SOME APPROACHES TO THE SYNTHESIS OF TETRACYCLINE

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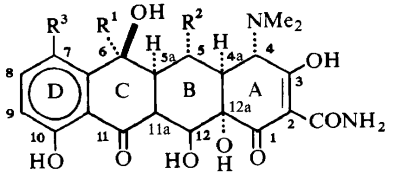
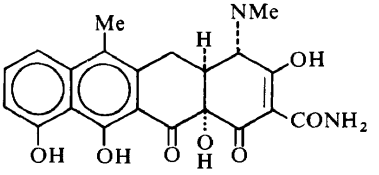
ABSTRACT

Some approaches to the synthesis of tetracycline are described.

Tetracycline [(I), $R^1 = Me$, $R^2 = R^3 = H$] is a member of the important group of tetracycline antibiotics. Other members of this group of medicinal importance are aureomycin [(I), $R^1 = Me$, $R^2 = H$, $R^3 = Cl$], terramycin [(I), $R^1 = Me$, $R^2 = OH$, $R^3 = H$] and 6-demethyltetracycline [(I)], $R^1 = R^2 = R^3 = H$]. All these compounds represent challenging objectives for total synthesis.



(I)



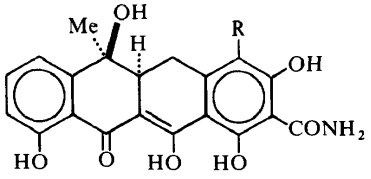
(II)

The total synthesis of 6-demethyl-6-desoxytetracycline was reported some years ago[1,2]. Although this is not a natural product it does have significant biological activity. The first synthesis of a naturally occurring tetracycline antibiotic was effected only recently[3]. It involved the synthesis of the compound (II) which had already been converted[4] into tetracyline [(I), $R^1 = Me$, $R^2 = R^3 = H$]. Finally, a beautiful total synthesis of terramycin [(I), $R^1 = Me$, $R^2 = OH$, $R^3 = H$], not involving any relay, has recently been described by Muxfeldt and his collaborators[5].

All these syntheses start with ring D, or with rings C and D, and then add stepwise the elements of rings A and B. All this synthetic work is scientifically

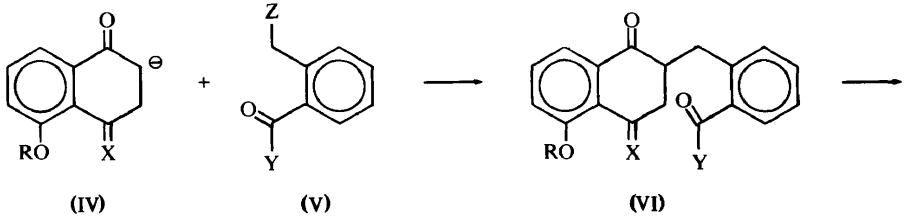
significant for a number of reasons. The tetracyclines are sensitive to acid and to base and have a sufficient number of asymmetric centres so that careful attention must be paid to the stereospecificity of the reactions used. The type of molecule does not have synthetic precedent. One has, therefore, the challenge of devising new chemistry involving molecules which will withstand only gentle reagents.

Our own approach to the synthesis of tetracycline itself, which began in 1957, has been to construct a molecule with rings A and D aromatic and to convert, at a late stage, ring A into the required hydroaromatic form. As a first synthetic objective we selected the molecule (III) where R = H, OH or NMe_2.

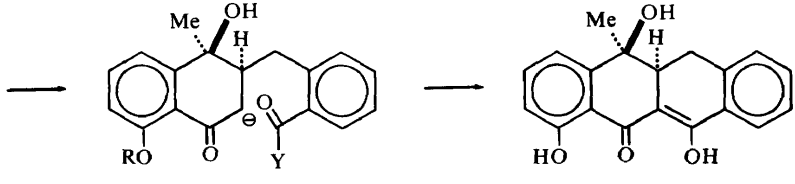


(III)

We have studied various methods of construction for the ring system of (III) starting with the simple and proceeding to the esoteric and more interesting. An obvious method of synthesis for molecules of type (III) is to condense a suitable α-decalone (IV) with a suitable *o*-substituted benzoic acid derivative (V) to give the intermediate (VI). By the addition of methyl carbanion to (VI) the correct stereochemistry at C-5a and C-6 should result. Furthermore by appropriate modification of the group X the intermediate (VII) would result whose ring closure to (VIII) would follow. We have only to make the correct choice of R, X, Y and Z.

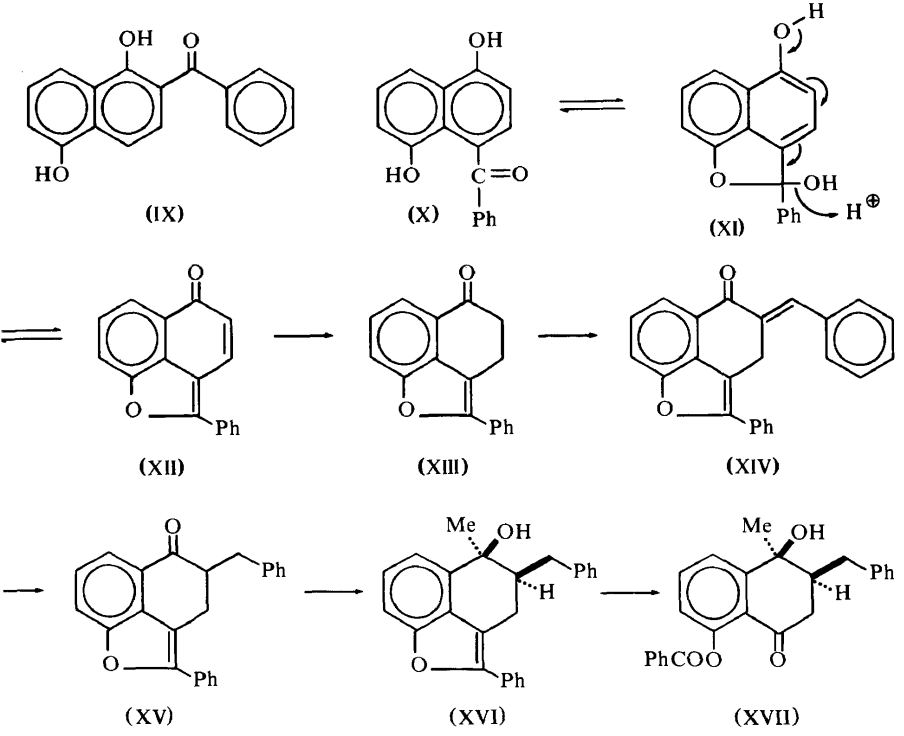


(IV) (V) (VI)



