acetate hydrogen atoms in compounds 108 and 109. The methyl group must be above the plane of ring A in these compounds and this situation can arise only if rings B and C are cis-fused. The spectra therefore provide definitive evidence for the stereochemistry and structures of the acetates and hence of their parent alcohols (106 and 107) and ketones (78 and 93).

The acetoxy-ketal 108 was selected for ozonolysis experiments and a thorough study of this reaction was made. Low temperatures and chloroform solutions containing a participating solvent (methanol) were used. It was found that the nature of the product depended on the work-up procedure.

Hydrogenation over 1% palladised charcoal afforded a mixture from which the phenolic-ketone 110 was isolated. The infrared spectrum showed hydroxyl and

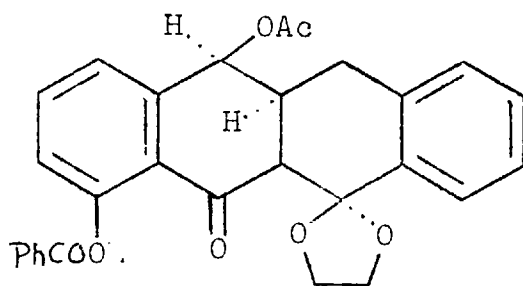


110.

ester absorptions, and the position of the remaining carbonyl band (1643 cm^{-1}) indicated the strong hydrogen-bonding expected to occur.³³ When the compound was treated with mineral acid the ultraviolet spectrum changed and the trace eventually became almost

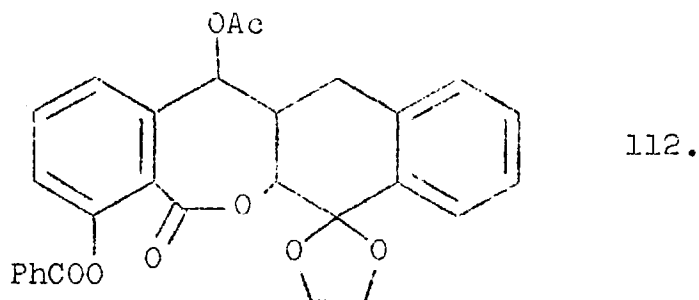
identical in shape to that reported previously¹ for the β -diketone 16. The mass spectrum was readily understandable in terms of the gross structure 110 and the stereochemistry shown follows from the method of preparation.

When hydrogenation was carried out over 1% palladised calcium carbonate the phenolic-ketone 110 and the benzoate 111 (see later) were detected in the total product by thin-layer chromatography.

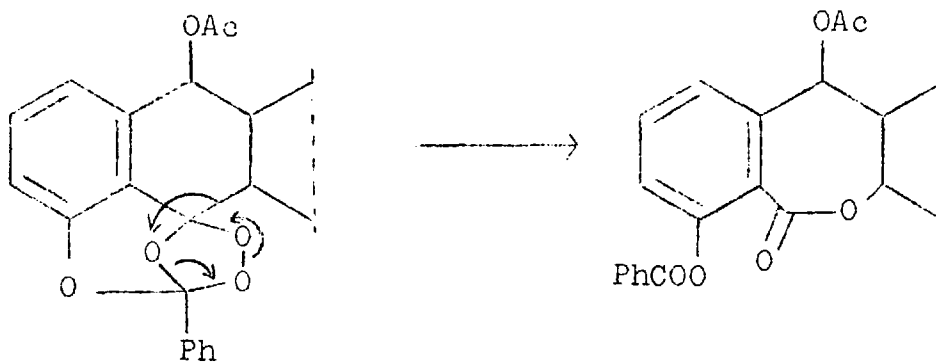


111.

Attempted reduction of the ozonolysis mixture with zinc dust or with acidified potassium iodide afforded a compound believed to be the lactone 112. In addition to a band at $1737\text{--}1729\text{ cm.}^{-1}$ the infrared spectrum (chloroform) showed hydroxyl absorption. The



substance is, however, very unstable and was never obtained pure. The mass spectrum revealed clearly the presence of a benzoate group and indicated the incorporation of a single oxygen atom into the starting material. These facts are best accounted for by structure 112 and a possible mechanism for its formation is shown in the following scheme:

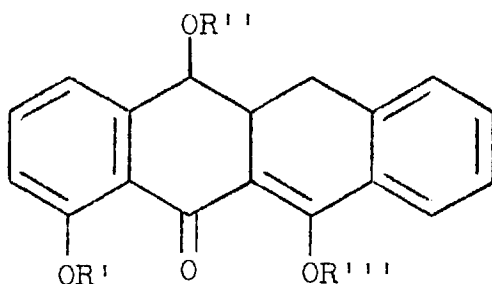


Finally, triphenyl phosphine was used to reduce³⁴ the ozonolysis mixture. Essentially one compound was formed. It was isolated in good yield as an almost pure oil and was obtained crystalline. A mass measurement established the molecular formula $C_{29}H_{24}O_7$ corresponding to the keto-benzoate lll and this structure was supported by the infrared spectrum. A band occurred at 1736 cm.^{-1} and another, half as intense, at 1700 cm.^{-1} . After treatment with acid the compound had an ultraviolet absorption maximum at $385\text{ m}\mu$. The β -diketone 16 absorbs at 392 and $412\text{ m}\mu$ so it is clear that the benzoyloxy-group was not hydrolysed under the mild conditions used.

In the hope that purification might be simplified triphenylphosphine was replaced by triethylphosphite but a complex mixture was obtained.

The next stage of the synthetic work required hydrolysis of the two ester groups in compound lll. Use of sodium carbonate in hot, aqueous acetone rapidly afforded three new compounds. The composition of the mixture could not be altered by prolonged heating or by treatment of the three compounds with ammonium hydroxide or with aqueous, ethanolic potassium hydroxide. The mixture had $\lambda_{\text{max.}}$

(ethanol) 263-238, 362m μ and λ_{max} . (ethanol — hydrochloric acid) 378m μ , and may have contained compounds of the type expressed by formula 113, as β -keto-ketals are known³⁵ to afford vinylogous esters

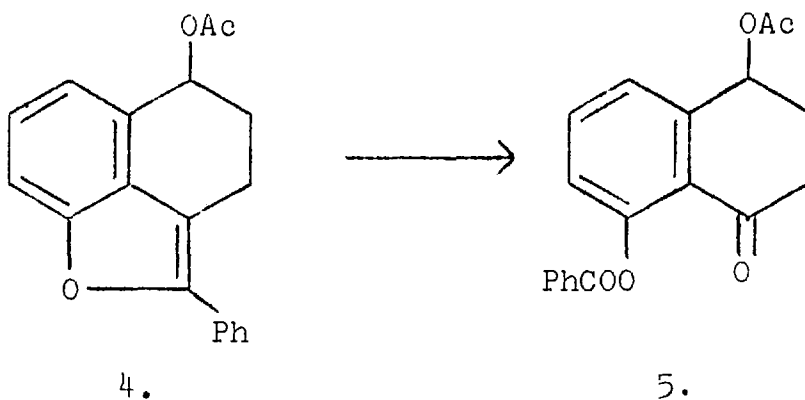


113.

on treatment with base.

The hydrolysis was investigated further by using the crystalline³⁶ model 5 which was obtained³⁶ by the triphenylphosphine procedure from the acetate 4.

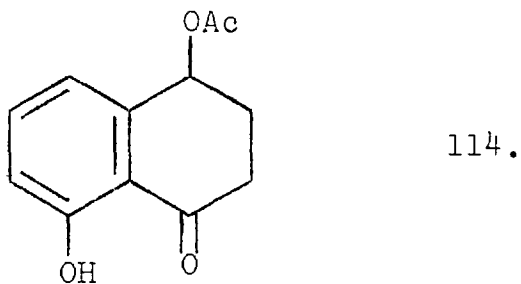
The carbonyl band in the infrared spectrum of the model 5 is at 1689 cm.⁻¹ This value is 11 cm.⁻¹ lower (bathochromic shift) than for the corresponding band in the keto-benzoate 111. Presumably the difference is the result of some steric factor. There was much closer similarity between



the ultraviolet spectra of the two compounds:

Compound 111	Compound 5
286 mμ (ε 2,872)	286 mμ (ε 2,763)
232 mμ (ε 21,770)	233 mμ (ε 22,760)

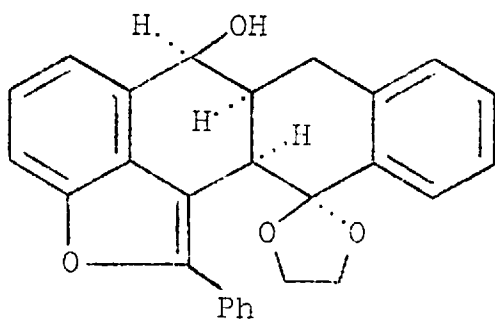
The response of model 5 to various nucleophiles was examined. With aqueous ammonia an oily substance was formed. It had $\nu_{\text{max.}}$ 1733, 1643 cm.^{-1} and is, therefore, the phenolic ketone 114.



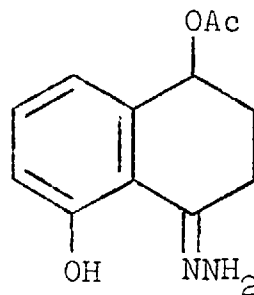
Compound 5 was rapidly destroyed by aqueous sodium hydroxide; several substances were formed but even after 24 hr. the phenolic-ketone 114 was still a major component of the mixture.

When aqueous hydrazine in dimethylsulphoxide was employed the phenolic ketone 114 was obtained. Prolonged treatment or use of a higher temperature afforded another oily compound believed to be the hydrazone 115 on the basis of infrared bands at 1727, 1627, 1603 cm^{-1}

Because of the difficulty encountered in hydrolysing the acetoxy-group the alcohol 106 was subjected to the normal ozonolysis procedure. Although

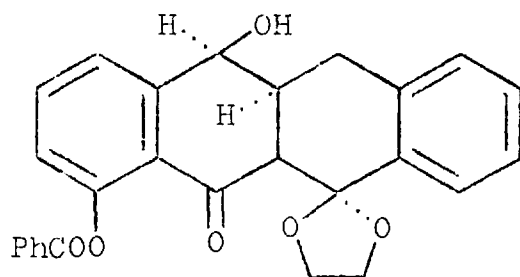


106.



115.

a sample of the required product 116 was isolated the reaction was of little synthetic value, since even

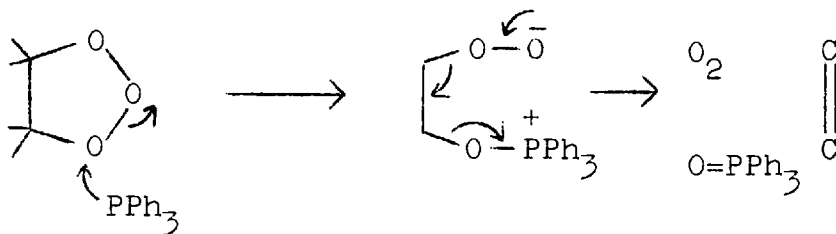


116.

at very low temperatures two major products were formed.

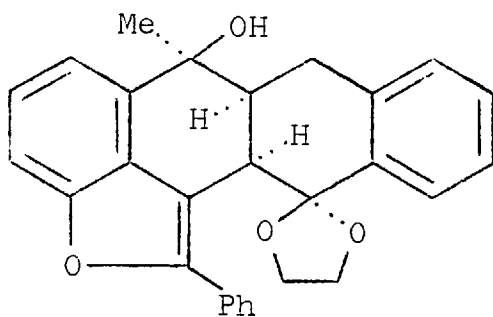
When ozonolysis of the alcohol was carried out in the presence of triphenylphosphine the substrate did not appear to be attacked until all the phosphine had been oxidised. This phenomenon was reinvestigated in a quantitative manner using the CD-model 4 and the original impression was confirmed. The simplest explanation is that triphenylphosphine competes successfully for ozone and is oxidised more rapidly than the less nucleophilic substrate. A more interesting possibility is that triphenylphosphine

attacks the molozonide:



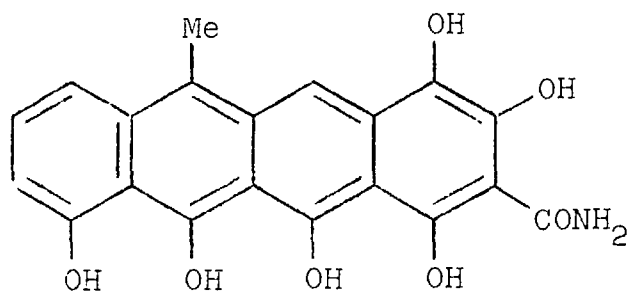
and if this is the case, the oxygen produced would be expected to exist in an excited (singlet) state.³⁷

Because acetylation of the eventual C-6 hydroxyl group led to the difficulties described, it was clear that an alternative method of protection was needed and it was decided to make the tertiary alcohol 117.



117.

The stability towards ozone of a hydroxyl group in the new environment had been discovered previously¹ and introduction of the methyl group was now a vital part of our synthetic work. In 1965 McCormick and his associates had isolated a biogenetic precursor of aureomycin.³⁸ The new compound, 4-hydroxy-6-methyl-pretetramid (118), became the primary objective of the tetracycline group.

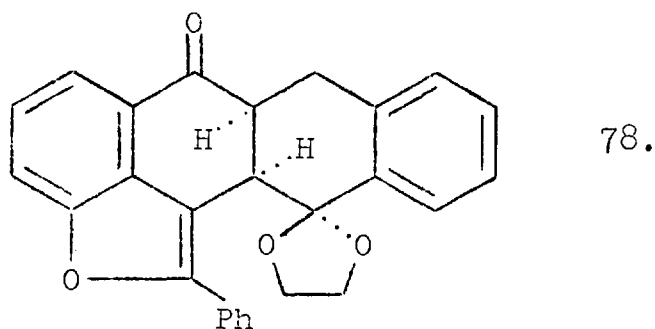


118.

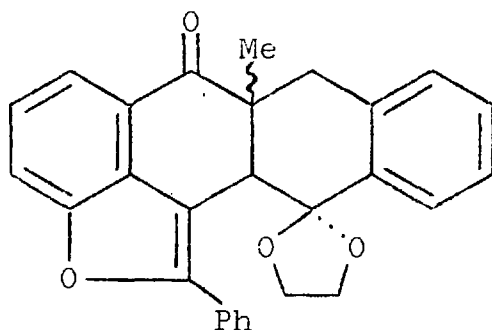
Methylmagnesium bromide in tetrahydrofuran or ethylmagnesium iodide — triethylamine complex* in benzene³⁹ failed to react with the ketone 78 at room

* The methyl analogue has not been reported; therefore the ethyl reagent was used to test the method.

temperature. A rise in temperature produced no significant change in the first case, but the amine complex destroyed the starting material.



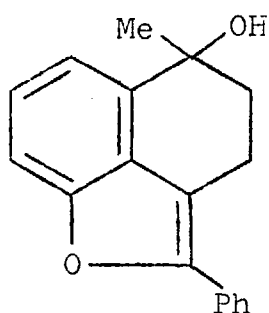
Treatment of lithium with methyl iodide in tetrahydrofuran afforded a mixture which methylated the ketone, presumably at the position α to the carbonyl group (119). The crystalline product had ultraviolet and infrared spectra very similar to those of the starting material, but the mass spectrum showed that a methyl group had been incorporated. Our attention was then drawn to the published⁴⁰ observation that the reagent, as we had made it, was not methyl-lithium. Clearly a base was present and the enolate derived from the starting material was methylated on carbon.



119.

Addition of an etherial solution of methyl-lithium to a benzene solution of the ketone brought about the desired change and the tertiary alcohol 117 was obtained as a crystalline compound. No compelling evidence for the stereochemistry is yet available; that shown is predicted on steric grounds. The n.m.r. spectrum of the alcohol showed a methyl signal at 8.28τ and it will be interesting to compare this value with that for compound 120.

The success of the methylation has brought the tetracycline group close to achieving total synthesis of 4-hydroxy-6-methylpretetramid. The photolysis has provided us with ABCD-tetracyclic compounds



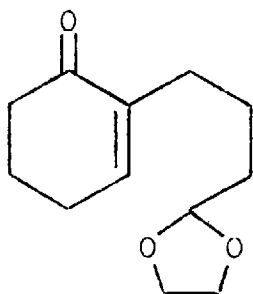
120.

appropriately substituted in ring A¹ and the procedure for ozonolysis has been defined by the experiments in the model series (ring A **unsubstituted**).

For synthesis of a tetracycline, however, there still remains the problem of reducing ring A. Some progress has now been made on this project and the new approach seems fruitful.

The mechanism of the photolytic cyclisation of the model aldehyde and its derivatives merits further study: it may be possible to define better reaction conditions than those used, and it is of interest to

determine whether the method is applicable⁴¹ to simple compounds such as the cyclohexenone 121.



121.

Experimental.