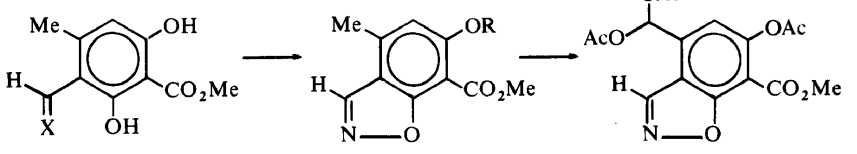
(VII) (VIII)

We decided to construct rings C and D from the readily available 1,5-dihydroxynaphthalene. Friedel–Crafts type condensation of this diphenol with benzoic acid using zinc chloride as catalyst gave only minor amounts of the expected 2-benzoyl-derivative (IX). The major product (40 per cent) was the nicely crystalline methylenequinone (XII) which had clearly been formed from 4-benzoyl-1,5-dihydroxynaphthalene (X) by the acid catalysed process indicated [(X) → (XI) → (XII)]. In suitable cases this process is reversible, compounds of type (XII) giving back compounds of type (X). Having discovered the formation of (XII) in such good yield, we decided to take advantage of its unique functionality. Hydrogenation over Raney nickel gave in high yield the dihydro-derivative (XIII). This condensed smoothly under basic conditions with benzaldehyde to afford the derivative (XIV). Further hydrogenation over Raney nickel gave the benzyl derivative (XV). As anticipated this reacted smoothly with methyl magnesium iodide to afford stereospecifically the tertiary carbinol (XVI) which on ozonolysis with a reductive work-up gave the keto-benzoate (XVII). We had thus solved, in principle, all problems of functionality and of stereochemistry in rings C and D. The ozonolysis step [(XVI) → (XVII)] clearly constituted an elegant procedure for unmasking the desired keto-phenol function at C-10 and C-11 at a late or terminal stage of a tetracycline synthesis.



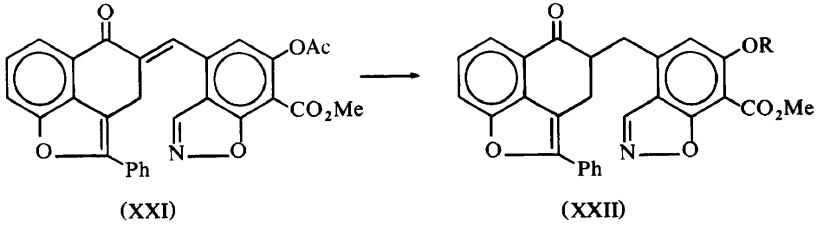
We now consider the introduction of the appropriate functional groups into ring A with the intention of preparing the compound [(III), R = H]. The obvious precursor of the A ring is 3,5 dihydroxytoluene (orcinol) which

may be purchased relatively cheaply in large quantities. Orcinol is readily carboxylated at the 4-position to give orcinol *p*-carboxylic acid and thence the methyl ester. Formylation of this ester under Gattermann conditions gave the expected aldehyde [(XVIII), X = O] in excellent yield. The problem of masking this aldehyde function whilst transforming the methyl group into another aldehyde function was easily solved as follows. The aldehyde [(XVIII), X = O] was converted into its oxime [(XVIII), X = N—OH] which was readily monoacetylated to give the oxime acetate [(XVIII), X = NOAc]. Pyrolysis of the latter in refluxing xylene afforded in excellent

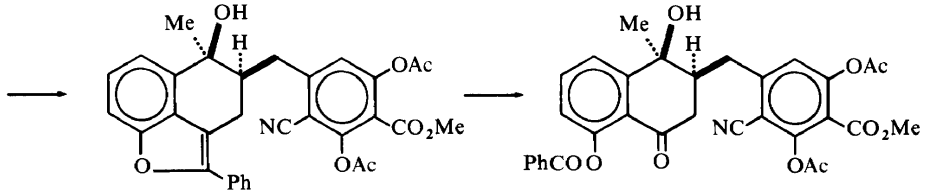


(XVIII) (XIX) (XX)

yield the isoxazole [(XIX), R = H]. Of course, such isoxazoles readily isomerize to cyano-phenols under the influence of mild base, but they are perfectly stable to acid conditions. Thus acid-catalysed acetylation gave the acetate [(XIX), R = Ac] which was smoothly, albeit in modest yield, oxidized under Thiele conditions (acetic anhydride–sulphuric acid–chromium trioxide) to the aldehyde diacetate (XX). The latter condensed readily with the ketone (XIII) under acid catalysis (acetic acid–sulphuric) to furnish the benzylidene-derivative (XXI). The conjugated double bond in the latter could not be reduced selectively. We required a reductant which would be effective under acid conditions. After some reflection we decided to use the classical reagent dry hydrogen iodide. Reduction with this reagent at room

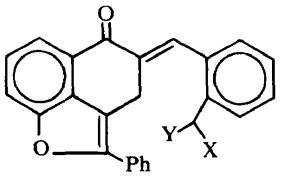


(XXI) (XXII)

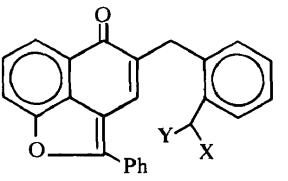


(XXIII) (XXIV)

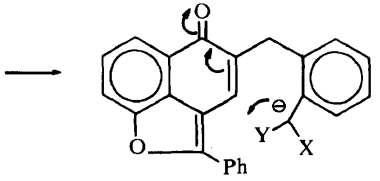
temperature gave in good yield the phenol [(XXII), R = H] smoothly acetylated with acetic anhydride–sulphuric acid to the acetate [(XXII), R = Ac]. Treatment of the latter with pyridine–acetic anhydride cleaved the isoxazole to the corresponding cyanophenol which was acetylated to the cyano-diacetate. This reacted smoothly with excess of methyl magnesium iodide to give, after reacetylation with pyridine–acetic anhydride, the desired diacetate ester (XXIII). The selectivity of the Grignard reaction was gratifying, both the ester and the nitrile groups being unattacked, no doubt because of the generation of phenolate anions from the acetate functions in ring A. Ozonolysis of the derivative (XXIII) with reductive work-up gave without difficulty the desired ketone (XXIV). However, all attempts with sodium hydride to cyclize the anion of this ketone on to the nitrile function proved abortive.