Unless otherwise specified, the following data apply to the experiments described in this section:

Measurements.

Melting points were taken on a Kofler block.

Infrared spectra were measured in chloroform.

N.m.r. spectra were taken at room temp. on dilute solutions in deuteriochloroform with a Varian A 60 spectrometer.

Mass spectra were determined with an Associated Electrical Industries MS9 high resolution mass spectrometer (ionisation potential 70 e.v., ionising current 18 μ A). Samples were ionised by electron bombardment after evaporation into the electron beam.

Mass measurements were determined relative to heptacosafuorobutylamine by the Nier-Johnson technique.

Materials.

Acetone was dried over potassium carbonate.

Alumina for column chromatography was neutral and of activity 3 (Brockmann scale). Material for t.l.c. was type G (Merck). The plates were activated at 110° for 1 hr.

Ammonia was dried by distillation from sodium.

Benzene was dried over sodium wire.

t-Butanol was dried by distillation from sodium.

Ether was dried over sodium.

Light petroleum refers to the fraction with b. p. 40-60°.

Nitrogen was dry and oxygen-free.

Silica gel for column chromatography was supplied by H. and W. (M.F.C. 7555). Material for t.l.c. was type GF₂₅₄ (Merck). The plates were activated at 110° for 1 hr.

Tetrahydrofuran was distilled from lithium aluminium hydride before use.

Triethylamine was dried by distillation from sodium.

Technique.

For work with ACD-tricyclic and ABCD-tetracyclic compounds distilled solvents were used.

Crystalline compounds were dried in vacuo, usually at room temp., but sometimes at ca. 40°.

Evaporation of solutions was effected in vacuo.

When compounds were purified by t.l.c. the appropriate bands were eluted with dichloromethane or chloroform (AnalaR).

Sodium sulphate was used to dry solutions of organic compounds.

Methyl p-orsellinate (25).

p-Orsellinic acid ¹, ⁵ was esterified as described by Saraiya and Shah. ¹, ⁴²

Methyl 2,6-dimethoxy-4-methylbenzoate (26).⁵

Dimethyl sulphate (11.7 ml.) was added to a solution of methyl p-orsellinate (5.35 g.) in aqueous sodium hydroxide (2.0N; 60 ml.) (nitrogen atmosphere). The mixture was cooled (water bath) and stirred vigorously. After 45 min. aqueous sodium hydroxide (4.0N; 30 ml.) was added and stirring continued for 2 hr. The solid was collected, dissolved in benzene and washed with water. The solution was dried and evaporated to give the crystalline ester (3.38 g.; from aqueous alcohol), m.p. 73-84° (lit., ⁵ 86°), $\nu_{\max}$. (carbon tetrachloride) 1739 cm.⁻¹ The crude product was suitable for the next stage.

2,6-Dimethoxy-4-methylbenzoic acid (27).⁵

A mixture of methyl 2,6-dimethoxy-4-methylbenzoate (3.37 g.), sodium hydroxide (7 g.), water 27 ml.), and ethanol (91 ml.) was refluxed for 2 hr. The solution was concentrated till semisolid and dissolved in water. Acidification with conc. hydrochloric acid gave, after cooling, the dimethoxy-acid (2.89 g.), m.p. 185-188° (change of form ca. 150° to m. p.) lit.,⁵ m. p.,

180-182°), $\nu_{\text{max.}}$ (Nujol) 1693 cm.^{-1}

2,6-Dimethoxy-4-methylbenzamide (24).⁵

A solution of 2,6-dimethoxy-4-methylbenzoic acid (2.79 g.) in thionyl chloride (50 ml.) was refluxed for 4 hr. (exclusion of moisture). Excess of reagent was evaporated and the residue [$\nu_{\text{max.}}$ (carbon tetrachloride) 1790 cm.^{-1}] dissolved in anhydrous benzene (50 ml.), cooled, and treated with dry, gaseous ammonia. The mixture was filtered and the solid washed thoroughly with water. The dry amide (1.91 g.), $\nu_{\text{max.}}$ 3540, 3430, 1675 cm.^{-1} , was used for the next stage. A portion was recrystallised from benzene and had m. p. 201-205° (lit.,⁵ 199°).

1,4-Dihydro-2,6-dimethoxy-4-methylbenzamide (31).

Sodium 370 mg.; in small pieces) was added rapidly to a stirred solution of 2,6-dimethoxy-4-methylbenzamide (543 mg.) in anhydrous liquid ammonia (50 ml.) and absolute ethanol (9 ml.). After the resulting blue colour had faded ammonium chloride (2.7 g.) was added and the ammonia evaporated by warming the reaction vessel. The residue was mixed with water (50 ml.) and extracted with dichloromethane. The organic solution was dried and evaporated to leave the crude product (423 mg.), $\nu_{\text{max.}}$ 3500, 3400, 1690, 1680 cm.^{-1}

Two recrystallisations from chloroform-ether furnished the dihydro-amide (70 mg.), m. p. 172-177° (partial melting and evaporation of the liquid ca. 125°), λ_{max} . (ethanol) 205 m μ . The compound was pure as judged by t.l.c. (alumina; chloroform:methanol::2:1; iodine). The n.m.r. spectrum showed signals at (τ values): ca. 4.1 (very broad, 2 protons), 5.22 (centre of doublet, $J = 2$ c./sec., 2 protons), 6.38 (singlet, 6 protons), 8.87 (centre of doublet, $J=8$ c./sec., 3 protons). An analytical sample had m. p. 185-189° (from ethanol). (Found: C, 61.24; H, 7.81; N, 7.44. $\text{C}_{10}\text{H}_{15}\text{NO}_3$ requires C, 60.89; H, 7.67; N, 7.10%).

4-Methyl-2,6-dioxocyclohexane carboxamide (32).

2,6-Dimethoxy-4-methylbenzamide (540 mg.) was reduced by the method already described and the crude product dissolved in ethanol (22 ml.). Hydrochloric acid (6N; 30 drops) was added and the solution kept for 2.3hr. at room temp. (ultraviolet control). The solution was evaporated below 55° and the residue warmed (55°) with a saturated aqueous solution of sodium hydrogen carbonate (10 ml.). Insoluble material was removed and acidification (conc. hydrochloric acid) of the cooled filtrate afforded the crystalline β -diketone (153 mg.), m. p. 138-148.5° (change of form ca. 120° to

m. p.). A portion (57.5 mg.) was recrystallised twice from aqueous methanol to furnish the pure compound (50.5 mg.) m. p. 146-150°, λ_{max} . (ethanol) 260 m μ , identified as 4-methyl-2,6-dioxocyclohexane carboxamide by comparison [m. p.; mixed m. p.; infrared spectrum (Nujol)] with an authentic sample. 1, 43

2,6-Dihydroxy-4-methyl-3-phenylazobenzoic acid (34).

2,6-Dihydroxy-4-methyl-3-phenylazobenzoic acid was prepared by the method described in the literature⁷ and the crude material (m. p. 179-183°) used in the next stage. A sample melted at 180-185° [lit.,⁷ 184° (from acetone)] after recrystallisation from tetrahydrofuran.

Methyl 2,6-dimethoxy-4-methyl-3-phenylazobenzoate (35).

A mixture of 2,6-dihydroxy-4-methyl-3-phenylazobenzoic acid (9.48 g.), anhydrous potassium carbonate (19.60 g.), and dimethyl sulphate (10.6 ml.; distilled in vacuo and stored in contact with anhydrous potassium carbonate) in dry acetone (ca. 250 ml.) was refluxed with stirring (exclusion of moisture). Potassium carbonate and dimethyl sulphate (9.8 g. and 5.3 ml., respectively) were added after 15 hr. and again after 41 hr. After a further 4.5 hr more potassium carbonate (4.0 g.) was added and the reaction continued for 43 hr. The mixture was

filtered, the solid washed with dry acetone and the combined filtrates evaporated. The residue was chromatographed over alumina with benzene and crystallised from aqueous ethanol to give methyl 2,6-dimethoxy-4-methyl-3-phenylazobenzoate (8.61 g.), m. p. 118-121°, ν_{max} . 2880, 1725 cm^{-1} . The n.m.r. spectrum showed signals at (τ values): 1.97-2.59 (multiplet, 5 protons), 3.37 (singlet, 1 proton), 6.05, 6.11, 6.13 (singlets, 9 protons), 7.47 (singlet, 3 protons). An analytical sample had m. p. 120.5-121°. (Found: C, 65.16; H, 5.93; N, 8.69. $\text{C}_{17}\text{H}_{18}\text{O}_4\text{N}_2$ requires C, 64.96; H, 5.77; N, 8.91%).

Methyl 3-amino-2,6-dimethoxy-4-methylbenzoate (36).

Methyl 2,6-dimethoxy-4-methyl-3-phenylazobenzoate (4.56 g.) in methanol (85 ml.) containing conc. hydrochloric acid (4.5 ml.) was hydrogenated over Adams' catalyst (94 mg.). The mixture was filtered, made alkaline (saturated aqueous sodium hydrogen carbonate), and extracted with dichloromethane. The purple organic solution was dried and evaporated, and the residue extracted with several portions of boiling ether. The combined extracts were filtered, concentrated, and cooled to ca. -60°. The resulting crystals were filtered off and a second crop obtained from the mother

liquors. A total of 2.28 g. of the crude amine, m. p. 90-100°, ν_{max} . 3490, 3410, 2860, 1725 cm^{-1} , suitable for the next stage was obtained.

Methyl 3-dimethylamino-2,6-dimethoxy-4-methylbenzoate (37).

Anhydrous potassium carbonate (2.1 g.) and dimethyl sulphate (0.55 ml.) were added to methyl 3-amino-2,6-dimethoxy-4-methylbenzoate (314 mg.) in dry acetone (ca. 6 ml.). The mixture was refluxed with stirring overnight, filtered, evaporated to dryness, taken up in chloroform, washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The residue was chromatographed over alumina with benzene to give methyl 3-dimethylamino-2,6-dimethoxy-4-methylbenzoate (291 mg.; from light petroleum), m. p. 71-72°, ν_{max} . 2860, 2800, 1723 cm^{-1} (Found: C, 61.44; H, 7.41; N, 5.58.

$\text{C}_{13}\text{H}_{19}\text{NO}_4$ requires C, 61.63; H, 7.56; N, 5.53%). The n.m.r. spectrum showed singlets at (τ values): 3.50 (1 proton), 6.10, 6.23, 6.25 (9 protons), 7.27 (6 protons), 7.72 (3 protons).

3-Dimethylamino-2,6-dimethoxy-4-methylbenzoic acid (38).

A mixture of methyl 3-dimethylamino-2,6-dimethoxy-4-methylbenzoate (169 mg.), aqueous sodium hydroxide (4N; 2.55 ml.), and ethanol (5.1 ml.) was refluxed for 5.6 hr. [t.l.c. control (alumina; benzene; iodine)].

The clear solution was cooled, diluted with water and extracted with ether. The aqueous layer was acidified (acetic acid) and continuously ether extracted for 15 hr. Evaporation of the extract gave the crude amino-acid (140 mg.), $\nu_{\max}$. 2860, 2800, 1720 (broad) cm^{-1} . The compound was used directly for the next stage.

3-Dimethylamino-2,6-dimethoxy-4-methylbenzamide (33).

3-Dimethylamino-2,6-dimethoxy-4-methylbenzoic acid (204 mg.) was dissolved in oxalyl chloride (1 ml.) (exclusion of moisture). The solution was kept for 15 min. at room temp. and then refluxed gently for 2 hr. The solvent was removed and the residue, in anhydrous benzene, treated with dry, gaseous ammonia. The resulting mixture was added to saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic solution was dried and evaporated to give 3-dimethylamino-2,6-dimethoxy-4-methylbenzamide (125 mg.; from benzene), m. p. 176-180°, $\nu_{\max}$. 3520, 3430, 2890, 2820, 1678, 1600 cm^{-1} (Found: C, 61.39; H, 7.78; N, 11.61. $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_3$ requires C, 60.46; H, 7.61; N, 11.76%). [Mass measurement on molecular ion (also base peak): 238.131095. Mass calculated for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_3$: 238.131734]. The n.m.r. spectrum showed signals at (τ values): 3.48 (singlet,

1 proton), ca. 4 (very broad, 2 protons), 6.13, 6.19 (singlets, 6 protons), 7.21 (singlet, 6 protons), 7.68 (singlet, 3 protons).

Attempted reduction of 3-dimethylamino-2,6-dimethoxy-4-methylbenzamide (33).

Procedure A.

Sodium (70 mg.; in several pieces) was added rapidly to a stirred solution of the amide (33) (141) mg.) in dry, liquid ammonia (ca. 50 ml.) and absolute ethanol (1.8 ml.). A fleeting blue colour was produced and, after 5 min., ammonium chloride (1 g.) was added to the colourless solution. The ammonia was evaporated, water was added to the residue, and the mixture extracted with dichloromethane. The organic solution was dried and evaporated to give a partially crystalline oil, ν_{max} . 3520, 3420, 2880, 1705 (shoulder), 1680 cm^{-1} . T.l.c. (alumina; acetone; iodine) showed, besides starting material, two slower-running substances. The n.m.r. spectrum confirmed that the major component was starting material and showed, also, weak singlets at 8.95 and 9.05 τ . The ultraviolet spectrum was similar to that of the starting material but showed a shoulder at ca. 240 m μ . Dissolution of the total product in ethanol containing hydrochloric acid (6N; several drops)

produced slight changes in the ultraviolet spectrum but no peak developed at ca. 260 m μ , even on heating.

Procedure B.

Sodium (479 mg.; in small pieces) was added rapidly to a stirred solution of the amide (33) (125 mg.) in dry, liquid ammonia (ca. 12 ml.) and absolute ethanol (1.6 ml.). After 30 min. ammonium chloride (500 mg.) was added to the blue solution and the total product isolated as already described. The oil had $\nu_{\text{max.}}$ 3520, 3420, 1705 cm.⁻¹ The n.m.r. spectrum showed strong singlets at 8.92 and 9.03 τ , and a methylene envelope between 7.3 and 8.8 τ . Treatment with hydrochloric acid again failed to produce a band in the ultraviolet spectrum at ca. 260 m μ .

Procedure C.

Lithium (65 mg.; in several pieces) was added rapidly to a stirred solution of the amide (33) (70 mg.) in dry, liquid ammonia (40 ml.) and anhydrous t-butanol (1.6 ml.). After 10 min. ammonium chloride (ca. 1g.) was added to the blue solution and the mixture worked up in the usual way. The oily product had $\nu_{\text{max.}}$ 3300, 1705 cm.⁻¹ and no β -diketone formed on treatment with acid, even after warming (ultraviolet control).

2,5-Dihydroanisole.

2,5-Dihydroanisole, made by the procedure of Wilds and Nelson,⁴⁴ was stored in contact with anhydrous potassium carbonate (nitrogen atmosphere) at ca. 5°. The compound had $\nu_{\max}$. (film) 1687 cm^{-1} . The extinction coefficient at 268 m μ was 421, indicating the presence of ca. 10% 2,3-dihydroanisole. The n.m.r. spectrum showed, besides several small peaks due to impurities, signals at (τ values): 4.38 (singlet, 2 protons), 5.48 (broad singlet, 1 proton), 6.50 (singlet, 3 protons), 7.32 (centre of multiplet, 4 protons).

Ethylazidoformate.

Ethylazidoformate was prepared by the method of Forster and Fierz,⁴⁵ and had $\nu_{\max}$. (film) 2225, 2160, 1750, 1723 cm^{-1} . The dry liquid was stored in the dark.

Photolysis of ethylazidoformate in the presence of 2-5-dihydroanisole.Procedure A.

Ethylazidoformate (1.31 g.) was added to a solution of 2,5-dihydroanisole (1.12 g.) in cyclohexane (ca. 60 ml.; distilled from sodium) stirred with a stream of nitrogen. The mixture was irradiated with a low-pressure mercury lamp and after 5 hr. most of the

ethylazidoformate had decomposed (infrared control with respect to azide band). The solvent was removed (water pump; steam bath) to leave an oil. This had $\nu_{\text{max.}}$ (film) 3380, 2200 (weak), 1720, 1687, 1672 cm.^{-1} and contained at least 6 components (tlc ; alumina; benzene; iodine). The n.m.r. spectrum showed inter alia a triplet-quartet pattern (ethoxyl-group). Chromatography over alumina with benzene gave cyclohexylurethan (infrared spectrum). A portion of the total product failed to give an isolable 2,4-dinitrophenylhydrazone.

Procedure B.

A mixture of 2,5-dihydroanisole (6.56 g.) and ethylazidoformate (1.71 g.) was irradiated as before but without solvent. The azide decomposed slowly (infrared control) and even after 30 hr. some was still present. At this stage a portion (1.02 g.) of the mixture was concentrated (water pump; steam bath). The residue had $\nu_{\text{max.}}$ (film) 3460, 1710, 1690, 1675 (shoulder) cm.^{-1} . Further evaporation (oil pump; room temp.) afforded a thick oil (100 mg.) with $\nu_{\text{max.}}$ (film) 3450, 1710, 1670 (shoulder) cm.^{-1} . The only recognisable features of its n.m.r. spectrum were a triplet-quartet pattern (ethoxyl-group) and a number of signals in the O-methyl region (ca. 6.5 τ). A sample that had been distilled provided

a similar n.m.r. spectrum and contained, apparently, 10 major components [g.l.c. (Pye Argon chromatograph; polyethylene glycol adipate column at 150°; gas flow rate 12 ml./min.)]. The following experiments were performed on the oily product.

An attempt to obtain a 2,4-dinitrophenylhydrazone afforded a dark precipitate from which no single compound could be isolated.

The oil (50 mg.) in methanol (4 ml.) was hydrogenated over 5% palladised charcoal (45 mg.) until there was no further uptake. Removal of the catalyst and evaporation of the solvent (oil pump; room temperature) gave an oil (43 mg.) containing at least 3 components [t.l.c. (alumina; benzene; iodine)]. The oil had $\nu_{\max}$. (film) 1710 cm^{-1} and its n.m.r. spectrum showed a number of signals in the O-methyl region.

A solution of the oil (122 mg.) and O-chloranil (208 mg.) in xylene (6 ml.) was refluxed for 1.5 hr., kept overnight at room temp., diluted with dichloromethane, and washed with aqueous sodium bisulphite. The organic solution was dried and evaporated (water pump; steam bath). The resulting oil (311 mg.) had $\nu_{\max}$. (film) 3520, 3430, 1720 cm^{-1} . Sublimation afforded two partially crystalline fractions. Both gave a purple

colour with neutral ferric chloride solution. The major fraction had $\nu_{\max}$. 3510, 3420, 3200 (broad), 1720 cm^{-1}

Hydroxylamine-O-sulphonic acid.

Hydroxylamine-O-sulphonic acid was made by the procedure of Inorganic Syntheses⁴⁶ and obtained 90% pure (titration). The compound was stored in a sealed ampoule in an atmosphere of nitrogen.

Treatment of 2,5-dihydroanisole with hydroxylamine-O-sulphonic acid — sodium methoxide.

Hydroxylamine-O-sulphonic acid (956 mg.) in methanol (ca. 10 ml.) was added to a stirred solution of sodium methoxide [from sodium (382 mg.)] in methanol (ca. 10 ml.) containing 2,5-dihydroanisole (4.63 g.) (nitrogen atmosphere). After 1.5 hr. a portion of the mixture (10 ml.) was acidified (hydrochloric acid), concentrated, diluted with water, and extracted with dichloromethane. The aqueous layer was made alkaline (sodium hydrogen carbonate) and extracted with dichloromethane. The extract was dried, evaporated at atmospheric pressure and kept for a few min. in vacuo (water pump; room temp.). The resulting oil (10 mg.) had $\nu_{\max}$. 3400 (strong), 1710 cm^{-1}

The remainder of the mixture was worked up in the

same way after a reaction period of ca. 15 hr. The infrared spectrum of the oily product (6.7 mg.) was similar to that obtained previously.

When the oil was warmed with acetic anhydride, no evidence (infrared) could be obtained for production of an N-acetate.

Treatment of 2,5-dihydroanisole with cyclohexanespiro-3'-(oxaziridine).

Procedure A.

An ice-cold ethereal solution of cyclohexanespiro-3'-(oxaziridine) was prepared by the method described in the literature,¹⁵ the compound being obtained in 9.6% yield (based on hydroxylamine-O-sulphonic acid).

The ethereal solution [35 ml.; equivalent to 3.4 millimole cyclohexanespiro-3'-(oxaziridine)] was added to a solution of 2,5-dihydroanisole (4.26 g.) in ether (45 ml.) and the mixture stirred at 0° for 15 hr. Aliquots (10 ml.) were withdrawn at intervals and shaken with a mixture of potassium iodide (5 g.), water (25 ml.), sulphuric acid (1N; 10 ml.), starch solution⁴⁷ (1 ml.), and chloroform (40 ml.). Liberated iodine was determined by titration with sodium thio-sulphate solution (0.1N; blank correction for effect of 2,5-dihydroanisole). No uptake of the oxidant was observed. The remainder of the reaction mixture was

diluted with chloroform, dried, and evaporated (water pump; steam bath) to give an oil (149 mg.) consisting mainly of a ketone (infrared spectrum). Further concentration gave an oil, ν_{max} . 3500, 3400, 1677, 1597 cm^{-1} . This (34 mg.), after treatment with acetic anhydride at room temp. for 2 hr., was recovered unchanged (infrared spectrum).

Procedure B.

The above experiment was repeated at 10-20°, an ethereal solution of cyclohexanespiro-3'-(oxaziridine) being kept at the same temp. as a control. The amount of oxidant in each solution did not decrease during 15 hr. (titration).

Picryl Chloride.

Picryl chloride was made by the method of Brady and Horton.⁴⁸

Picryl Azide.

Picryl azide was made and recrystallised as described by Schrader.⁴⁹ The dry compound was then dissolved in benzene and the solvent evaporated below 39° (water pump). This process was repeated twice more. Finally, the azide was precipitated from benzene by addition of light petroleum. It then had m. p. 89-91° (decomp.) [lit.,⁴⁹ 93° (from ethanol)] and was free from

ethanol (n.m.r. and infrared control).

Reaction between picryl azide and 2,5-dihydroanisole.

Procedure A.

Picryl azide (354 mg; free from ethanol) was added to 2,5-dihydroanisole (6 ml.; dry and free from ethanol) and the mixture stirred in the dark (nitrogen atmosphere). Gas was evolved briskly, a red colour developed, and the homogeneous mixture became warm. The mixture was cooled and kept at room temp. for 20 hr. by which time a yellow precipitate had formed. [A portion of the supernatant liquid was evaporated (oil pump; room temp.) and the residue found to contain no azide (infrared spectrum).] The mixture was filtered and the solid washed with light petroleum, dried (protection from light), and chromatographed over alumina with benzene to give N-(3-methoxycyclohex-2-enylidene)picrylamine (46) (312 mg.), m. p. 158-162°, $\lambda_{\text{max.}}$ (ethanol) 253, 323 m μ , $\nu_{\text{max.}}$ 1640, 1615, 1592, 1340 cm.⁻¹ The n.m.r. spectrum showed signals at (τ values): 1.02 (singlet, 2 protons), 4.60 (singlet, 1 proton), 6.23 (singlet, 3 protons), 7.52 (centre of multiplet, 4 protons), 7.93 (centre of multiplet, 2 protons). An analytical specimen, prepared by recrystallising a sample 4 times from methanol (no decomposition;

infrared control), was homogeneous as judged by t.l.c. (alumina; benzene; iodine) and had m. p. 150-157° and λ_{max} . (ethanol) 253, 323 m μ (ϵ 24,060, 15,330); (Found: C, 46.30; H, 3.56; N, 16.42. $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}_7$ requires C, 46.41; H, 3.60; N, 16.66%).

Procedure B.

Picryl azide (267 mg.; free from ethanol) was dissolved in a solution of 2,5- dihydroanisole (234 mg.; free from ethanol) in chloroform (ca. 20 ml.; dry and stabilised by methanol). The mixture was refluxed in the dark until the azide had reacted (3.6 hr.; infrared control) and the solvent was removed in vacuo. The residue was chromatographed over alumina with benzene to give N-(3-methoxycyclohex-2-enylidene)picrylamine as yellow crystals (186 mg.; from methanol), m. p. 156-159°. An authentic sample, made by Procedure A, had m. p. 156-160°. The mixed m. p. was 155-160° and the identity of both samples was further shown by a comparison of their infrared spectra (Nujol).

Chemical proof for the structure N-(3-methoxycyclohex-2-enylidene)picrylamine (46).

Hydrochloric acid (6N; 5 drops) was added to a solution of N-(3-methoxycyclohex-2-enylidene)picrylamine (60 mg.) in dioxan (4 ml.). The mixture was

kept at 80° for 8 hr. [disappearance of starting material followed by t.l.c. (silica; ethyl acetate:acetic acid:: 9:1; sulphuric acid)], evaporated to small bulk, saturated with sodium chloride, and extracted with chloroform.

The extract was dried and evaporated, and the residue (61 mg.) chromatographed over silica gel with chloroform. Picramide (18 mg.), identified by comparison [m. p.; mixed m. p.; infrared spectrum (Nujol)] with an authentic sample, was obtained. Further elution with ethyl acetate — acetic acid (9:1) gave pure (t.l.c.; silica; ethyl acetate:acetic acid::9:1; iodine) dihydro-resorcinol. This (10 mg.), in saturated aqueous sodium hydrogen carbonate (1 ml.) and water (0.5 ml.), was treated at 0° with a solution (3°) of benzenediazonium chloride [0.3 ml.; made from aniline (933 mg.) in hydrochloric acid (6N; 10 ml.), and sodium nitrite (759 mg.) in water (3 ml.) followed by treatment with urea and excess sodium hydrogen carbonate]. The precipitate was chromatographed over alumina with chloroform to give the pure (t.l.c.; alumina; chloroform) azo-dye (9 mg.). This had m. p. 134-143° (from cyclohexane). An authentic sample melted at 135-143° (from cyclohexane) and the mixed m. p. was 135-143°. Identity was established by comparing the infrared

spectra (chloroform and Nujol) of both samples.

Resorcinol dimethyl ether.⁵⁰

Resorcinol (110 g.) was dissolved at ca. 30° in a solution of sodium hydroxide (160 g.) in water (500 ml.). Dimethyl sulphate (378 ml.) was then added, the reaction mixture being stirred vigorously (Hershberg stirrer) and kept below 45° during the addition and for 1 hr. afterwards. The mixture was extracted with ether, the extract washed with conc. aqueous ammonia, with aqueous sodium hydroxide (4N), dried, and distilled (water pump) to give the dimethyl ether (87 g.). The n.m.r. spectrum showed signals at (τ values): 2.84 (centre of multiplet, 1 proton), 3.50 (centre of multiplet, 3 protons), 6.28 (singlet, 6 protons).

2,5-Dihydroresorcinol dimethyl ether.

2,5-Dihydroresorcinol dimethyl ether made by the method described in the literature,⁵¹ dried over anhydrous potassium carbonate, distilled (water pump), and stored under nitrogen had $\nu_{\max}$. (film) 1699, 1667 cm.⁻¹ The n.m.r. spectrum showed signals at (τ values): 5.33 (centre of multiplet, 2 protons), 6.43 (singlet, 6 protons), 7.18 (centre of multiplet, 4 protons).

N-Iododimethylamine.⁵²

Iodine (7.6 g.) dissolved in water (20 ml.) containing potassium iodide (10 g.) was added with stirring to a cold (-5 to -1°) solution of dimethylamine hydrochloride (2.4 g.) in water (20 ml.) containing sodium hydroxide (2.4 g.). The mixture was protected from light, stirred for 10 min. at 0° and filtered. The yellow precipitate was washed with ice-cold water and dried at ca. 5° in vacuo, first over anhydrous calcium chloride and then over sodium hydroxide (protection from light). The product (6.4 g.) decomposed rapidly at room temp. but could be kept for several days in a refrigerator. N-Iododimethylamine has $\lambda_{\text{max.}}$ (tetrahydrofuran) 368, 294 m μ .

Photolysis of N-iododimethylamine in the presence of 2,5-dihydroresorcinol dimethyl ether.

N-Iododimethylamine (800 mg.) was added to 2,5-dihydroresorcinol dimethyl ether (282 mg.) in dry tetrahydrofuran (100 ml.). The solution was kept in an ice bath and irradiated with a tungsten lamp (300 W) (nitrogen atmosphere). A mixture with the same initial composition as that irradiated was kept in an ice bath in the dark as a control.

Samples were withdrawn periodically from each mixture and treated with acidified potassium iodide solution. Liberated iodine was determined by titration and it was found that the titers for the reaction mixture and the control remained constant during 2.3 hr. The reaction mixture was evaporated (oil pump; room temp.) to leave an oily residue (711 mg.), $\nu_{\text{max.}}$ 1600 (strong) cm.^{-1} . A portion of this oil, in chloroform, was extracted with hydrochloric acid (6N). The material obtained by evaporation of the aqueous extract was probably dimethylamine hydrochloride [singlet at ca. 7τ in n.m.r. spectrum (deuterium oxide)].

Photolysis of N-iododimethylamine in the presence of cyclohexene.

Procedure A.

A solution of N-iododimethylamine and excess cyclohexene in dry tetrahydrofuran (nitrogen atmosphere) was irradiated with a tungsten lamp (300 W). No reaction occurred (titration) during 2.75 hr. at $5-10^{\circ}$ or during a further period (ca. 15 hr.) at 16° . The mixture was concentrated (atmospheric pressure) and acid-soluble material isolated. No (substituted) cyclohexylamine was obtained (n.m.r. spectrum).

Procedure B.

The photolysis was repeated using a high-pressure mercury lamp. The temp. of the reaction mixture, initially 0°, rose slowly to 50°. After 2.75 hr. acid-soluble material was isolated but no (substituted) cyclohexylamine was present (n.m.r. spectrum).

Treatment of 2,5-dihydroresorcinol dimethyl ether with iodine isocyanate.

Iodine (1.27 g.; finely powdered) was added in a single portion to a vigorously stirred mixture of 2,5-dihydroresorcinol dimethyl ether (750 mg.) and silver isocyanate (1 g.) in dry ether (10 ml.) at -5° (nitrogen atmosphere; protection from light). After 1.75 hr. at -5 to 0° the mixture was concentrated and the residue taken up in ethanol (ca. 10 ml.), refluxed for 1.75 hr., and left overnight at room temp. No isocyanate was now present (infrared spectrum). The solution was concentrated, washed with aqueous sodium thiosulphate and extracted with ether. The extract was dried and evaporated. The residue (572 mg.) had ν_{max} . (carbon tetrachloride) 3520, 3450, 1734, 1600 (strong) cm^{-1} and the n.m.r. spectrum showed signals due to methoxyl, ethoxyl, and aromatic protons. No pure compound could be isolated by chromatography over

alumina with benzene.

Treatment of 2,5-dihydroresorcinol dimethyl ether with N-iododimethylamine and silver oxide.

N-Iododimethylamine (850 mg.) was added in one batch to a solution of 2,5-dihydroresorcinol dimethyl ether (700 mg.) in dry tetrahydrofuran (100 ml.) cooled in an ice bath (nitrogen atmosphere; protection from light). Silver oxide (2.5 g.; freshly prepared) was added and the mixture stirred vigorously for 4 hr. Stirring was continued at room temp. for 28 hr. by which time no halo-amine was present (titration). The mixture was filtered through Celite and evaporated below 42°. The residue (594 mg.) was mainly 2,5-dihydroresorcinol dimethyl ether but aromatic material was also present (infrared and n.m.r. spectra).

N-Chlorodimethylamine.

N-Chlorodimethylamine, made as described by Berg,⁵³ was kept at ca. 5° and had ν_{max} . (carbon tetrachloride) 3000-2780 (series of sharp bands), 1470, 1445, 1436, 1185, 1150, 1010, 920 cm^{-1}

Treatment of 2,5-dihydroresorcinol dimethyl ether with N-chlorodimethylamine and silver oxide.

This reaction was carried out as described for the corresponding experiment with N-iododimethylamine.

Starting material was recovered (infrared and n.m.r. spectra).

Reaction between N-chlorodimethylamine, silver trifluoroacetate, and 2,5-dihydroresorcinol dimethyl ether.

Procedure A.

2,5-Dihydroresorcinol dimethyl ether (1.7 g.) in dry ether (ca. 20 ml.) was cooled in an ice bath and stirred with silver trifluoroacetate⁵⁴ (1.147 g.) (protection from light), the reaction flask flushed with nitrogen and closed with a serum cap. N-Chlorodimethylamine (402 mg.; freshly distilled) in dry ether (ca. 2 ml.) was injected slowly and the mixture stirred in the ice bath for 20 min. By this time a yellow precipitate had formed and most of the halo-amine had reacted (starch-iodide paper). After 10 min. at room temp. the mixture began to darken rapidly. It was filtered (Celite) and the filtrate stored under nitrogen for 50 hr. at ca. 5° (protection from light). The resulting clear liquid was decanted from a few droplets of reddish oil, dried, and evaporated (steam bath, 1 atmosphere; water pump, room temp.). The blue residue (1.35 g.) had $\nu_{\max}$. 2850, 1700, 1665, 1605 (strong), 1150 cm^{-1} and its n.m.r. spectrum defined the composition as a fairly clean mixture of 2,5-dihydro-

resorcinol dimethyl ether and resorcinol dimethyl ether in the molar ratio of 62:37.

The reddish oil contained aromatic material (strong infrared absorption at 1608 cm.^{-1}).