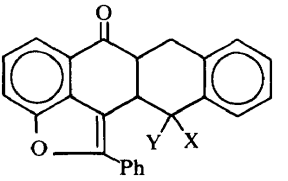
(XXV)



(XXVI)

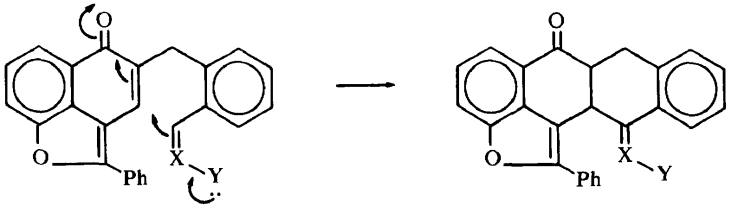


(XXVII)



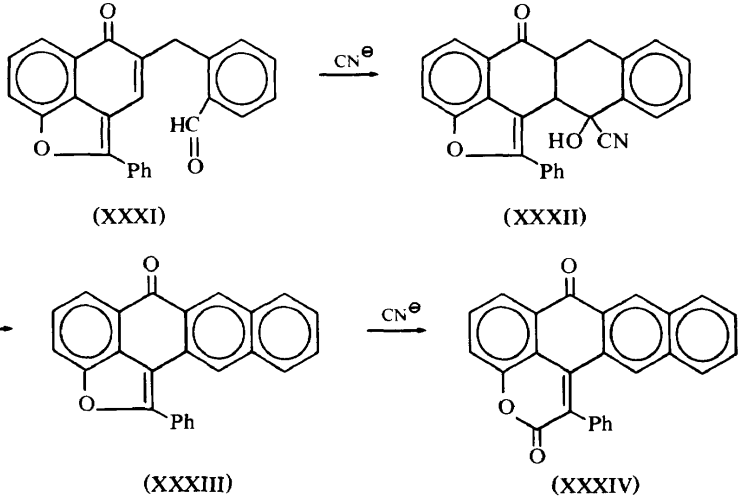
(XXVIII)

The above approach to the tetracycline nucleus involved the conceptual attack of an anion at C-11a upon an electrophilic centre at C-12. An alternative scheme would involve the attack of an anion generated at C-12 upon an electrophilic centre at C-11a. The scheme summarized in the formulae (XXV), (XXVI), (XXVII) and (XXVIII) represents our initial thinking about this alternative approach. It remains to define the nature of X and Y and to show that the rearrangement of (XXV) to (XXVI) is indeed a thermodynamically possible process with the equilibrium largely on the side of (XXVI). We did not neglect, also, consideration of a modified scheme indicated in (XXIX) → (XXX). In this scheme (=X—Y) should clearly be a suitable aldehyde derivative (oxime, phenylhydrazone, substituted phenylhydrazone, semicarbazone etc.). There is good analogy in sugar chemistry for such carbon–carbon bond forming processes. Unfortunately all attempts that we made under mild acid or mild basic conditions to effect the ring closure (XXIX) → (XXX) gave no sign of cyclization. It is possible that the thermodynamics for this process are wrong and one has to remember that the C-11a, C-12 bond in a molecule such as (XXX) is strongly hindered by the phenyl residue attached to the modified ring B.



(XXIX) (XXX)

We turn now from conception to execution. The condensation of *o*-phthalaldehyde with the ketone (XIII) in ethanol–triethylamine under reflux afforded an excellent yield of the hoped for derivative (XXXI). In the chemistry of aromatic aldehydes there is already a well known reaction, the benzoin condensation, which allows, by the intermediate formation of the cyanohydrin, the aldehyde carbon to support a negative charge. We anticipated, therefore, that treatment of the aldehyde (XXXI) with cyanide ion would give the cyanhydrin which on ring closure would afford the cyanohydrin (XXXII) or its derived ketone (cf. the benzoin condensation). In the event treatment of the aldehyde (XXXI) with cyanide ion in refluxing ethanol gave smoothly a major product (XXXIII) and a minor product (XXXIV). The major product must be formed according to the hypothetical mechanism,

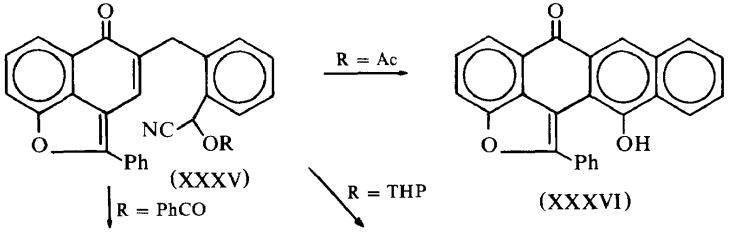


(XXXI) (XXXII)

(XXXIII) (XXXIV)

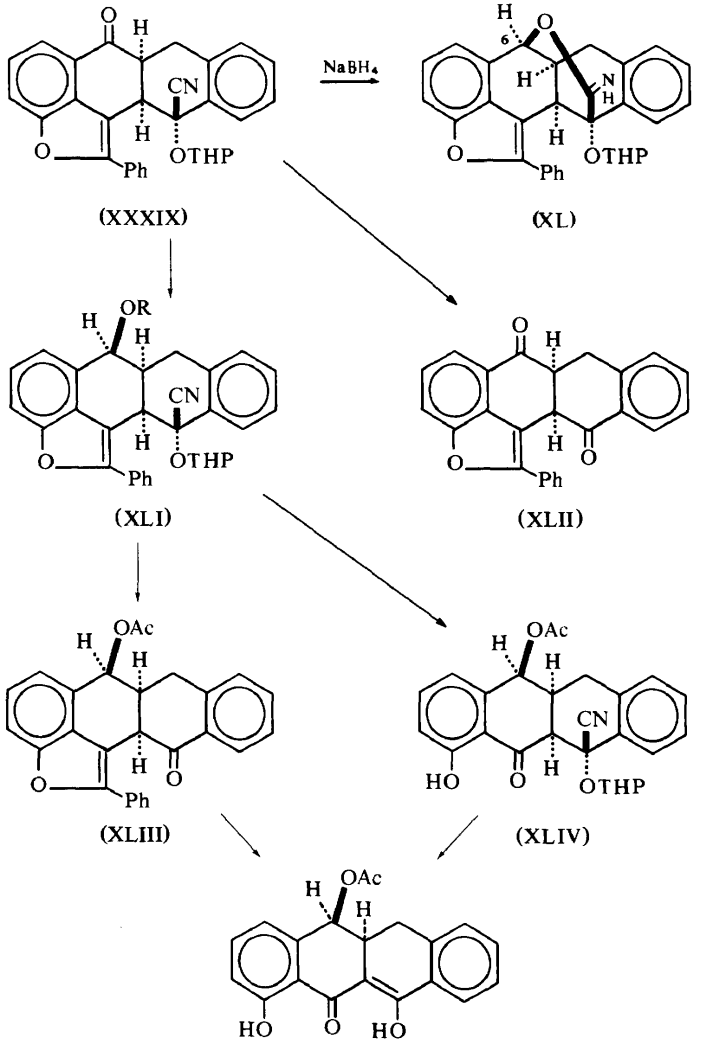
but the intermediate cyanohydrin (XXXII) must lose, by obvious anionic mechanisms, the elements of water and then of hydrogen cyanide to give the naphthalene (XXXIII). The minor product was shown to be formed from the major product (XXXIII) by further reaction with excess of cyanide ion. The mechanism of formation of the lactone (XXXIV) requires the nucleophilic addition of cyanide ion to the methylenequinone system of (XXXIII) followed by regeneration of the methylenequinone system by phenolate anion (C-10) elimination. Addition of the latter to the electrophilic cyanide group then affords, after hydrolysis, the observed lactone (XXXIV).