In a control experiment N-chlorodimethylamine did not react (volumetric assay) with silver trifluoroacetate in ether, either at -10° for 10 min. or at room temp. for 14 hr.

Procedure B.

The reaction was repeated using aqueous tetrahydrofuran as solvent. The halo-amine was not all consumed during 1 hr. at ice-bath temp., but after an overnight reaction-period at room temp., the mixture had no oxidising power. Work-up as above afforded an oil which had $\nu_{\text{max.}}$ (film) $1603\text{ (strong) cm.}^{-1}$

Treatment of cyclohexene with N-chlorodimethylamine and silver trifluoroacetate.

A mixture of N-chlorodimethylamine (400 mg.), silver trifluoroacetate (1.4 g.), cyclohexene (431 mg.; distilled from sodium) in dry ether (54 ml.) was stirred under nitrogen for 15 min. and refluxed overnight (protection from light). By this time about half of the original charge of halo-amine was still present (titration). The mixture was filtered, extracted with

hydrochloric acid (6N) and the aqueous extract evaporated. The residue showed only a singlet at ca. 7.1τ in its n.m.r. spectrum (deuterium oxide).

Treatment of 2,5-dihydroresorcinol dimethyl ether with N-iododimethylamine and silver trifluoroacetate.

N-Iododimethylamine (855 mg.) was stirred under nitrogen with a cold ($0-5^{\circ}$) solution of 2,5-dihydroresorcinol dimethyl ether (760 mg.) in dry tetrahydrofuran (100 ml.) until about half had dissolved. Then, silver trifluoroacetate (1.74 g.) in dry tetrahydrofuran (20 ml.) was added over 30 min. A precipitate formed at the beginning of the addition, and 2 hr. later, ca. 97% of the halo-amine had reacted (titration). The solution was filtered and evaporated (atmospheric pressure, below 85° ; water pump, room temp.). The blue residue had $\nu_{\max}$. 1600 (strong) cm^{-1} and its n.m.r. spectrum confirmed the presence of a substantial quantity of aromatic material.

N,N-Dimethylhydroxylamine hydrochloride

N,N-Dimethylhydroxylamine hydrochloride was prepared by the method of Org.Synth.⁵⁵ and stored in vacuo over potassium hydroxide.

N,N-Dimethyl-O-tosylhydroxylamine (48).

Treatment of N,N-dimethylhydroxylamine hydrochloride with tosyl chloride in dry pyridine led to no useful result.^{21b}

Procedure A.

N,N-Dimethylhydroxylamine (2 moles; prepared from the hydrochloride in acetonitrile by addition of 1 equivalent of triethylamine, dilution with ether, and removal of the triethylamine hydrochloride) gave the required tosylate when treated with tosyl chloride (1 mole) at 0° for 3.75 hr. and then at room temp. for 3 hr. The product was isolated by washing the reaction mixture with water and evaporating the dried organic solution.

The following method is simpler and was used routinely.

Procedure B.

N,N-Dimethylhydroxylamine hydrochloride (1.074 g.) was dissolved in boiling chloroform (250 ml.; distilled from phosphorus pentoxide). The solution was cooled to room temp. and triethylamine (2.228 g.) in purified chloroform (6 ml.) added. The mixture was stirred and cooled in an ice bath during dropwise addition of a solution of dry tosyl chloride (1.906 g.) in pure

chloroform (15 ml.). The solution was stirred overnight in the dark at room temp., washed with water (40 ml.) and evaporated at room temp. The product (1.305 g.) was stored in a refrigerator in vacuo over calcium chloride but decomposed slowly. It was repurified by chromatography over silica gel with ethanol-free chloroform. Removal of the solvent at room temp. gave the pure (t.l.c.; silica; chloroform; iodine) compound.

N,N-Dimethyl-O-tosylhydroxylamine has ν_{max} . (carbon tetrachloride) 1600, 1380, 1190, 1180 cm^{-1} . It can be recrystallised, though with high losses due to thermal decomposition, from light petroleum or cyclohexane. An analytical sample (from cyclohexane) melted mainly at 87-89° but traces of solid remained till ca. 104°.

(Found: C, 50.60; H, 6.67; N, 6.44; S, 15.53.

$\text{C}_9\text{H}_{13}\text{NO}_3\text{S}$ requires C, 50.21; H, 6.09; N, 6.51; S, 14.89%).

The n.m.r. spectrum showed signals at (τ values):

2.03-2.70 (multiplet, 4 protons), 7.37 (singlet, 6 protons), 7.55 (singlet, 3 protons).

For comparison, N,N-dimethyl-p-toluenesulphonamide⁵⁶ was prepared. Its infrared and n.m.r. spectra are different from those recorded above.

Treatment of 2,5-dihydroresorcinol dimethyl ether with N,N-dimethyl-O-tosylhydroxylamine.

When an excess of 2,5-dihydroresorcinol dimethyl ether in benzene was treated at room temp. with N,N-dimethyl-O-tosylhydroxylamine (nitrogen atmosphere; protection from light) aromatisation of the enol ether took place (n.m.r. spectrum) and formation of a new substance was observed by t.l.c. (silica; chloroform; sulphuric acid). The new material could not be obtained pure: the best sample had $\nu_{\max}$. (carbon tetrachloride) 1720, 1670, 1610 cm^{-1} , $\lambda_{\max}$. (ethanol) ca. 238 m μ , $\lambda_{\max}$. (after addition of dilute hydrochloric acid) ca. 251 m μ . The n.m.r. spectrum showed a number of signals that may represent methyl groups bonded to oxygen and/or nitrogen.

3,3-Diethoxy-5 α -cholestane.

5 α -Cholestan-3-one⁵⁷ was converted into 3,3-diethoxy-5 α -cholestane by the method of Serini and Koster.⁵⁸

3-Ethoxy-5 α -cholest-2-ene (49).^{58, 59}

A crystal of p-toluenesulphonic acid and a boiling stone were added to 3,3-diethoxy-5 α -cholestane (2.19 g.) heated to 160° in vacuo (oil pump) in a long-necked flask. The temp. was raised slowly to 240°. When the reaction was over (ca. 70 min.; infrared and t.l.c. control) the

melt was cooled to ca. 110° and dry triethylamine (several drops) added. The mixture was cooled, taken up in ether, and washed with saturated aqueous sodium hydrogen carbonate. The ether extract was concentrated and diluted with methanol containing a trace of pyridine to give crystalline 3-ethoxy- 5α -cholest-2-ene (1.7 g.), m. p. $75-85^{\circ}$. The compound was stored over sodium hydroxide. Examination by t.l.c. (alumina; light petroleum; iodine) showed a trace of a polar impurity. Pure material (obtained by chromatography over alumina with light petroleum) had m. p. $85-89^{\circ}$ (from di-isopropyl ether) [lit.,⁵⁸ $87-88^{\circ}$ (from ethanol)] and $\nu_{\max}$. (film). 1670 cm.^{-1}

Treatment of 3-ethoxy- 5α -cholest-2-ene with N,N-dimethyl-O-tosylhydroxylamine.

Procedure A.

Treatment of the steroidal enol ether (49) with N,N-dimethyl-O-tosylhydroxylamine in benzene (nitrogen atmosphere) resulted in formation of 5α -cholestan-3-one [infrared spectrum; t.l.c. (alumina; benzene; sulphuric acid)] and 3,3-diethoxy- 5α -cholestane [infrared spectrum; t.l.c. (alumina; light petroleum; iodine); n.m.r. spectrum].

Procedure B.

The reaction was repeated in the presence of sodium hydride (nitrogen atmosphere; stirring). After ca. 15 hr. at room temp. some of the tosylate was still present (t.l.c.; silica; chloroform; iodine) and little, if any, ketal had been formed (t.l.c.; alumina; light petroleum; iodine). The enol ether was recovered (m. p.; mixed m. p.; infrared spectrum).

Procedure C.

The reaction was carried out as for Procedure B but quartz apparatus was used and the mixture irradiated for 7 hr. with a high-pressure mercury lamp. The enol ether was not attacked (t.l.c.) and was recovered (m. p.; mixed m. p.; t.l.c.).

Action of base on N,N-dimethyl-O-tosylhydroxylamine

Diethylamine (ca. 4 ml.) was added to a solution of N,N-dimethyl-O-tosylhydroxylamine (138 mg.) in benzene (ca. 1 ml.). After 14 hr. the salt of diethylamine and p-toluenesulphonic acid (m. p.; mixed m. p.; infrared spectrum) was filtered off, the filtrate acidified with hydrochloric acid (6N) and steam distilled. The vapours were passed into a saturated aqueous solution of dimedone and formaldehyde dimedone derivative (26 mg.) was obtained (m. p.; mixed m. p.).

In a separate experiment the reaction mixture was examined for the presence of the tosylate before removal of the amine salt. No tosylate was present (t.l.c.; silica; chloroform; iodine).

Reaction of N,N-dimethyl-O-tosylhydroxylamine with Grignard reagents.

A. Phenylmagnesium bromide.

A suspension of N,N-dimethyl-O-tosylhydroxylamine (295 mg.) in ether was added to a stirred, ether solution of phenylmagnesium bromide [from magnesium (400 mg.) and phenyl bromide (1.8 ml.)]. After 10 min. at room temp. excess of Grignard reagent was destroyed with water, and the mixture diluted with aqueous sodium hydrogen carbonate and extracted with ether. The organic extract was washed with hydrochloric acid (6N) and the aqueous solution evaporated to leave N,N-dimethylaniline hydrochloride (124 mg.) identified by comparison (infrared spectrum) with an authentic sample.

The free base (82 mg.), liberated by treatment with aqueous sodium hydrogen carbonate, was treated with picric acid in ethanol to give N,N-dimethylaniline picrate (m. p.; mixed m. p.; infrared spectrum).

B. Cyclohexylmagnesium bromide.

N,N-Dimethyl-O-tosylhydroxylamine (311 mg.) in ether (ca. 15 ml.) was added dropwise to a stirred, ether solution of cyclohexylmagnesium bromide [from magnesium (500 mg.) and cyclohexyl bromide (3.265 g.)]. A thick, white precipitate formed, but dissolved within 10 min. At this stage the mixture was worked up as described above. The crystalline hydrochloride (35 mg.) showed signals in its n.m.r. spectrum (deuterium oxide) at (τ values): 7.0 (singlet, 6 protons), 7.5-9.2 (broad envelope, 11 protons). The structure was confirmed by comparison [m. p.; mixed m. p.; infrared spectrum (Nujol)] with an authentic sample.⁶⁰

Attempted reaction between sodium 2,6-di-*t*-butylphenoxide and N,N-dimethyl-O-tosylhydroxylamine.

Sodium hydride (148 mg.; 50% ^w/w oil suspension) was added to a stirred solution of 2,6-di-*t*-butylphenol (623 mg.) in dry tetrahydrofuran (nitrogen atmosphere). When hydrogen evolution ceased, N,N-dimethyl-O-tosylhydroxylamine (292 mg.) in dry tetrahydrofuran (ca. 10 ml.) was added dropwise over 5 min. The mixture became brown and a sludge (crystalline?) was deposited. After 25 min. the colour appeared to be darkening. The mixture was diluted with water, concentrated at room temp. and

extracted with ether. The organic solution was washed with hydrochloric acid (6N; 1X5, 1X15 ml.), dried, and evaporated. The residue (600 mg.) was mainly 2,6-di-*t*-butylphenol [infrared spectrum; t.l.c. (alumina; benzene; iodine)].

The aqueous extract was made basic (sodium hydrogen carbonate) and extracted with ether. The organic solution was dried and evaporated to give an oil (30 mg.) which contained 2 major components (t.l.c.; silica; chloroform; iodine).

N,N-Dimethyl-O-mesylhydroxylamine (50).

N,N-Dimethylhydroxylamine hydrochloride (215 mg.) was dissolved in hot chloroform (ca. 50 ml.; distilled from phosphorus pentoxide). Triethylamine (445 mg.; distilled from sodium) in a little (purified) chloroform was added to the cooled (0°), stirred solution (nitrogen atmosphere). Mesyl chloride (0.16 ml.; freshly distilled) in (purified) chloroform (10 ml.) was added dropwise over ca. 10 min. and the mixture kept overnight in the dark at ca. 3°. The solution was washed with water (30 ml.), dried, and evaporated below room temp. The residue (203 mg.), when kept at 0° in vacuo (oil pump) for 3 hr., crystallised slowly as colourless needles which melted below 25°.

N,N-Dimethyl-O-mesylhydroxylamine has $\nu_{\max}$. 2900, 2810 (shoulder), 2790 (shoulder) cm^{-1} . The n.m.r. spectrum showed that the compound contained a small amount of impurity but the sharp singlets at (τ values): 6.90 (3 protons) and 7.09 (6 protons) are compatible with the required structure.

N,N-Dimethyl-methanesulphonamide⁶¹ has different spectral (infrared and n.m.r.) characteristics from the O-mesylate.

Treatment of 3-ethoxy-5 α -cholest-2-ene with N,N-dimethyl-O-mesylhydroxylamine.

3-Ethoxy-5 α -cholest-2-ene (171 mg.) was dissolved in a solution of N,N-dimethyl-O-mesylhydroxylamine (203 mg.) in dry benzene (ca. 2 ml.) and the mixture was stirred at room temp. overnight (nitrogen atmosphere). At this stage hardly any enol ether remained (t.l.c.; alumina; benzene; iodine). The mixture was treated with triethylamine (several drops), poured into water, and extracted with ether. The extract was dried and evaporated below 50°. The residue (188 mg.) had $\nu_{\max}$. (carbon tetrachloride) 1710 (weak), 1675 (weak) cm^{-1} [Cf. 3-Ethoxy-5 α -cholest-2-ene has $\nu_{\max}$. (carbon tetrachloride) 1670 cm^{-1}]. The total product was chromatographed over

alumina, first with benzene and then with benzene-chloroform mixtures. Fractions were obtained rich in 3,3-diethoxy-5 α -cholestane [infrared spectrum; t.l.c. (alumina; benzene; sulphuric acid)] and in 5 α -cholestan-3-one [infrared band at 1712 cm.⁻¹ (carbon tetrachloride); t.l.c. (alumina; benzene; sulphuric acid)]. Further elution with chloroform gave a complex (t.l.c.) oil (24 mg.) with ν_{max} . (carbon tetrachloride) 1680 cm.⁻¹. This fraction did not have λ_{max} . (ethanol) 233 m μ and an attempt²³ to obtain a 2,4-dinitrophenylhydrazone gave none of the derivative of 5 α -cholest-1-ene-3-one (t.l.c.).

Xanthen-9-carboxylic acid chloride.⁶²

A solution of xanthen-9-carboxylic acid (3 g.) in purified⁶³ thionyl chloride (ca. 25 ml.) was refluxed for 2 hr. and evaporated. The residue was taken up in dry, light petroleum, filtered, and cooled (0°). Crystalline xanthen-9-carboxylic acid chloride (2.3 g.), m.p. 87-92°, ν_{max} . (carbon tetrachloride) 1776 cm.⁻¹ was obtained and stored in the dark.

N,N-Dimethyl-O-(xanthen-9-carbonyl)hydroxylamine (53).

Xanthen-9-carboxylic acid chloride (490 mg.) was stirred for 5 min. with an ice-cold solution of N,N-dimethylhydroxylamine hydrochloride (197 mg.) in

dry pyridine (3 ml.). Stirring was continued at room temp. for 1.5 hr. (protection from light). The solution was poured into a mixture of ice and hydrochloric acid (1N), and extracted with ether. The organic solution was washed with ice-cold aqueous sodium hydroxide (1N) and then with water. The solution was dried and evaporated below 40° to give the crude product (403 mg.), $\nu_{\max}$. (carbon tetrachloride) 1749 cm^{-1} T.l.c. (silica; chloroform; iodine) revealed only trace impurities. Recrystallisation from light petroleum afforded purer material (304 mg.), m. p. $60-63^{\circ}$, $\lambda_{\max}$. (ethanol) 208, 250, 283, 287, 290 m μ . The n.m.r. spectrum showed signals at (τ values): 2.81 (centre of multiplet), 5.05 (singlet, 1 proton), 7.39 (singlet, 3 protons). In the mass spectrum ions occurred at (m/e values): 269 (molecular ion), 225, 181 (base peak), 152. An analytical sample of N,N-dimethyl-O-(xanthen-9-carbonyl)hydroxylamine (53) had m. p. $65.5-66.5^{\circ}$ (from light petroleum). (Found: C, 71.09; H, 5.73; N, 5.51. $C_{16}H_{15}NO_3$ requires C, 71.36; H, 5.61; N, 5.20%). Photolysis of N,N-dimethyl-O-(xanthen-9-carbonyl)hydroxylamine (53) in cyclohexane.