We considered next that if the cyanohydrin derived from the aldehyde (XXXI) could be stabilized against reversal then the desired ring closure would take place under more carefully defined conditions. A cyanohydrin may be stabilized by acylation or by etherification. The cyanhydrin [(XXXV), R = H] was readily prepared from the aldehyde (XXXI) and converted into its acetate [(XXXV), R = Ac] and its benzoate [(XXXV), R = PhCO]. Treatment of the acetate [(XXXV), R = Ac] with sodium hydride in dimethylsulphoxide afforded smoothly the phenol (XXXVI), characterized as its acetate. Clearly the elements of hydrogen cyanide had been lost followed by oxidation of the intermediate ketone by the dimethylsulphoxide (or possibly air). Under the same conditions the benzoate [(XXXV), R = PhCO] gave the nitrile (XXXVII) in good yield by the elimination of benzoate anion followed by oxidation.



We turned therefore, to etherification. The cyanhydrin [(XXXV), R = H] afforded readily a tetrahydropyranyl derivative [(XXXV), R = THP] under the usual acid conditions. This pyranyl ether was smoothly cyclized by sodium tert.-butoxide in ether to the desired ketone derivative (XXXVIII). It is clear that the tetrahydropyranyl ethers of the cyanohydrins of aromatic aldehydes should find a useful role in organic synthesis. We may add, in passing, that the corresponding ethers of aliphatic aldehyde cyanohydrins do not furnish anions readily and we do not foresee immediate applications for such compounds.

It was possible to show that the cyclized tetrahydropyranyl ether (XXXVIII) had the stereochemistry summarized in (XXXIX). The *cis*-ring fusion was indicated by n.m.r. spectroscopy. It was proved chemically by reducing the ketone group with sodium borohydride to furnish the iminolactone (XL). This iminolactone can only be formed if the ring fusion is *cis*- and the less bulky nitrile function within the fold of the molecule as indicated. There is every reason to believe (see further below) that the three asymmetric centres in (XL) are in their most stable arrangement.



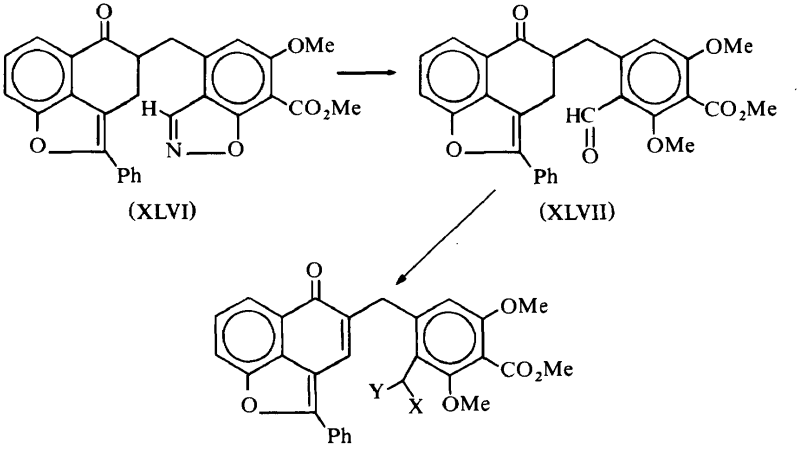
(XXXIX) (XL) (XLI) (XLII) (XLIII) (XLIV) (XLV)

Reduction of the ketone (XXXIX) with the milder reagent lithium tri-tert.-butoxy aluminium hydride gave without difficulty the alcohol [(XLI), R = H]. The stereochemistry at C-6 in both the iminolactone (XL) and the alcohol [(XLI), R = H] is predicted, because of the *cis*-ring fusion, to be as indicated. The n.m.r. spectra of (XL) and of [(XLI), R = H] confirmed this assignment.

On mild acid hydrolysis the ether (XXXIX) gave the corresponding cyanohydrin which, on chromatography over alumina, afforded the desired diketone (XLII). As expected treatment with basic reagents in air readily dehydrogenated this diketone to the phenol (XXXVI).

The alcohol [(XLI), R = H] gave on acetylation the acetate [(XLI), R = Ac] which, on similar acid hydrolysis and chromatography over alumina, afforded the acetoxy-ketone (XLIII). Ozonolysis of the latter with hydrolytic, not reductive, work-up gave the desired tetracycline model (XLV). A better yield of the phenol (XLV) was obtained by prior ozonolysis as above of the acetate [(XLI), R = Ac] to the keto-phenol (XLIV) followed by acidic hydrolysis and chromatography over alumina. The model compound (XLV) has the correct stereochemistry as follows from its method of synthesis.