N,N-Dimethyl-O-(xanthen-9-carbonyl)hydroxylamine (134 mg.) in boiling cyclohexane (ca. 50 ml.; distilled

from sodium) was irradiated for 3 hr. in quartz apparatus with a high-pressure mercury lamp. During this time a stream of dry nitrogen (free from carbon dioxide) was passed through the reaction mixture and the exit gases were led through two wash bottles containing aqueous barium hydroxide. (The contents of the second wash bottle remained clear throughout the reaction.) The photolysis solution was cooled, decanted from a small amount of insoluble material, diluted with ether, extracted with hydrochloric acid (1N; 1x10, 2x5 ml.), dried, and evaporated. The residue (116 mg.), which contained no starting material (infrared spectrum), was chromatographed over alumina with benzene and then had $\nu_{\text{max.}}$ 1487, 1467 cm.^{-1} , $\lambda_{\text{max.}}$ (ethanol) 210, 240, 286 $\text{m}\mu$. Fractional sublimation and recrystallisation from ethanol afforded material containing only trace impurities (t.l.c.; alumina; light petroleum; sulphuric acid). The n.m.r. spectrum in carbon tetrachloride showed signals at (τ values): 2.97 (broad singlet, 8 protons), ca. 6.3 (broad singlet, 1 proton), 8.2-9.3 (broad envelope, 11 protons). Further chromatography over alumina with light petroleum (distilled) gave pure (t.l.c.) 9-cyclohexylxanthen (13 mg.), m. p. 106.5-108° (from ethanol). (Found: C, 86.64; H, 7.63. $\text{C}_{19}\text{H}_{20}\text{O}$ requires C, 86.32;

H, 7.63%). Barium carbonate (286 mg.) was obtained from the first wash bottle.

Photolysis of N,N-dimethyl-O-(xanthen-9-carbonyl)hydroxylamine in the presence of 3-ethoxy-5 α -cholest-2-ene.

Procedure A.

A refluxing solution of N,N-dimethyl-O-(xanthen-9-carbonyl)hydroxylamine (137 mg.) and 3-ethoxy-5 α -cholest-2-ene (211 mg.) in carbon tetrachloride (ca. 45 ml.; distilled from phosphorus pentoxide) was irradiated with a high-pressure mercury lamp (200 W) in quartz apparatus (nitrogen atmosphere). When all the ester had reacted [infrared and t.l.c. control (alumina; benzene; sulphuric acid)], the mixture was evaporated to give a residue which had an infrared band at 1680 cm.⁻¹ and showed this same absorption after being treated with dilute hydrochloric acid. Chromatography of a portion of the photolysis product over alumina afforded an oil (17 mg.) with $\nu_{\text{max.}}$ 1757 (weak), 1723 (medium), 1680 (strong) cm.⁻¹, $\lambda_{\text{max.}}$ (ethanol) 230 m μ . This fraction was taken up in acetic acid and heated for 5 min. with 2,4-dinitrophenylhydrazine (9 mg.) (nitrogen atmosphere). The solution was cooled and a crystalline solid (3 mg.) separated. It had $\lambda_{\text{max.}}$ (chloroform) 382-388 m μ . (Values within

this range were obtained in successive measurements). Comparison (t.l.c.; benzene: light petroleum::2:5) with an authentic sample²³ of the 2,4-dinitrophenylhydrazone of 5 α -cholest-1-ene-3-one [λ_{max} . (chloroform) 382 m μ] revealed the presence of this compound in the above crystalline solid. Another (minor) component was also present.

The combined fractions from the chromatography showed no signals in their n.m.r. spectrum attributable to a dimethylamino-group.

Procedure B.

A melt (80-90 $^{\circ}$) of the enol ether (206 mg.) and the ester (140 mg.) was irradiated in quartz apparatus with a high-pressure mercury lamp (nitrogen atmosphere). After 70 min. all the ester had reacted and the mixture had ν_{max} . (carbon tetrachloride) 1669 cm.⁻¹ A portion of the oil was treated with 2,4-dinitrophenylhydrazine in acetic acid, and the total product examined by t.l.c. (alumina; benzene). The major component corresponded in R_f and colour to the 2,4-dinitrophenylhydrazone²³ of 5 α -cholestan-3-one.

The remainder of the photolysis mixture (195 mg.) was chromatographed over alumina (40 g.). 3-ethoxy-5 α -cholest-2-ene was obtained by elution with light

petroleum [infrared spectrum; t.l.c. (alumina; light petroleum; iodine)]. Further elution with benzene afforded two fractions, A (17.4 mg.), and B (19.2 mg.). Both consisted, essentially, of the same two components, but in different proportions (t.l.c.; alumina; benzene; iodine).

Fraction A had $\nu_{\max}$. (carbon tetrachloride) 1666, 1615, 1610 cm^{-1} , $\lambda_{\max}$. (chloroform) 238, 263, 287, 345 μ (unchanged by dilute hydrochloric acid), $[\alpha]_D +0.64$ (c 1.8 in chloroform). [Xanthone has $\lambda_{\max}$. (chloroform) 247, 263, 287, 344 μ .] The n.m.r. spectrum showed signals at (τ values): 1.6 (centre of doublet), 2.6 (centre of multiplet), 7.92 (singlet). A high-field envelope, probably of steroidal origin, was also present.

The infrared spectrum of fraction B was similar to that of fraction A. Sublimation of fraction B afforded oily crystals m. p. 54-65°. T.l.c. (alumina; benzene) showed two components, one having the same R_f and colour (sulphuric acid) as xanthone. The mass spectrum showed a molecular ion with mass 239.094277. Mass calculated for $\text{C}_{15}\text{H}_{13}\text{NO}_2$ (a dimethylaminoxanthone): 239.094623.

Reaction between 4-(1-cyclohex-1-enyl)morpholine and
N,N-dimethyl-O-tosylhydroxylamine.

N,N-Dimethyl-O-tosylhydroxylamine (207 mg.) was dissolved in a stirred solution of 4-(1-cyclohex-1-enyl)-morpholine⁶⁴ (329 mg.) in dry benzene (ca. 4 ml.) (nitrogen atmosphere). After ca. 15 hr. the mixture was diluted with ether, extracted with hydrochloric acid (6N), and the aqueous layer evaporated. The residue had $\nu_{\max}$. 1708 cm^{-1} and the ketonic component was isolated in fairly pure form as a crystalline 2,4-dinitrophenylhydrazone (23 mg.), $\nu_{\max}$. 3320, 2850, 2800, 1620 cm^{-1} . A good n.m.r. spectrum could not be obtained but the trace suggested that the compound was 2-(4-morpholinomethyl) cyclohexanone 2,4-dinitrophenylhydrazone. Recrystallisation of the compound gave material (14 mg.) m. p. 150-155°, $\lambda_{\max}$. (ethanol) 365 m μ . The mass spectrum showed a molecular ion at m/e 377 and the infrared spectrum was identical with that of an authentic sample of 2-(4-morpholinomethyl)cyclohexanone 2,4-dinitrophenylhydrazone.

2-(4-Morpholinomethyl)cyclohexanone 2,4-dinitro-phenylhydrazone

The method of Harradence and Lions⁶⁵ was used to prepare 2-(4-morpholinomethyl)cyclohexanone. The 2,4-dinitrophenylhydrazone had m. p. 154-158° (from ethanol). An analytical sample was prepared by recrystallising the compound from ethyl acetate. (Found: C, 54.23; H, 6.42; N, 18.52. $C_{17}H_{23}N_5O_5$ requires C, 54.11; H, 6.14; N, 18.56%). The compound was identical [infrared spectrum; t.l.c. (alumina; benzene)] with the sample described above.

Photolysis of ethylazidoformate in the presence of 3-ethoxy-5 α -cholest-2-ene.

A solution of 3-ethoxy-5 α -cholest-2-ene (200 mg.) in ethylazidoformate (ca. 3 ml.) was irradiated in quartz apparatus with a low-pressure mercury lamp (nitrogen atmosphere). After 4 hr. no enol ether was present (infrared spectrum). The mixture was taken up in ethanol and hydrochloric acid (6N; several drops) added. After 2 hr. the solution was poured into saturated aqueous sodium hydrogen carbonate and extracted with ether. The extract was dried and evaporated. A portion of the residue (196 mg.) in carbon tetrachloride was left for several hr. White crystals (18 mg.) were deposited. They had $\nu_{\max}$. 3420, 1730 cm^{-1}

but were obviously non-steroidal (no significant absorption at ca. 3000 cm.^{-1}).

The remainder of the total product (211 mg.) was chromatographed over alumina with chloroform and the major (by weight) fraction rechromatographed (alumina; benzene). In this way an essentially pure oil (5 mg.) was obtained. It had $\nu_{\text{max.}}$ (carbon tetrachloride) 3380 (sharp), 2940 (strong), 1727 (strong), 1677 (strong) cm.^{-1} . The mass spectrum showed a molecular ion at m/e 516 and an abundant ion at m/e 471 (loss of $\text{C}_2\text{H}_5\text{O}$ from molecular ion).

6,7-Dihydro-5-oxo-8-phenylnaphtho[1,8a,8-bc]furan (3).

The naphthofuran (2) was hydrogenated in benzene over Raney nickel (W-2)⁶⁶ as described previously¹ and the dihydronaphthofuran (3) purified by chromatography over alumina with benzene.

The hydrogenation can be carried out on a large scale [16 g. naphthofuran (2)] provided sufficient benzene is used to dissolve all the starting material at room temp.

6-2'-Formylbenzyl-5-oxo-8-phenylnaphtho[1,8a,8-bc]furan (7).

The aldehyde (7) was made as described previously,¹ but the reaction mixture was kept under nitrogen and protected from light.

6-[2-2'-(1',3'-Dioxolanyl)benzyl]-5-oxo-8-phenylnaphtho[1,8a,8-bc]furan (69).

The acetal (69) had been made previously in connection with ozonolysis experiments.¹ The procedure described here gives more satisfactory results.

A mixture of the aldehyde (7) (2 g.), p-toluenesulphonic acid monohydrate (13 mg.), ethylene glycol (10 ml.), and anhydrous benzene (250 ml.) was refluxed in the dark for 48 hr. with continuous removal of water (Soxhlet apparatus; thimble packed with calcium hydride). The mixture was cooled, diluted with

anhydrous triethylamine (ca. 2 ml.), poured into saturated aqueous sodium hydrogen carbonate, and extracted with ether. The extract was dried and evaporated to give the acetal (69) (2 g.; from benzene—light petroleum), m. p. 175–179°, $\nu_{\max}$. 1639 cm^{-1} . The n.m.r. spectrum showed signals at (τ values): 1.87–2.78 (multiplet), 3.92 (singlet, 1 proton), 5.72–6.13 (multiplet, 6 protons). Peaks occurred in the mass spectrum at (m/e values): 408 (molecular ion), 407 (ca. 14% of molecular ion), 380 (loss of C_2H_4 from molecular ion; $m^{\ddagger}$ 353.5), 162 (base peak).

6-[2-2'-(1',3'-Dioxolanyl)-3,5-dimethoxy-4-methoxycarbonyl-benzyl]-5-oxo-8-phenylnaphtho[1,8a,8-bc]furan (79).

The substituted aldehyde (55) had been made previously¹ and a crude sample was available.

The substituted aldehyde (55) (79 mg.), *p*-toluene-sulphonic acid monohydrate (several crystals), ethylene glycol (1 ml.), and anhydrous benzene (30 ml.) was refluxed for 48 hr. with continuous removal of water (Soxhlet apparatus; thimble packed with calcium hydride). The mixture was cooled, diluted with anhydrous triethylamine (ca. 1 ml.), poured into saturated aqueous sodium hydrogen carbonate, and extracted with ether. The extract was dried and evaporated, and the residue

chromatographed over alumina with benzene—chloroform to give the acetal (79) (46 mg.; from benzene—light petroleum). The compound has $\nu_{\text{max.}}$ 1723, 1637 cm.^{-1}
6-2'-Diacetoxymethylbenzyl-5-oxo-8-phenylhaphtho-
[1,8a,8-bc]furan (91).

Boron trifluoride etherate (40%; 1 drop) was added to a stirred, ice-cold solution of the aldehyde (7) (554 mg.) in dry benzene (10 ml.) and acetic anhydride (6 ml.). After 20 min. the mixture was removed from the cooling-bath and kept at room temp. for 1 hr. Boron trifluoride etherate (40%; 1 drop) was added and, after a further 1.7 hr. (stirring), all the aldehyde had reacted (infrared control). The mixture was poured into ice-cold water and extracted with dichloromethane. The extract was dried and evaporated to give the formyldiacetate (91) (571 mg.; from di-isopropyl ether), m. p. 171–174 $^{\circ}$, $\nu_{\text{max.}}$ (Nujol) 1751, 1632 cm.^{-1} . The n.m.r. spectrum showed signals at (τ values): 1.87–2.83 (multiplet), 5.82 (broad singlet, 2 protons), 8.02 (singlet, 6 protons). Peaks occurred in the mass spectrum at (m/e values): 364 [molecular ion of aldehyde (7)], 336 (loss of CO from parent ion; $m^{\pm}$ 310), 335 (loss of HCO from parent ion; $m^{\pm}$ 310). An analytical specimen had m. p. 172–175 $^{\circ}$ (from acetonitrile) and

λ_{max} . (chloroform) 267, 397 m μ (ϵ 14,470, 28,050).

(Found C, 74.86; H, 4.87. $\text{C}_{29}\text{H}_{22}\text{O}_6$ requires C, 74.67; H, 4.75%).

6-[2-2'-(1',3'-Dithiolanyl)benzyl]-5-oxo-8-phenylnaphtho-[1,8a,8-bc]furan (92).

Boron trifluoride etherate (40%; 0.5 ml.) was added to a stirred solution of the aldehyde (7) (509 mg.) in a mixture of dry benzene (20 ml.), acetic acid (30 ml.), and ethanedithiol (4 ml.) (protection from light). When all the aldehyde had reacted [t.l.c. control (silica; benzene:chloroform::5:2; sulphuric acid)] the mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The extract was dried and evaporated, and the residue chromatographed over silica gel with benzene—chloroform (protection from light) to give the thioacetal (92) (562 mg.; from dichloromethane—ethanol), m. p. 185-187.5, ν_{max} . (Nujol) 1633 cm^{-1} . The n.m.r. spectrum showed signals at (τ values): 1.84-2.87 (multiplet, 13 protons), 4.07 (singlet, 1 proton), 5.87 (centre of doublet, 2 protons, $J=1.25$ c./sec.), 6.62 (centre of multiplet, 4 protons). Peaks occurred in the mass spectrum at (m/e values): 440 (molecular ion), 379 (base peak). An analytical specimen had m. p.

183-185° (from dichloromethane — ethanol) and $\lambda_{\text{max.}}$ (chloroform) 266, 397 m μ (ϵ 15,260, 27,710).

Found: C, 73.30; H, 4.53; S, 14.71. $\text{C}_{27}\text{H}_{20}\text{O}_2\text{S}_2$

Requires C, 73.58; H, 4.58; S, 14.55%.

6-[2-bis-(2'-Hydroxyethylthio)methylbenzyl]-5-oxo-8-phenylnaphtho[1,8a,8-bc]furan (96).

Boron trifluoride etherate (40%; 2 drops) was added to a stirred solution of the aldehyde (7) (123 mg.) in anhydrous benzene (3 ml.) containing acetic acid (1 ml.) and β -mercaptoethanol (0.6 ml.) (protection from light). After 30 min. no aldehyde remained (t.l.c.; silica; benzene: chloroform::5:2; sulphuric acid). The mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The extract was dried and evaporated to give yellow crystals (119 mg.; from acetonitrile). This product contained two substances (t.l.c.; above system), and was chromatographed over silica gel with ethyl acetate (reagent grade) (protection from light). One of the fractions contained a single compound (96) (22 mg.; from acetonitrile), m. p. 151-158°, $\nu_{\text{max.}}$ 3480, 1635 cm.^{-1} Peaks occurred in the mass spectrum at

(m/e values): 502 (molecular ion), 457 (loss of C_2H_5O from molecular ion; $m^{\#}$ 416), 425 (loss of C_2H_5OS from molecular ion; $m^{\#}$ 360), 379, 365 (base peak), 347.

2,2-Dimethyl-1,3-oxathiolan.

2,2-Dimethyl-1,3-oxathiolan was prepared as described by Djerassi and Gorman.⁶⁷ The n.m.r. spectrum showed signals at (τ values): 5.82 (centre of triplet, 2 protons), 6.88 (centre of triplet, 2 protons), 8.35 (singlet, 6 protons).

6-[2-2'-(1',3'-Oxathiolanyl)benzyl]-5-oxo-8-phenyl-naphtho[1,8a,8-bc]furan (95).

Boron trifluoride etherate (40%; 3 drops was added to a stirred solution of acetone hemithioacetal (6 ml.) and the aldehyde (7) (506 mg.) in anhydrous benzene (9 ml.) (protection from light). When all the aldehyde had reacted (ca. 20 min.; infrared control) the mixture was poured into aqueous sodium hydrogen carbonate and extracted with dichloromethane. The extract was dried and evaporated, and the residue chromatographed over alumina (2x23 cm.) with benzene — chloroform (protection from light) to give the hemithioacetal (95) (434 mg.; from acetonitrile), m. p. 156-162°, $\nu_{\max}$. (Nujol) 1638 cm^{-1} The n.m.r.

spectrum showed signals at (τ values): 1.83-2.90 (multiplet), 3.72 (singlet, 1 proton), 5.28-5.68 (multiplet, 1 proton), 5.94 (centre of doublet, 2 protons, $J=1.25$ c./sec.), 6.05-7.02 (multiplet, 3 protons). Peaks occurred in the mass spectrum at (m/e values): 424 (molecular ion), 423 (ca. 4% of molecular ion), 396 (loss of C_2H_4 from molecular ion; $m^{\ddagger}$ 370), 150 (base peak). The analytical specimen had m. p. $157-163^{\circ}$ (from acetonitrile) and $\lambda_{max.}$ (chloroform) 267, 395 $m\mu$ (ϵ 14,140, 26,090). (Found: C, 76.52; H, 4.61; S, 7.42. $C_{27}H_{20}O_3S$ requires C, 76.38; H, 4.75; S, 7.55%).

Photolysis of ACD-tricyclic compounds.

Unless otherwise stated the following procedure was used:

The photolysis apparatus consisted of a RB flask (usually 100 ml.) fitted with a nitrogen inlet, a sample port (normally closed by a stopper), and a reflux condenser carrying a calcium chloride tube. The flask was clamped immediately above a tungsten lamp (750 W) and protected from draughts by a screen of aluminium foil. A sheet of foil beneath the lamp acted as a reflector and the draught from a small fan was directed onto the lamp so that the reaction mixture did not boil too vigorously. (With less powerful lamps the fan was unnecessary.)

The apparatus was dried ($> 100^{\circ}$), assembled rapidly, and allowed to cool under nitrogen. The starting material was tipped into the flask and covered with benzene (AnalaR; dried over sodium). The mixture was swirled to produce a clear solution, a boiling stone added and the lamp — fan system switched on. Dibenzoyl peroxide (H. and W.; dried in vacuo; 1-3 grains) was added at the start of the reaction and at 24-hr. intervals. (When the reaction was first carried out nitrogen was passed through

the solution for ca. 10 min. before irradiation and throughout the photolysis.) This technique was later abandoned since the starting material crystallised in the nitrogen inlet-tube. The yield was no better than that obtained when nitrogen was passed over the mixture during the whole experiment.

The reaction was monitored by one or more of the following techniques:

- (a) T.l.c.
- (b) Infrared examination (disappearance of 1639 cm^{-1} band).
- (c) Ultraviolet examination: A sample of the mixture was evaporated to dryness, taken up in hot ethanol and evaporated again. The ultraviolet spectrum of the residue was measured to determine the ratio (E') of the optical densities at 353 and 403 m μ . E' for the starting material is 0.27.

When chromatographing the tetracyclic compounds the development of the column can be followed by examination in ultraviolet light: the products fluoresce brightly.

5 α ,6,11,11 α -Tetrahydro-5-oxo-12-phenylnaphthaceno-[1,12a,12-bc]furan-11-spiro-2'-(1',3'-dioxolan) (78).

The acetal (69) (518 mg.) in benzene (42 ml.) was photolysed by the standard procedure, the mixture being topped up with benzene at 24-hr. intervals. After 140 hr. ($E' = 11.81$) the solution was evaporated and the residue chromatographed over alumina (2x21 cm.) with benzene to give the pure (t.l.c.; silica; benzene:chloroform::5:2; sulphuric acid) ketal (78) (341 mg.; 68%). For convenience in handling the crystalline mass was recrystallised from acetonitrile to give the product as white platelets (306 mg.).

The ketal (78) has m. p. 224-232° (distillation above ca. 220°), $\nu_{\max}$. (Nujol) 1701, 1691 cm^{-1} and $\lambda_{\max}$. (ethanol) 279, 296, 308, 352 $\text{m}\mu$ (ϵ 20,360, 13,990, 11,610, 15,710). (Found: C, 79.50; H, 5.16. $\text{C}_{27}\text{H}_{20}\text{O}_4$ requires C, 79.40; H, 4.94%). The n.m.r. spectrum showed signals at (τ values): 1.72-2.94 (multiplet), 5.62-7.33 (multiplet, 8 protons), 5.67 (doublet, 1 proton, $J=5.5$ c./cec.). Peaks occurred in the mass spectrum at (m/e values): 408 (molecular ion), 162 (base peak).

Cyclisation of the acetal (69) was repeated

many times; the technique described gave yields in the range 62-71%. A period of ca. 7 days was generally required to cyclise a 500-mg, batch of the acetal. 5 α ,6,11,11 α -Tetrahydro-8,10-dimethoxy-9-methoxy-carbonyl-5-oxo-12-phenylnaphthaceno[1,12a,12-bc]furan-11-spiro-2'-(1',3'-dioxolan) (80).

The acetal (79) (34 mg.) in benzene (ca. 25 ml.) was photolysed in the usual way, dibenzoyl peroxide (1 grain) being added at the start and again after 10.3 hr. After 15.75 hr. the solvent was evaporated and the residue chromatographed over alumina with benzene — chloroform. Since no separation of the starting material from the tetracyclic product (80) was achieved, the latter was isolated by t.l.c. (alumina; benzene:chloroform::2:1). The compound (1 mg.) was crystalline and had $\nu_{\max}$. 1722, 1695 cm^{-1} and $\lambda_{\max}$. (ethanol) 268 (shoulder), 276, 294, 306, 351 $\text{m}\mu$. Peaks occurred in the mass spectrum at (m/e values): 526 (molecular ion), 280 (base peak).

The main component of the photolysis mixture was the starting material (t.l.c.; alumina; benzene:chloroform::2:1; sulphuric acid).

5 α ,6,11,11 α -Tetrahydro-5,11-dioxo-12-phenylnaphthaceno[1,12a,12-bc]furan (77).

The aldehyde (7) (48 mg.) in refluxing benzene (ca. 150 ml.) was irradiated with a tungsten lamp (300 W). The reaction was carried out by the usual technique except that no initiator was added. After 15 hr. very little starting material was left (t.l.c.; alumina; benzene:chloroform::2:1; sulphuric acid). The solution was evaporated and the residue chromatographed over alumina with benzene — chloroform to give the diketone (77) (14 mg.). One recrystallisation from acetone gave material identical with an authentic sample¹ [m. p; mixed m. p.; infrared spectrum (Nujol)].

Irradiation of 6-2'-diacetoxymethylbenzyl-5-oxo-8-phenylnaphtho[1,8a,8-bc]furan (91).

The formyl diacetate (91) (294 mg.) in benzene (30 ml.) was irradiated in the usual way, dibenzoyl peroxide (1 grain) being added at the start, after 14 hr., and again (5 mg.) after 18 hr. During an irradiation period of 21 hr. the starting material remained almost unchanged [t.l.c. (silica; ethyl acetate:chloroform::1:14; sulphuric acid); infrared spectrum; ultraviolet control ($E' = 0.32$ after 21 hr.; $E' = 0.27$ before irradiation)].

5 α ,6,11,11 α -Tetrahydro-5-oxo-12-phenylnaphthaceno-
[1,12a,12-bc]furan-11-spiro-2'-(1',3'-dithiolan) (93).

The thioacetal (92) [415 mg.; dried for 2 days at ca. 45° (protection from light)] in benzene (35 ml.) was photolysed in the usual way, dibenzoyl peroxide (2 grains) being added at the start of the reaction and again (1 grain) after 18 hr. After 25 hr. no starting material was left [t.l.c. (silica; benzene:chloroform::5:2; sulphuric acid); $R_f=10$]. The solution was evaporated and the residue chromatographed over alumina (2x17 cm.) with benzene to give the thioketal (93) (253 mg.; from acetonitrile), m. p. 221-228° (distillation above ca. 214°), $\nu_{\max}$. (Nujol) 1695 cm^{-1} . The n.m.r. spectrum showed signals at (τ values): 1.93-3.08 (multiplet), 5.31 (centre of doublet, 1 proton, $J=5$ c./sec.), 5.74-7.47 (multiplet, 6 protons). Peaks occurred in the mass spectrum at (m/e values): 440 (molecular ion), 412, 379, 166 (base peak). An analytical sample had m. p. 222-226° (distillation above ca. 216°) and $\lambda_{\max}$. (chloroform) 278, 352 m μ (ϵ 19,000, 11,570). (Found: C, 73.75; H, 4.62; S, 14.54. $\text{C}_{27}\text{H}_{20}\text{O}_2\text{S}_2$ requires C, 73.58; H, 4.58; S, 14.55%).

5 α ,6,11,11 α -Tetrahydro-5-oxo-12-phenylnaphthaceno-
[1,12a,12-bc]furan-11-spiro-2'-(1',3'-oxathiolan) (97, 98).

Experiment A.

The hemithioacetal (95) [105 mg.; dried for 2 days in vacuo at ca. 35⁰ (protection from light)] in benzene (35 ml.) was photolysed in the usual way [ultraviolet control (after 3 min. $E'=0.37$; after 4.5 hr. $E'=10.4$)]. After 4.5 hr. the solution was evaporated and the residue chromatographed over alumina with benzene to give the crystalline product (48 mg.; from acetonitrile). Examination of this material by t.l.c. (silica; benzene:chloroform::5:2; sulphuric acid or ultraviolet light) showed that it was composed of two substances. Separation by t.l.c. (above system) and crystallisation from acetonitrile afforded the two isomers: F (faster-running) (13 mg.), m. p. 225-232⁰ (distillation above ca. 215⁰), $\nu_{\max.}$ 1689 cm.⁻¹, $\lambda_{\max.}$ (chloroform) 279, 353 m μ (ϵ 21,420, 12,170), and S (slower-running) (11.5 mg.), m. p. 225-230⁰ (distillation above ca. 220⁰), $\nu_{\max.}$ 1693 cm.⁻¹, $\nu_{\max.}$ (Nujol) 1691 cm.⁻¹, $\lambda_{\max.}$ (chloroform) 276, 292, 304, 346 m μ (ϵ 17,410, 12,260, 9,618, 14,140). The cracking patterns of the isomers are identical — peaks occurred in the mass spectra at (m/e values):

424 (molecular ion), 396 (loss of C_2H_4 from molecular ion; m^+ 370), 178, 150 (base peak).

Experiment B.

The hemithioacetal (95) [358 mg.; dried for 2 days in vacuo at ca. 35° (protection from light)] in benzene (40 ml.) was photolysed in the usual way [ultraviolet control (after 4.5 hr. $E'=1.19$; after 23 hr. $E'=11.8$)]. After 23 hr. the solution was evaporated and the residue chromatographed over alumina (2x16 cm.) with benzene to afford the mixture of diastereoisomeric hemithioketals (97, 98) (290 mg.; from acetonitrile), m. p. $222-229^\circ$ (distillation above ca. 211°). The material was pure as judged by t.l.c. (silica; benzene:chloroform::5:2; sulphuric acid).

Cyclisation of 6-[2-2'-(1',3'-dioxolanyl)benzyl]-5-oxo-8-phenylnaphtho[1,8a,8-bc]furan (69) using a mercury-discharge lamp.

The acetal (69) (424 mg.) in refluxing benzene (40 ml.) was photolysed in the usual way except that a mercury-discharge lamp [Osram MB/U (quartz bulb); 400 W] was used. The reaction was worked up after 4.8 hr. ($E'=14.3$) and the ketal (78) isolated in 39% yield (163 mg.).

Cyclisation of 6-[2-2'-(1',3'-dioxolanyl)benzyl]-5-oxo-8-phenylnaphtho[1,8a,8-bc]furan (69) using a mercury-discharge lamp and a filter.

The acetal (69) (454 mg.) in refluxing benzene (40 ml.) was photolysed as in the previous experiment except that a filter (Chance-Pilkington OY 10), placed in a dish of cold water, was held between the lamp and the reaction vessel [flat-bottomed flask (100 ml.)]. The reaction mixture was worked up after 17.25 hr. ($E' = 16$) and the ketal (78) isolated in 53% yield (244 mg.).

Hydrolysis of 5 α ,6,11,11 α -tetrahydro-5-oxo-12-phenylnaphthaceno[1,12a,12-bc]furan-11-spiro-2'-(1',3'-dioxolan) (78).

Procedure A.

The ketal (78) (several mg.) in dioxan — hydrochloric acid (6N) was left overnight at room temp. Examination of the mixture by the t.l.c. (silica; benzene:chloroform::10:3; ultraviolet light) showed that the ketal had not been hydrolysed.

Procedure B.

A solution of the ketal (78) (18 mg.) and p-toluenesulphonic acid monohydrate in acetone (AnalaR) was refluxed for 6.5 hr. (nitrogen atmosphere). At this stage only a small amount of diketone (77) had been formed (t.l.c.; above system). More acid was added, the mixture diluted with a little water and refluxed overnight. Because the ketal was still unchanged the mixture was concentrated, heated to 100° for 10 hr. (sealed tube), and kept at room temp. for 12 hr. The brown solution was poured into saturated aqueous sodium hydrogen carbonated and extracted with chloroform. The extract was dried and evaporated, and the residue chromatographed over alumina with

benzene — chloroform to afford the diketone (77) (4 mg.; from acetone) identical with an authentic sample¹ [m. p.; mixed m. p.; infrared spectrum (Nujol)].

Stability of 5 α ,6,11,11 α -tetrahydro-5-oxo-12-phenylnaphthaceno[1,12a,12-bc]furan-11-spiro-2'-(1',3'-dioxolan) (78) to photolysis conditions.

A refluxing solution of the ketal (78) (9.3 mg.) in benzene (ca. 50 ml.) was irradiated with a tungsten lamp (300 W) in the usual way, dibenzoyl peroxide (0.2 mg.) being added at the start and again (12 mg.) after 24 hr. During an irradiation time of 48 hr. the ketal (78) did not decompose significantly (t.l.c.; alumina; benzene:chloroform::5:2; sulphuric acid).

Miscellaneous experiments with 6-[2-2'-(1',3'-dioxolanyl)benzyl]-5-oxo-8-phenylnaphtho[1,8a,8-bc]furan (69).

A. Attempted thermal reaction in benzene.

A solution of the acetal (69) (45 mg.) and dibenzoyl peroxide (1 mg.) in dry benzene (110 ml.) was refluxed in the dark (nitrogen atmosphere). After 3 hr. the acetal had not decomposed (t.l.c.; alumina; benzene:chloroform::10:3; sulphuric acid).

Dibenzoyl peroxide (26 mg.) was added and heating continued for ca. 15 hr. The acetal was still intact (t.l.c., above system).

B. Photolysis in the presence of an excess of dibenzoyl peroxide.

Dibenzoyl peroxide (10 mg.) was added to the above solution and the latter was irradiated in the usual way with a tungsten lamp (300 W). Further portions of dibenzoyl peroxide (5 — 10 mg.) were added after 1.5 and 3 hr. No acetal remained after 4.3 hr. (t.l.c.; above system). The solvent was evaporated and the residue dissolved in chloroform, washed with aqueous ferrous sulphate, and with aqueous sodium hydrogen carbonate. The organic solution was dried and evaporated to leave an oil (87 mg.) with $\nu_{\max}$. 1713 (strong), 1690 cm^{-1} . Chromatography over alumina with benzene afforded the ketal (78) (12 mg.). Further elution with benzene — chloroform gave fractions rich in an ester [$\nu_{\max}$. 1718, 1639 cm^{-1} , $\lambda_{\max}$. (ethanol) 405 $\text{m}\mu$.]. These fractions were combined and stored for ca. 2 months in the presence of traces of chloroform. Re-examination showed that some changes had occurred: the material had $\nu_{\max}$.

3400 (strong) cm^{-1} An ester (2 mg.) was isolated by t.l.c. (alumina; benzene:chloroform::5:4) and had ν_{max} . 3440, 1719, 1639 cm^{-1} and λ_{max} . (ethanol) 251, 267, 405 $\text{m}\mu$. Peaks occurred in the mass spectrum at (m/e values): 424 or 423 (poor spectrum; molecular ion), 406 [loss of H_2O from molecular ion (424); $m^{\ddagger}$ 389], 362 [base peak; loss of $\text{C}_2\text{H}_6\text{O}_2$ from molecular ion (424); $m^{\ddagger}$ 309]. These data are consistent with formulation of the ester as 6-(2-2'-hydroxyethoxycarbonylbenzyl)-5-oxo-8-phenylnaphtho[1,8a,8-bc]furan (100).