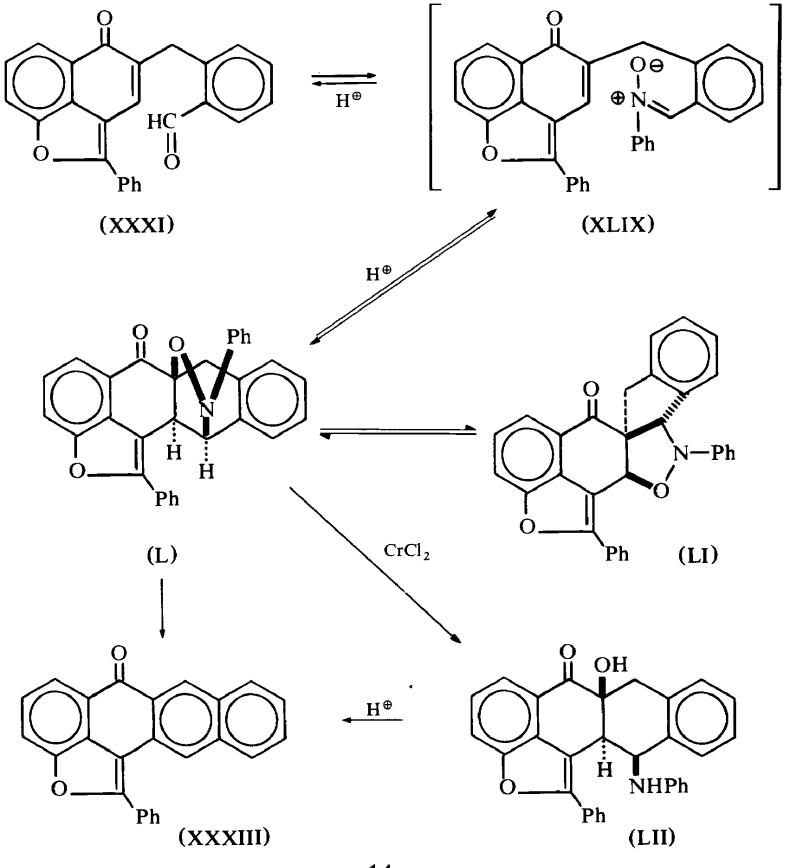
The applicability of this synthetic scheme to the preparation of a tetracycline analogue with the correct functionality in ring A was then explored. The compound [(XXII), R = H], obtained directly by hydrogen iodide reduction of (XXI), was methylated with methyl iodide–silver oxide to give the methyl ether (XLVI). On hydrogenation the isoxazole ring was smoothly reduced to the corresponding phenolic imine, which on mild acid hydrolysis followed by methylation as above gave the dimethyl ether (XLVII). Dehydrogenation with dichlorodicyanoquinone converted the latter into desired unsaturated aldehyde [(XLVIII), X + Y = O]. It was necessary to adopt this indirect route because the exocyclic ethylenic linkage of (XXI) could not be isomerized to the endocyclic linkage by acid and the use of basic reagents was forbidden by the presence of the isoxazole ring. Furthermore, the isoxazole ring in (XXI) could not be hydrogenated smoothly in spite of many efforts.



The aldehyde [(XLVIII), X + Y = O] afforded without difficulty the required cyanohydrin tetrahydropyranyl ether [(XLVIII), X = CN, Y = OTHP] but all attempts at base catalysed cyclization were abortive. It seemed that the required anion was being formed but that it did not cyclize, no doubt due to the extra steric compression due to the substituents in ring A.

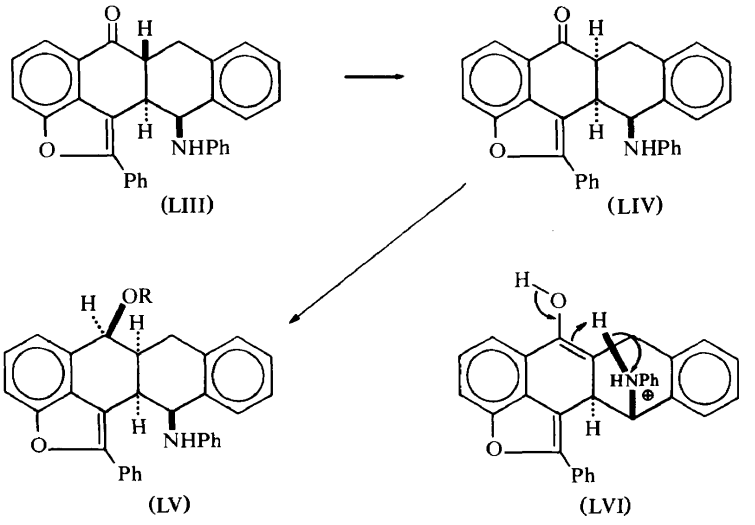
Another mechanistic type of reaction which could, in principle, form the C-11a, C-12 bond is a molecular process where discrete ions are not involved.

The reaction of a nitrone to an ethylenic linkage is a molecular process (1,3-dipolar addition), which gives an adduct containing an extra carbon–carbon bond. We examined the application of this idea to tetracycline synthesis in the following way. The readily available aldehyde (XXXI) was treated with a slight excess of phenylhydroxylamine in ethanol at room temperature for five days to give a major adduct (87 per cent) and a minor adduct (11 per cent). We considered that these two adducts must be formed by the intramolecular cyclization of the initial nitrone (XLIX) and that they must, therefore, be (L) and (LI). It was easy to differentiate between these two structures by n.m.r. spectroscopy and, fortunately, the major adduct had the constitution (L) whilst the minor adduct was (LI). The two adducts were readily equilibrated, by reversal to the nitrone (XLIX), simply by heating under reflux in ethanol. The equilibrium between the two compounds corresponded to the percentages originally isolated. It was possible, therefore, to obtain an essentially quantitative yield of the desired adduct (L). Treatment with acid hydrolysed the latter back to the initial aldehyde (XXXI), a process anticipated because of the ease of the equilibration reaction.



Chemical proof for the constitution of the adduct (L) was provided as follows. Treatment with potassium tert. butoxide in benzene gave the now familiar ketone (XXXIII). More significantly reduction of the adduct (L) with chromous chloride gave in excellent yield the dihydro-derivative (LII). In cold concentrated sulphuric acid this afforded smoothly the same ketone (XXXIII). This latter elimination could not, of course, involve reformation of the nitrone (XLIX) and reequilibration. It was of interest that the minor adduct (LI) was inert to chromous chloride. Clearly the reduction of the adduct (L) involves a prior coordination of the reagent with the ketone and ethereal oxygen functions that is obviously not possible with the adduct (LI).

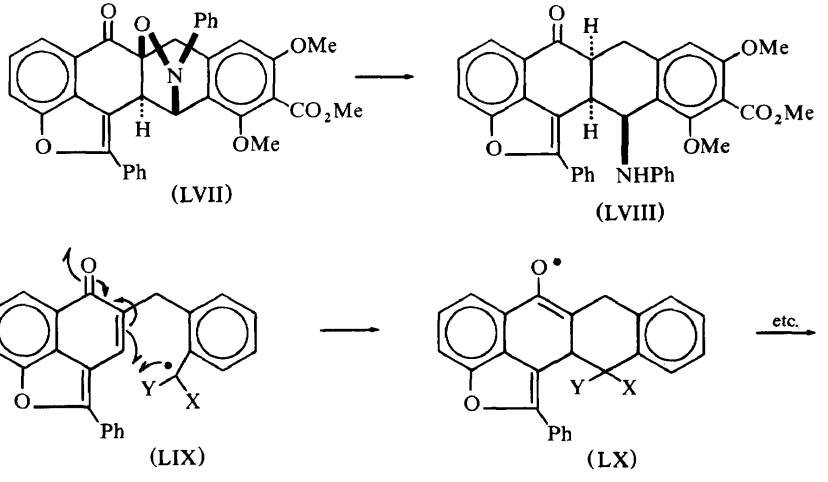
Further reactions on the derivative (LII) were now explored. Brief reduction with zinc dust in acetic acid containing a trace of hydrochloric acid afforded the desoxy-compound (LIII) in high yield. On chromatography over alumina this isomerized to the more stable *cis*-isomer (LIV). The latter was smoothly reduced by lithium aluminium hydride to the secondary alcohol [(LV), R = H], characterized as its acetate [(LV), R = Ac]. An n.m.r. analysis of the spectra of (LIII), (LIV), [(LV), R = Ac] and [(LV), R = H] provided proof for the stereochemistry assigned. It is clear that in the initial zinc dust reduction the initial enol (LVI) must be protonated by intramolecular transfer of hydrogen from the nitrogen function in order to explain the exclusive formation of the less stable *trans*-isomer (LIII).



We now treated the ring A substituted aldehyde (XLVIII) with phenylhydroxylamine and were gratified to obtain the desired adduct (LVII) in excellent yield. Reduction of this adduct as described above for the ring A unsubstituted series gave a good yield of the ketone (LVIII). For the first time we had in hand tetracycline type compounds which had the correct substitution pattern, at least in potential form, in all four rings (A, B, C and D).

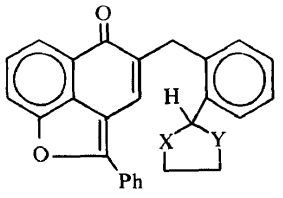
We would have continued with our studies of the ketone (LVIII) if, in the meantime, we had not discovered an even more interesting method of

constructing the tetracycline nucleus. For the formation of the critical C-11a, C-12 carbon–carbon bond we have used so far anionic and molecular (1,3-dipolar) reaction mechanisms. Another possibility, first emphasized by our colleague Dr D. L. J. Clive, would be a radical cyclization as indicated in formulae (LIX) and (LX). Again, the problem is the appropriate choice of X and Y. It was proposed that the first experiments should be carried out

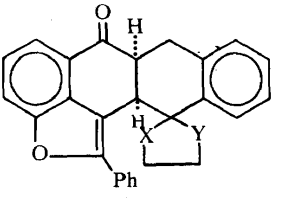


on the ethylene–acetal [(LXI), X = Y = O], formed in the conventional manner from the readily available aldehyde (XXXI). We appreciated, of course, that the radical [(LIX), X + Y = O—CH_2—CH_2—O] would readily rearrange to the corresponding β-ethenylacyl ester radical and most of our group were, in fact, not at all optimistic about the possibility of such radical cyclizations. The first experiment by Dr Clive was carried out in benzene containing benzoyl peroxide with ultra-violet irradiation to facilitate the radical fission of the peroxide. It gave readily a nicely crystalline product which was shown to be the 'expected' ketone [(LXII), X = Y = O]. We were astonished. Similarly the dithioacetal [(LXI), X = Y = S] cyclized even more readily to the ketone [(LXII), X = Y = S]. The hemithioacetal [(LXI), X = O, Y = S] cyclized readily to a mixture of two stereoisomers [(LXII), X = O, Y = S] and [(LXII), X = S, Y = O] to which stereochemistry was assigned by various spectroscopic considerations. Finally even the aldehyde (XXXI) cyclized to the diketone (XLII) in 28 per cent yield. In fact, specimens of this aldehyde which had been left exposed to laboratory lighting for some months already contained significant amounts of the diketone (XLII). Acidic hydrolysis of the ketal [(LXII), X = Y = O] gave the same diketone (XLII) as did treatment of the dithioketal [(LXII), X = Y = S] with mercuric chloride in aqueous acetic acid containing potassium acetate. The best yield (70 per cent) in the cyclization of [(LXI), X = Y = O] using benzoyl peroxide was secured using a tungsten lamp.

We were reluctant to accept that reactions which gave such yields of highly hindered products could really be radical in character. Indeed, when



(LXI)



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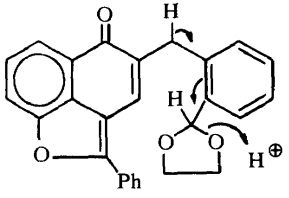

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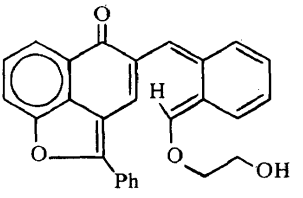

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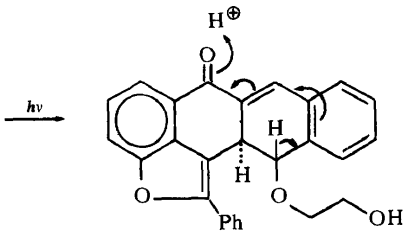
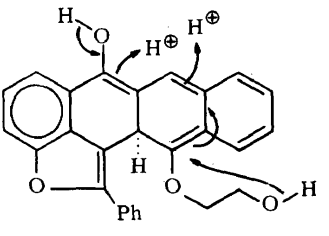
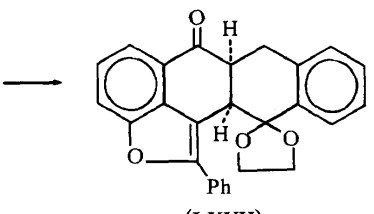


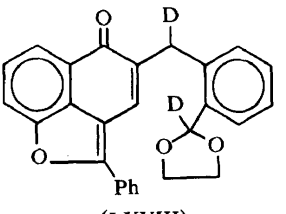
(LXV)



(LXVI)



(LXVII)



(LXVIII)

the acetal [(LXI), X = Y = O] was heated under reflux in benzene containing benzoyl peroxide no cyclization occurred even though the peroxide was decomposed in the usual way. The products of the thermal reaction were the conventional ones expected from the rearrangement, without cyclization, of the radical [(LIX), X + Y = O—CH_2—CH_2—O]. Nevertheless benzoyl peroxide was needed for the photocyclization. It could, however, be decomposed completely thermally before the addition of the acetal [(LXI), X = Y = O] without any diminution of yield in the subsequent photochemical reaction. We investigated the active agent from decomposed benzoyl peroxide and quickly established that it was simply benzoic acid.