C. Attempted thermal reaction in toluene.

A solution of the acetal (69) (74 mg.) and dibenzoyl peroxide (2.5 mg.) in toluene (20 ml.; dried over sodium) was refluxed in the dark. A further portion of dibenzoyl peroxide (4.7 mg.) was added after 8 hr. During 22.5 hr. the acetal remained intact (t.l.c.; alumina; benzene; chloroform::10:3; sulphuric acid). The following ultraviolet data were obtained during the experiment:

Time (hr.)	E'
0	0.27
2	0.26
7	0.26
22.5	0.29

D. Photolysis at 19°.

The acetal (69) (45 mg.) in dry benzene (100 ml.) was irradiated at 19° with a tungsten lamp (700 W) (nitrogen atmosphere). After 6 hr. little starting material was left; many products had been formed, including the ketal (78) (t.l.c.; alumina; benzene:chloroform::10:3; sulphuric acid). The solvent was evaporated to leave a residue with ν_{max} . 1719 and 1711 (strong; poorly resolved), 1689 cm^{-1}

E. Photolysis in the presence of a trace of chloroform.

A refluxing solution of the acetal (69) (51 mg.) in dry benzene (ca. 140 ml.) was irradiated with a tungsten lamp (300 W) (nitrogen atmosphere). Bench chloroform (2 drops) was added at the start and again after 18.25 hr. Very little starting material was left after 24 hr. (t.l.c.; alumina; benzene:chloroform::5:2; sulphuric acid). Evaporation of the solvent afforded a residue with an infrared spectrum that indicated that the reaction had followed the same course as when a trace of dibenzoyl peroxide is used as initiator.

F. Photolysis in chloroform.

A refluxing solution of the acetal (69) (46 mg.) in bench chloroform (ca. 50 ml.) was irradiated with

a tungsten lamp (300 W) for 20.5 hr. (nitrogen atmosphere). At this stage no starting material was present (t.l.c.). The solution was evaporated and the residue chromatographed over alumina with benzene — chloroform to give 6-(2-2'-chloroethoxycarbonylbenzyl)-5-oxo-8-phenylnaphtho[1,8a,8-bc]furan (99) (3.6 mg.; from ethanol), m. p. 130-134°, $\nu_{\text{max.}}$ 1719, 1639 cm^{-1} , $\lambda_{\text{max.}}$ (chloroform) 267, 395 m μ (ϵ 14,720, 27,300). Peaks occurred in the mass spectrum at (m/e values): 442 [molecular ion; (M+2)/M = 32%], 362 (base peak; loss of $\text{C}_2\text{H}_5\text{ClO}$ from molecular ion; $m^{\#}$ 297).

G. Effect of dibenzoyl peroxide on the cyclisation.

Two photolysis reactions were set up in equivalent positions on either side of a tungsten lamp (300 W) (nitrogen atmosphere). The acetal (69) was recrystallised from ethanol and dried in vacuo before use, and solvent benzene (AnalaR) was distilled and dried over sodium. A solution of dibenzoyl peroxide (0.8 mg.) in benzene (1 ml.) was prepared and added in portions to one of the reaction mixtures. The progress of each reaction was monitored by measuring E' :

Time (hr.)	Volume initiator solution added to reaction B (ml.) [‡]	E ¹	
		A	B
0.0	0.1	0.28	0.28
0.75	0.2	-	-
2.0	0.25	0.42	0.35
3.0 [A ridge of crystals had formed above the liquid level in flask A. Benzene (10 ml.) was added to each mixture.]			
3.3	-	0.37	0.38
3.75	0.3	-	-
5.0	-	0.43	0.49
18.75	-	0.69	1.1
23.5	-	2.3	4.5

[‡] Reaction A: acetal {55 mg.} + benzene {20 ml.}
 Reaction B: acetal {53 mg.} + benzene {20 ml.}.

Both solutions were evaporated. The residues had (A) $\nu_{\max}$. 1709, 1695 cm^{-1} , and (B) $\nu_{\max}$. 1693 cm^{-1} . Examination by the t.l.c. (alumina; benzene:chloroform::5:2; sulphuric acid) revealed that residue B contained only the acetal (69) and the ketal (78) but that residue A contained, in addition, a large amount of a slower-running substance.

H. Photolysis in the presence of azobisisobutyronitrile.

Experiment A.

Azobisisobutyronitrile⁶⁸ (1.1 mg.) was added to

a refluxing solution of the acetal (69) (53 mg.) in benzene (25 ml.) and the mixture was irradiated in the usual way. After 41.3 hr. E' had risen to 11.85. The solvent was evaporated and the residue found to contain little ketonic impurities (slight shoulder on low-wavelength side of 1693 cm.^{-1} band in the infrared spectrum).

Experiment B.

The previous experiment was repeated with the acetal (69) (73 mg.) and azobisisobutyronitrile (15 mg.). No dramatic rate enhancement was observed and more by-products were formed than in the previous experiment (t.l.c.; alumina; benzene:chloroform::5:2; sulphuric acid). Despite the large amount of initiator used little ketonic impurities were formed (infrared spectrum).

Reactions of ABCD-tetracyclic compounds.

5 α ,6,11,11 α -Tetrahydro-5 β -hydroxy-12-phenylnaphthaceno[1,12a,12-bc]furan-11-spiro-2'-(1',3'-dioxolan)
(106).

Procedure A.

Powdered lithium aluminium hydride (241 mg.) was added to a vigorously stirred solution of the ketone (78) (137 mg.) in dry tetrahydrofuran (ca. 7 ml.) (nitrogen atmosphere). After 2 hr. examination of the mixture by t.l.c. (silica; benzene:chloroform::2:1; sulphuric acid) showed that the product was contaminated by a small amount of faster-running material [probably the starting material (same R_f and colour response to ultraviolet light and to sulphuric acid)]. A further portion of lithium aluminium hydride (40 mg.) was added and stirring continued for 1 hr. There was no change in the composition of the reaction mixture (t.l.c.). Ethyl acetate was added dropwise (ice bath) and then saturated aqueous sodium sulphate. The mixture was filtered and the precipitate extracted thoroughly with boiling tetrahydrofuran. The combined filtrate was concentrated below 60°, poured into water and extracted with chloroform. The extract was dried and evaporated below 60°. The infrared spectrum showed

a weak carbonyl band. Recrystallisation from acetonitrile gave the alcohol (106) in two crops: A, (104 mg.), m. p. 239-243° (distillation above 220°), and B, (4.2) mg.), m.p. 238-243° (distillation above 223°). Both samples contained a trace of the (less polar) impurity (t.l.c.). In a previous experiment, carried out in the same way, the infrared spectrum of the recrystallised product [m. p. 235-244° (distillation above 230°)] showed no carbonyl absorption.

Procedure B.

Repetition of the experiment at reflux temp. gave the same result as by method A.

Procedure C. (This is the best method).

The ketone (78) (122 mg.) in tetrahydrofuran (15 ml.) and methanol (7.5 ml.) was stirred for 16 hr. with sodium borohydride (89 mg.) (nitrogen atmosphere). A further portion of the hydride (15 mg.) was added and stirring continued for 4.5 hr. At this stage only a minute trace of starting material was left (t.l.c.). The mixture was concentrated at room temp., poured into water, and extracted with dichloromethane. The extract was dried and evaporated, and the residue recrystallised from acetonitrile to give the alcohol (106) (111 mg.), m. p. 239-245° (distillation above

ca. 224°), $\nu_{\max}$. 3450 cm.^{-1} , $\lambda_{\max}$. (chloroform) 296 (shoulder), 310 , $322 \text{ m}\mu$ (ϵ $22,890$, $30,120$, $22,370$). The n.m.r. spectrum showed signals at (τ values): 1.70 - 2.95 (multiplet, 12 protons), 5.0 - 7.43 (multiplet, 10 protons). Doublets were present at 5.28τ ($J=4.5 \text{ c./sec.}$) and 5.78τ ($J=5 \text{ c./sec.}$). Peaks occurred in the mass spectrum at (m/e values): 410 (molecular ion), 392 (loss of H_2O from molecular ion; $m^{\ddagger}$ 375), 162 (base peak). (Previous experiments carried out in the manner described gave material which, before recrystallisation, showed no infrared carbonyl absorption.)

$5\alpha,6,11,11\alpha$ -Tetrahydro- 5β -hydroxy- 12 -phenylnaphthaceno [$1,12a,12$ -bc]furan- 11 -spiro- $2'-(1',3'$ -dithiolan) (107).

The ketone (93) (157 mg.) in tetrahydrofuran (12 ml.) and methanol (6 ml.) was stirred overnight with sodium borohydride (100 mg.) (nitrogen atmosphere). At this stage no starting material remained (t.l.c.; silica; benzene:chloroform:: $5:2$; sulphuric acid). The mixture was concentrated at room temp., poured into water and extracted with dichloromethane. The extract was dried and evaporated to give the alcohol (107) (124 mg. ; from acetonitrile), m. p. 229 - 235° (distillation above ca. 225°), $\nu_{\max}$. 3500 cm.^{-1} $\lambda_{\max}$.

(chloroform) 305 m μ (ϵ 17,990). The n.m.r. spectrum showed signals at (τ values): 2.03-3.07 (multiplet), 4.96 (broad signal, 1 proton), 5.47 (centre of doublet, 1 proton, $J=4.25$ c./sec.), 6.52-7.85 (multiplet, 8 protons). Peaks occurred in the mass spectrum at (m/e values): 442 (molecular ion), 424 (loss of H_2O from molecular ion), 382 (loss of C_2H_4S from molecular ion), 166 (base peak).

6,7-Dihydro-5-hydroxy-8-phenylnaphtho[1,8a,8-bc]furan (122).

The ketone (3) was reduced with sodium borohydride as described previously¹ to obtain the alcohol (122), m. p. 135-138⁰, ν_{max} . 3560 (sharp), 3400 (broad), 1631 (weak), 1607 cm.⁻¹

5 β -Acetoxy-5 α ,6,11,11 α -tetrahydro-12-phenylnaphthaceno-[1,12a,12-bc]furan-11-spiro-2'-(1',3'-dioxolan) (108).

A solution of the alcohol (106) (110 mg.) in dry pyridine (7 ml.) and acetic anhydride (6 ml.) was stirred at 70-95⁰ for 12 hr. [nitrogen atmosphere; t.l.c. control (silica; benzene:chloroform::2:1; sulphuric acid)] and evaporated. The residue was chromatographed over alumina (ca. 1.3x10 cm.) with benzene to give the acetate (108) (82 mg.; from

acetonitrile), m. p. 233-240⁰ (distillation above ca. 220⁰), $\nu_{\text{max.}}$ 1720 cm.⁻¹ The n.m.r. spectrum showed signals at (τ values): 1.7-3.0 (multiplet), 3.61 (centre of doublet, 1 proton, $J=4$ c./sec.), 5.72 (centre of doublet, 1 proton, $J=4.75$ c./sec.), 5.85-7.41 (multiplet, 7 protons), 8.74 (singlet, 3 protons). Peaks occurred in the mass spectrum at (m/e values): 452 (molecular ion), 408 (loss of C₂H₂O from molecular ion), 390 (loss of a fragment from molecular ion; m^{z} 337), 162 (base peak). An analytical specimen had m. p. 236-241.5⁰ (distillation above ca. 225⁰) and $\lambda_{\text{max.}}$ (chloroform) 298 (shoulder), 310, 324 m μ (ϵ 21,130, 28,540, 22,060). (Found: C, 77.13; H, 5.36. C₂₉H₂₄O₅ requires C, 76.98; H, 5.35%).

5 β -Acetoxy-5 α ,6,11,11 α -tetrahydro-12-phenylnaphthaceno[1,12a,12-bc]furan-11-spiro-2'-(1',3'-dithiolan)
(109).

Acetic anhydride (3 ml.) was added to a solution of the alcohol (107) (120 mg.) in dry pyridine (3 ml.) and the mixture stirred overnight at room temp. At this stage no starting material was present (t.l.c.; benzene:chloroform::5:2; sulphuric acid). The mixture was evaporated at room temp. and the crystalline residue

chromatographed over alumina (1.4x10 cm.) with benzene to give the acetate (109) (95 mg.; from acetonitrile), m. p. 229-236° (distillation above ca. 220°). The n.m.r. spectrum showed signals at (τ values): 1.92-3.12 (multiplet), 3.63 (centre of doublet, 1 proton, $J=3.5$ c./sec.), 5.42 (centre of doublet, 1 proton, $J=4.5$ c./sec.), 6.62-7.52 (multiplet, 7 protons), 8.73 (singlet, 3 protons). An analytical specimen had m. p. 235-237° (distillation above ca. 225°) and λ_{max} . (chloroform) 310 m μ (ϵ 18,880). (Found: C, 71.95; H, 5.06; S, 12.96. $\text{C}_{29}\text{H}_{24}\text{O}_3\text{S}_2$ requires C, 71.93; H, 4.99; S, 13.23%).

5-Acetoxy-6,7-dihydro-8-phenylnaphtho[1,8a,8-bc]furan
(4).

The acetate (4) had been made previously but not obtained crystalline.¹

Acetic anhydride (10 ml.) was added to a solution of the alcohol (122)^x (963 mg.) in dry pyridine (10 ml.) and the mixture stirred at room temp. for 3.7 hr. [t.l.c. control (silica; benzene:chloroform::5:2; sulphuric acid)]. The mixture was evaporated below 40° and the residue chromatographed over silica gel (2x14 cm.) with benzene — chloroform to give the acetate (4)

^xSee p. 219.

[898 mg.; from light petroleum (b. p. 60-80°)],
 m. p. 89-91.5°, $\nu_{\text{max.}}$ 1723 cm.^{-1} The n.m.r. spectrum
 showed signals at (τ values): 2.1-2.95 (multiplet, 8
 protons), 3.8 (centre of triplet, 1 proton), 6.85
 (centre of multiplet, 2 protons), 7.75 and 7.93
 (centre of multiplet and singlet, respectively; 5
 protons). An analytical specimen had m. p. 85-87°
 (from ethanol). (Found: C, 78.05; H, 5.48. $\text{C}_{19}\text{H}_{16}\text{O}_3$
 requires C, 78.06; H, 5.52%).

5 α ,6,11,11 α -Tetrahydro-12-phenyl-5H-naphthaceno[1,12a,
 12-bc]furan-11-spiro-2'-(1',3'-dioxolan) (105).

The ketone (78) (22.1 mg.) in dimethylformamide
 (4 ml.; distilled from calcium hydride) was hydrogenolysed
 over 10% palladised charcoal (18 mg.) for ca. 15 hr.
 The catalyst was removed and rinsed with a little
 dichloromethane. The combined filtrate was evaporated
 below 80° and the residue examined by t.l.c. (silica;
 benzene:chloroform::2:1). Three spots were observed;
 the slower two corresponded to the ketone (78) and
 the alcohol (106), respectively (colour response to
 ultraviolet light and to sulphuric acid). The mixture
 was hydrogenolysed again for 24 hr. and worked up
 as before. Examination of the residue (17 mg.) by

t.l.c. (above system) showed a fast-running product contaminated by small amounts of the two slower-running components. The major product was isolated by t.l.c. (silica; benzene:chloroform::2:1) and recrystallised from acetonitrile. The compound (105) (6.9 mg.), m. p. 219-223.5° (distillation above ca. 205°), showed no hydroxyl or carbonyl absorption in its infrared spectrum, and had λ_{max} . (chloroform) 294 (shoulder), 306, 321 m μ (ϵ 24,030, 30,230, 20,840). Peaks occurred in the mass spectrum at (m/e values): 394 (molecular ion), 332 (loss of a fragment from molecular ion; $m^{\#}$ 280), 162 (base peak). (Mass measurement on molecular ion: 394.15806. Mass calculated for $\text{C}_{27}\text{H}_{22}\text{O}_3$: 394.15688). 5 α ,6,11,11 α -tetrahydro-5-hydroxy-5-methyl-12-phenyl-naphthaceno[1,12a,12-bc]furan-11-spiro-2'-(1',3'-dioxolan) (117). (Methyl group probably in α configuration).
Experiment A.

The ketone (78) was treated with methylmagnesium bromide in tetrahydrofuran (nitrogen atmosphere). Very slight reaction occurred (t.l.c.) at room temp. (2 hr.) but no significant change was observed after a 12-hr. period at 62° (t.l.c). (Grignard reagent was tested for and found to be present.)

Experiment B.

Ethylmagnesium iodide — triethylamine complex³⁹ in benzene did not react with the ketone (78) at room temp. (nitrogen atmosphere). On refluxing the solution many products were formed (t.l.c.)

Experiment C.