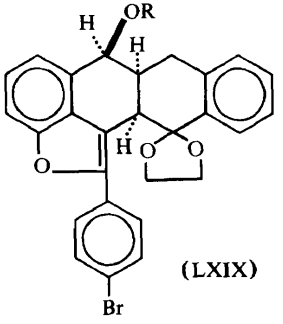
Other carboxylic acids had the same favourable effect on the photocyclization. It is, in fact, clear that this acid catalysed photocyclization involves protonation of the acetal [(LXI), X = Y = O] as in the formula (LXIII) and isomerization to the triene system (LXIV). A conventional conrotatory photocyclization of the triene then affords the intermediate (LXV) which by further protonation etc. [see (LXVI)] gives the product (LXVII). Some evidence in favour of this relatively involved scheme was secured as follows. *o*-Phthaldehyde was prepared with both of the aldehyde groups deuterated. This was condensed with ketone (XIII) with the usual triethylamine catalysis to furnish, after acetalization, the dideuterated derivative (LXVIII) (mass spectrum). Photocyclization gave the ketal (LXII) which had only one deuterium atom per molecule (mass spectrum). N.m.r. analysis showed that this deuterium atom was in the methylene group and approximately equally distributed between the two possible configurations. Of course, the deuterium atom in the methylene group could have been lost also if the equilibrium between (LXIII) and (LXIV) were prolonged. It is clear that under our conditions of photocyclization the triene (LXIV) must be cyclized as fast as it is formed.

The stereochemistry assigned to the ketal (LXVII) and its congeners was initially based on n.m.r. analysis. Although there was no reason to doubt the correctness of the configurational assignment we decided to confirm our conclusion by x-ray analysis. 1,5-Dihydroxynaphthalene was condensed with *p*-bromobenzoic acid to give the *p*-bromophenyl derivative corresponding to (XII). This compound was carried through the sequence of reactions to give the *p*-bromophenyl analogue of the ketal (LXVII). This was then reduced with sodium borohydride to the corresponding alcohol [(LXIX), R = H] which was readily acetylated to the acetate [(LXIX), R = Ac]. The n.m.r. spectrum of this acetate was fully in accord with the assigned stereochemistry. An x-ray analysis of this compound, kindly carried out by Professor D. Rogers and Dr D. L. Sales of Imperial College, fully confirmed the constitution and stereochemistry that we had assigned.

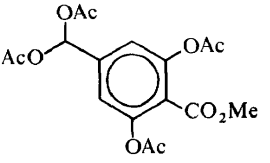
We were now in a position to apply the photocyclization reaction in the ring A substituted series with confidence that, because the light would provide the needed activation with plenty of energy to spare, the hindered C-11a, C-12 bond would be formed without difficulty. The diacetate of orcinol *p*-carboxylic acid methyl ester was oxidized under Thiele conditions to the aldehyde diacetate (LXX). The latter, condensed with the ketone (XIII) under the usual acid catalysed conditions, gave the expected exocyclic derivative. Acid catalysed hydrolysis gave the corresponding diphenol which with triethylamine was smoothly isomerized to the endocyclic derivative [(LXXI), R = H] in 80 per cent overall yield. This was formylated with ethyl orthoformate and aluminium trichloride to afford in high yield the aldehyde [(LXXII), R = H, X = O]. After methylation with potassium carbonate–methyl iodide in the usual way the resultant dimethyl ether [(LXXII), R = Me, X = O] was converted into its acetal [(LXXII), R = Me, X = O—CH_2—CH_2—O] in the usual way. Photocyclization as above gave without difficulty the desired ketone [(LXXIII), X = OMe] in 35 per cent yield. Attempted photocyclization of the corresponding diacetate [(LXXII),

R = Ac, X = O—CH_2—CH_2—O] gave only interactable products due, no doubt, to a competitive photo–Fries type reaction.

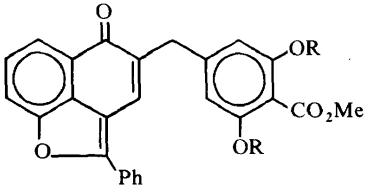
The ester [(LXXIII), X = OMe] was hydrolysed and converted into the corresponding amide [(LXXIII), X = NH_2] by standard reactions. The latter was treated with methyl lithium to furnish the crystalline amide (LXXIV). Ozonolysis with reductive work-up gave a good yield of the keto-benzoate [(LXXV), R = PhCO] which, with sodium methoxide, afforded the corresponding phenol [(LXXV), R = H]. On heating with hydriodic



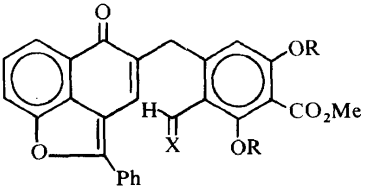
(LXIX)



(LXX)



(LXXI)



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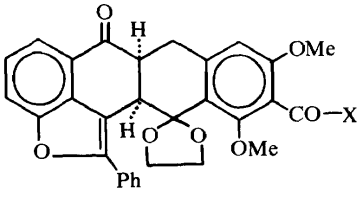
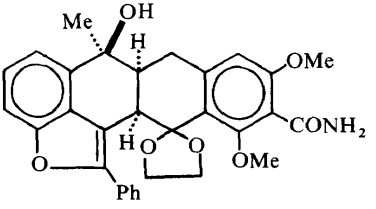
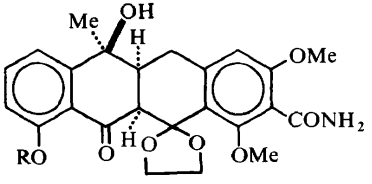


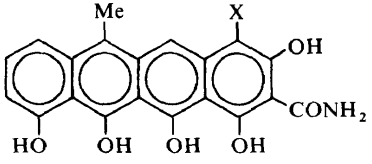
(LXXIII)



(LXXIV)



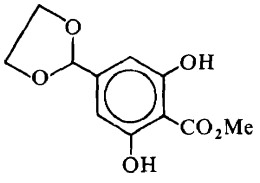
(LXXV)



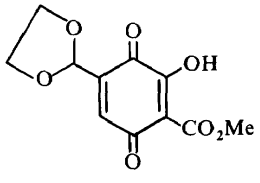
(LXXVI)

acid this afforded without difficulty 6-methylpretetramid [(LXXVI), X = H], identical with authentic material obtained by degradation of tetracycline[6]. Our work represents the first total synthesis of 6-methylpretetramid, which is an important biosynthetic intermediate in the formation of tetracycline *in vivo*[7].

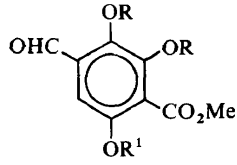
The above synthesis confirms that the photocyclization reaction is of general application. We decided next to apply the reaction to the preparation of compounds in which ring A is fully substituted. In this way we hoped to be able to prepare also 4-hydroxy-6-methylpretetramid [(LXXVI), X = OH], a further important intermediate in the biosynthesis of tetracycline[8,9,10].