Methyl iodide (0.5 ml.; distilled from phosphorous pentoxide) was added to a stirred mixture of dry tetrahydrofuran (ca. 5 ml.) and lithium (70 mg.) at -10° (nitrogen atmosphere). Stirring was continued for 1 hr. at -10° , the mixture was filtered and the ketone (78) (16 mg.) was added to the stirred filtrate. (nitrogen atmosphere). No reaction was observed during 30 min. at -10 to -5° (t.l.c.; silica; benzene:chloroform::5:2; sulphuric acid) but the solution had acquired a deep yellow colour. The cooling-bath was removed, the yellow colour faded during the next 3 hr. and the starting material was transformed into a new compound (t.l.c.; above system). The mixture was concentrated at room temp., diluted with water, and extracted with dichloromethane. The extract was dried and evaporated. The product was purified by t.l.c. (silica; benzene:chloroform::5:2) and had

m. p. 200-202° (distillation above ca. 194°), $\nu_{\text{max.}}$ 1691 cm.^{-1} , $\lambda_{\text{max.}}$ (chloroform) 276, 292, 303, 347 m μ (ϵ 18,430, 13,200, 10,970, 14,980). Peaks occurred in the mass spectrum at (m/e values): 422 (molecular ion), 162 (base peak). These data are consistent with the formulation 5 α ,6,11,11 α -tetrahydro-5a ξ -methyl-5-oxo-12-phenylnaphthaceno[1,12a,12-bc]furan-11-spiro-2'-(1',3'-dioxolan) (119).

Experiment D.

Methyl iodide (10.65 g.; distilled from phosphorus pentoxide) in dry ether (40 ml.) was added slowly to a stirred mixture of lithium (1.4 g.) and dry ether (10 ml.) kept at -10° (nitrogen atmosphere).⁵⁹ After the addition stirring was continued for 2 hr. at -10 to 0°. The mixture was filtered and the filtrate stored at -30°.

The methyl-lithium solution (5 ml.) was added in one lot to a stirred solution of the ketone (78) (26 mg.) in dry benzene (ca. 2 ml.) at 12° (nitrogen atmosphere). A yellow colour formed immediately and the solution rapidly became purple. After 30 min. very little starting material remained (t.l.c.; silica; benzene:chloroform::5:2; sulphuric acid).

A further portion of the methyl-lithium solution (2 ml.) was added and after ca. 10 min. the mixture was poured onto ice and extracted with dichloromethane. The extract was dried and evaporated to leave a residue with $\nu_{\text{max.}}$ 3450 (strong), 1658 (weak) cm^{-1} T.l.c. (above system) showed the presence of a trace of starting material, one major product [the required alcohol (117)], and 5 slower-running components. The alcohol (117) (10.3 mg.) was isolated by t.l.c. (silica; benzene:chloroform::5:2) and had $\nu_{\text{max.}}$ 3450, 1623 (shoulder), 1607, 1579 (shoulder) cm^{-1} Recrystallisation from acetonitrile afforded material (2 mg.) with $\lambda_{\text{max.}}$ (chloroform) 296 (shoulder), 308, 322 $\text{m}\mu$ (ϵ 22,420, 28,820, 21,430). The n.m.r. spectrum (Varian HA-100 spectrometer) showed signals at (τ values): 5.75 (centre of doublet, $J=5$ c./sec.), 8.28 (singlet). Peaks occurred in the mass spectrum at (m/e values): 424 (molecular ion), 406 (loss of H_2O from molecular ion; $m^{\#}$ 389), 162 (base peak).

Ozonolysis experiments.A. Work-up using 1% palladised charcoal — hydrogen.

5 β -Acetoxy-5,5 α ,6,11,11a ξ ,12-hexahydro-1-hydroxy-12-oxoaphthacene-11-spiro-2'-(1',3'-dioxolan) (110).

A solution of the acetate (108) (12 mg.) in a mixture of bench chloroform (16 ml.) and methanol (8 ml.) was cooled (external temp. -22°) and ozonised oxygen bubbled through it. When the reaction was ca. 95% complete (ultraviolet control with respect to optical density at 312 m μ) excess of ozone was expelled by passing a stream of dry nitrogen through the solution for 45 min. (-22°). Palladised charcoal (1%; 65 mg.) was then added and the mixture hydrogenated for ca. 15 min. at -22° . The cooling-bath was removed, hydrogenation continued for 1 hr., the catalyst filtered off, and the solvent evaporated. The resultant oil (12 mg.) had $\nu_{\max}$. 3400 (very broad), 1730 (strong; shoulder on long-wavelength side), 1640 (weak) cm.⁻¹ and t.l.c. (silica; chloroform; sulphuric acid) showed it to consist of two major components. The faster-running compound was isolated by t.l.c. (silica; chloroform) as an oil (1.4 mg.) which slowly crystallised. It had $\nu_{\max}$. 3400 (very broad), 1733 (shoulder

on long-wavelength side), 1643 cm.^{-1} , and $\lambda_{\text{max.}}$ (ethanol) 262, 340 m μ . A dilute solution of the compound in ethanol containing a few drops of hydrochloric acid (6N) showed, after 12 hr. at room temp., $\lambda_{\text{max.}}$ ca. 220, ca. 242, 249, ca. 262, 313, 392, 412 m μ , the trace being almost identical to that obtained with an authentic sample¹ of the β -diketone (16). Peaks occurred in the mass spectrum at (m/e values): 380 (molecular ion), 320 (loss of a fragment from molecular ion; m[#] 270), 162 (base peak).

On the basis of the above evidence the compound is formulated as the phenolic ketone (110).

B. Work-up using zinc dust.

The acetate (108) (20 mg.) in bench chloroform (20 ml.) and distilled methanol (6 ml.) was ozonised, with stirring, at -30° (to ca. 95% completion; ultra-violet control). Excess of ozone was expelled with a stream of nitrogen during 50 min. at -30° and activated zinc dust (300 mg.) added. Stirring was continued for ca. 2 hr. below -20° and then at room temp. for 15 hr. The mixture was filtered (Celite) and evaporated below 70° . The main product, isolated as an unstable oil (9 mg.), by chromatography over silica gel with

chloroform, had ν_{max} . 3550 (sharp), 3320 (broad), 1737-1729, 1603 cm^{-1} . Peaks occurred in the mass spectrum at (m/e values). 500 (molecular ion), 162, 142, 105 (base peak), 77 (loss of CO from base peak; $m^+ 56.5$).

The above evidence suggests that the reduction product is the lactone (112).

C. Work-up with acidified potassium iodide

The acetate (108) (30 mg.) in ~~dry~~ chloroform (17 ml.; distilled from phosphorus pentoxide and stabilised with dry methanol (19 ml.) was ozonised, with stirring, at -22° (to ca. 95% completion; ultra-violet control). Excess of ozone was removed with a stream of nitrogen during 1.3 hr. (-22°). Part of the reaction mixture (10 ml.) was shaken vigorously for 3 min. with an ice-cold aqueous solution of potassium iodide (4.5 g.) and sodium thiosulphate (4.5 g.) acidified with solid carbon dioxide. The mixture was stirred for 2 hr. at room temp. and extracted with chloroform. The extract was dried and evaporated to obtain an impure sample of the lactone (112) [infrared spectrum; t.l.c. (silica; chloroform; sulphuric acid)].

D. Work-up with 1% palladised calcium carbonate — hydrogen.

The acetate (108) (22 mg.) in dry chloroform (11 ml.; stabilised with methanol) and dry methanol (13 ml.) was ozonised at -28° by the procedure described in Experiment C and excess of ozone was removed in the usual way.

A portion of the mixture (14 ml.) was hydrogenated over 1% palladised calcium carbonate (92 mg.) at -50° for ca. 10 min. The cooling-bath was removed, hydrogenation continued for 3 hr., the catalyst filtered off, and the solvent evaporated. The residue had $\nu_{\max}$. 1700, 1640 cm^{-1} and was composed of a mixture of the keto-phenol[⌘] (110) and the keto-benzoate^{⌘⌘} (111) (t.l.c.; silica; chloroform; sulphuric acid).

⌘ See experiment A.

⌘⌘ See experiment E.

E. Work-up with triphenylphosphine.

5B-Acetoxy-1-benzoyloxy-5,5a α ,6,11,11a ξ ,12-hexahydro-12-oxo-naphthacene-11-spiro-2'-(1',3'-dioxolan) (111).

The acetate (108) (14 mg.) in dry chloroform (10 ml.; stabilised with methanol) and dry methanol (12 ml.) was ozonised at -20 to -30° as described in Experiment C and excess of ozone was removed in the usual way. A solution of triphenylphosphine (42 mg.) in dry chloroform (ca. 3 ml.; stabilised with methanol)

at -20° was added dropwise to the stirred ozonolysis mixture. Reduction appeared to be complete within a few min. (t.l.c.; silica; chloroform; sulphuric acid) but the mixture was kept for 10 min. at -30° and overnight at 0° . The solvent was evaporated below 60° and the keto-benzoate (111) (10.6 mg.) isolated by t.l.c. (silica; chloroform). The compound has $\nu_{\max}$. 1736, 1700 (half as intense as 1736 cm^{-1} band), 1608 cm^{-1} , $\lambda_{\max}$. (ethanol) 232, 286 m μ (ϵ 21,770, 2872) and $\lambda_{\max}$. (ethanol containing a trace of dilute hydrochloric acid) 385 m μ . (Mass measurement on molecular ion: 484.152376. Mass calculated for $\text{C}_{29}\text{H}_{24}\text{O}_7$: 484.152189). Crystallisation from ethyl acetate afforded material (2.4 mg.) m. p. $189-194^{\circ}$.

F. Work-up with triethyl phosphite.

Repetition of Experiment E followed by reduction of the ozonolysis mixture with triethyl phosphite (reagent grade) gave a mixture of products amongst which the lactone (112) was detected by t.l.c. (silica: chloroform; sulphuric acid).

5-Acetoxy-1-benzoyloxy-5,6,7,8-tetrahydro-8-oxo-naphthalene (5).

The acetate (4) (398 mg.) in dry chloroform

(60 ml.; stabilised with methanol) and dry methanol (75 ml.) was ozonised at -80° for ca. 15 hr. without stirring [no starting material left (ultraviolet spectrum)]. The mixture was warmed to -30° , excess of ozone removed with a stream of nitrogen, and a cold (-30°) solution of triphenylphosphine (1 g.) in chloroform added dropwise (stirring). After 30 min. at ca. -30° the solution was evaporated below 30° and the residue chromatographed over silica gel (2x15 cm.) with benzene — chloroform to obtain the keto-benzoate (5) (238 mg.; from ethanol), m. p. $124-128^{\circ}$, $\nu_{\max}$. 1739, 1689 cm^{-1} , $\nu_{\max}$. (Nujol) 1737, 1679 cm^{-1} . The n.m.r. spectrum showed signals at (τ values): ca. 1.7 - ca. 2.99 (multiplet), 3.87 (centre of triplet, 1 proton), 7.4, 7.7, 7.92 (centre of multiplet, centre of multiplet, singlet, respectively, ca. 7 protons). Peaks occurred in the mass spectrum at (m/e values): 324 (molecular ion), 282, 264 (loss of $\text{C}_2\text{H}_4\text{O}_2$ from molecular ion; $m^{\#}$ 215.5), 105 (base peak), 77 (loss of CO from base peak; $m^{\#}$ 56.5). The analytical specimen had m. p. $125.5 - 128.5$ and $\lambda_{\max}$. (ethanol) 233, 286 (broad) μ (ϵ 22,760, 2763). (Found: C, 70.60; H, 4.90. $\text{C}_{19}\text{H}_{16}\text{O}_5$ requires C, 70.36; H, 4.97%).

1-Benzyl-oxy-5,5 α ,6,11,11a ξ ,12-hexahydro-5-hydroxy-12-oxonaphthacene-11-spiro-2'-(1',3'-dioxolan) (116).

Experiment A.

The alcohol (106) (18 mg.) in dry chloroform (14 ml.; stabilised with methanol) and dry methanol (12 ml.) was ozonised, with stirring, at -20 to -30° (to about 95% completion; ultraviolet control). Excess of ozone was removed with a stream of nitrogen during 1 hr. (ca. -30°) and cold (-30°) solution of triphenylphosphine (45 mg.) in dry chloroform (ca. 3 ml.) added dropwise (stirring). The mixture was kept overnight at 0° and then evaporated at room temp. The residue contained two major components both of which were present at the beginning of the storage period (t.l.c.; silica; chloroform:ethylacetate::1:1; sulphuric acid). One of these, the keto-benzoate (116) was isolated as a fairly pure oil (5.5 mg.) by t.l.c. (silica; chloroform:ethyl acetate::1:1) and had $\nu_{\max}$. 3440, 1737, 1687 cm^{-1} . Peaks occurred in the mass spectrum at (m/e values): 442 (molecular ion), 424, 162 (base peak), 105, 77 [loss of CO from $\text{C}_6\text{H}_5\text{CO}^+$ (m/e 105); $m^{\#}$ 56.5]

Experiment B.

Repetition of the reaction at -75 to -80° also

afforded a mixture

Ozonolysis in the presence of triphenylphosphine.

The same ozone-oxygen stream was passed alternately, for short periods, through the following stirred solutions kept in the same cold-bath.

A: A solution of the acetate (4) (24 mg.) and triphenylphosphine (93 mg.) in dry chloroform (10 ml.; stabilised with methanol) and dry methanol (14 ml.).

B: The acetate (4) (25 mg.) in the same volume of the mixed solvent.

The mixtures were ozonised alternately for the times indicated. At the end of each period an aliquot was withdrawn and its optical density at 309 mμ determined. Mixture A was also examined for triphenylphosphine oxide by t.l.c. (silica; chloroform; iodine). The following results were obtained:

Time (min.)	Optical density at 309 mμ		Temp. at time given	t.l.c. (A) Ph ₃ PO
	A	B		
0	0.66	0.66	-22°	-
4	0.64	0.54	-	trace
1.5	0.62	0.42	-25°	trace
1.5	-	0.41	-22°	
2	0.63	0.32	-	
2	-	0.26	-23°	
1	-	0.27	-	
2	0.64	0.17	-25°	
2	-	0.11	-	small amount
2	0.65	0.10	-25°	

Treatment of ozonolysis products with base.

A.

A solution of the diester (111) (4 mg.) in acetone (2 ml.) and water (1 ml.) was refluxed for 10 min. with sodium carbonate (80 mg.) and then stirred overnight at room temp. (nitrogen atmosphere). After the initial reflux period no starting material was left (t.l.c.; silica; chloroform:ethyl acetate::1:1; sulphuric acid) and 3 compounds were present. No further change occurred at room temp. or during 7 hr. at reflux temp. The mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The extract was dried and evaporated.

B.

The residue from (A) was dissolved in tetrahydrofuran and conc. aqueous ammonia (4 drops) added. After 22 hr. at room temp. the clear solution was worked up as above. The constitution of the total product had not been altered (t.l.c.; above system).

C.

The oil from (B) was dissolved in ethanol and aqueous ethanolic potassium hydroxide (1 drop) added (nitrogen atmosphere). After 1 hr. at room temp. the

mixture was worked up as above. The composition of the oil had not changed (t.l.c.; above system). The oil had λ_{max} . (ethanol) 238-263 (broad), 362 m μ .

D.

Aqueous hydrazine (4.7 mg.; 64%^{w/w}) was added to a stirred solution of the ketone (5) (10.8 mg.) in dimethylsulphoxide (1 ml.) (nitrogen atmosphere). After 1 hr. at room temp. no starting material was present (t.l.c.; silica; chloroform:ethyl acetate::10:1; sulphuric acid) and 2 products had been formed. Solvents were evaporated and the products isolated by t.l.c. (silica; chloroform:ethyl acetate::10:1). They had (faster-running component) ν_{max} . 1731, 1643 cm.⁻¹, and (slower-running component) ν_{max} . 1727, 1627, 1603 cm.⁻¹. The first substance is probably 5-acetoxy-5,6,7,8-tetrahydro-1-hydroxy-8-oxonaphthalene (114) and the second the derived hydrazone (115)

E.

Experiment D was repeated at 85° for 30 min. The major product, isolated as an oil, ν_{max} . 1727, 1627, 1603 cm.⁻¹, is probably the hydrazone (115).

F.

The ketone (5) (several mg.) was shaken for 12 hr. with tetrahydrofuran and conc. aqueous ammonia

(two layers). The mixture was evaporated at room temp., mixed with water, and extracted with dichloromethane. The extract was dried and evaporated. The major component of the resulting oil, isolated by t.l.c. (silica; chloroform:ethyl acetate::10:1), had $\nu_{\max}$. 1733, 1643 cm^{-1} and is probably the phenolic ketone (114).

G.

Aqueous sodium hydroxide (4N; 1 drop) was added to a stirred solution of the ketone (5) (several mg.) in ethanol (ca. 2 ml.) (nitrogen atmosphere). Samples were withdrawn at intervals, quenched in aqueous tartaric acid (pH ca. 2.2), and extracted with ether. The extracts were examined by t.l.c. (silica; chloroform:ethyl acetate::10:1; sulphuric acid). The starting material was destroyed very rapidly and the mixture became black. After 24 hr. the phenolic ketone (114) was still present (t.l.c.). The mixture was poured into aqueous tartaric acid (pH ca. 2.2) and extracted with dichloromethane. The extract was dried and evaporated. The residue had $\nu_{\max}$. 1727, 1707, 1643 cm^{-1} . T.l.c. (silica; chloroform:ethyl acetate::10:1; sulphuric acid) revealed the presence of 6 compounds, the major one remaining near the origin.

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