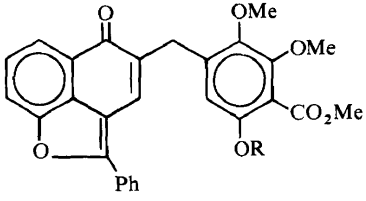
(LXXVII)



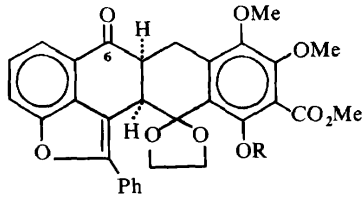
(LXXVIII)



(LXXIX)



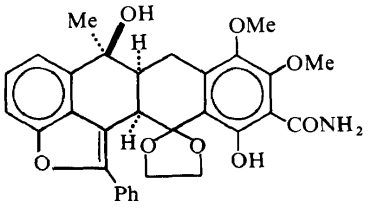
(LXXX)



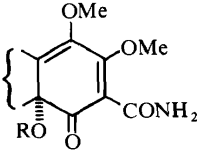
(LXXXI)

The tetraacetate (LXX) was hydrolysed with aqueous acid and the aldehyde group was acetalized in the usual way to give the derivative (LXXVII) in about 90 per cent overall yield. Oxidation with Fremy's salt afforded the hydroxyquinone (LXXVIII) (90 per cent) which on hydrogenation and mild acid hydrolysis furnished the aldehyde [(LXXIX), R = R^1 = H] (96 per cent overall). Methylation under standard conditions then gave the aldehyde [LXXIX), R = R^1 = Me]. This was condensed with the ketone (XIII) and further processed as above to give the methyl ester [(LXXX), R = Me] in about 90 per cent overall yield. The further steps in the synthesis were essentially as above, the photocyclization step to give the ketone [(LXXXI), R = Me] proceeding in the gratifying yield of 65 per cent. The reaction with methyl lithium on the corresponding ketone–amide proceeded normally as did the further steps as above, but the final reaction with hydriodic acid afforded not the expected 4-hydroxy-6-methylpretetramid [(LXXVI), X = OH] but again 6-methylpretetramid [(LXXVI), X = H]. We have thus carried out two different total syntheses of 6-methylpretetramid. Fortunately, whilst our work was in progress, the conversion of 6-methylpretramid to 4-hydroxy-6-methylpretatramid was reported[11] so we have, in effect, also completed a total synthesis of the latter.

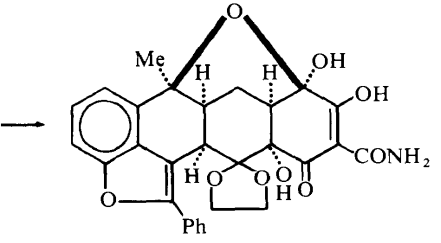
We may now consider the remaining problems in the synthesis of tetracycline by our approach. We envisage that there will be no difficulty in preparing the compound [(LXXXI), R = H] and in changing the ester grouping into an amide. The selective addition of methyl lithium to the 6-ketone function will not present any difficulty. We shall thus arrive at the compound (LXXXII). We have then to find a reaction which will introduce smoothly a hydroxyl group, or its equivalent, so that we obtain [(LXXXIII), R = H]. The required stereochemistry should follow automatically for this hydroxyl group because of the *cis*-folding of the molecule. Mild acid hydrolysis should then give us the compound (LXXXIV). The route from this compound to tetracycloxide (LXXXV) is obvious and the latter has already been converted back to tetracycline[12].



(LXXXII)



(LXXXIII)



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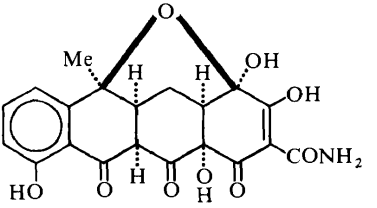
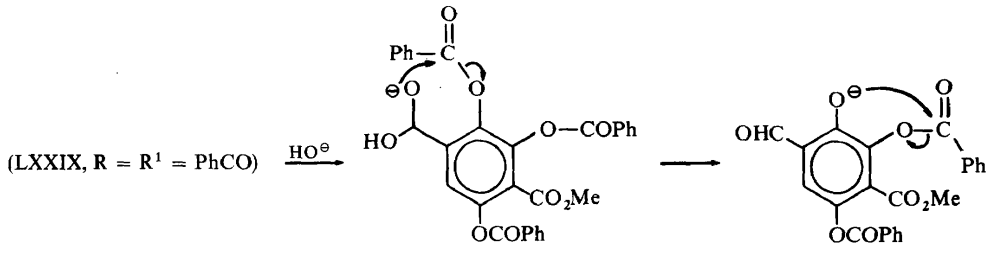
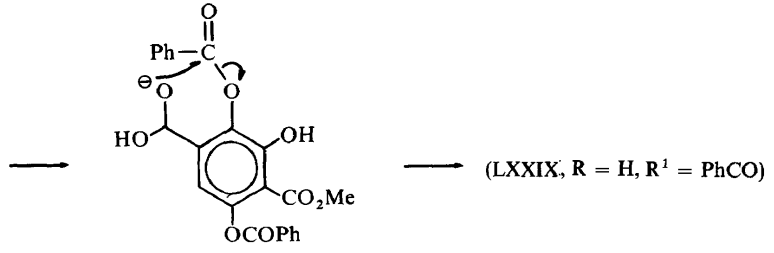


(LXXXV)

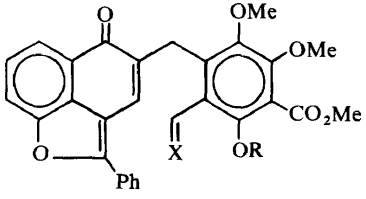
We have recently synthesized the compound [(LXXXI), R = $MeSO_2$] by the following route. The aldehyde [(LXXIX, R = R^1 = H] was converted quantitatively by benzoyl chloride in pyridine into its tribenzoate [(LXXIX), R = R^1 = PhCO]. We reasoned that this tribenzoate should be selectively hydrolysed by mild treatment with alkali to the monobenzoate [(LXXIX), R = H, R^1 = PhCO] by the mechanism which is summarized in the scheme [(LXXIX), R = R^1 = PhCO] → (LXXXVI) → (LXXVII) → (LXXVIII) → [(LXXIX), R = H, R^1 = PhCO]. In the event the latter monobenzoate was obtained selectively in 90 per cent yield by this procedure. Its constitution was confirmed by treatment with phosgene in pyridine which afforded the cyclic catechol carbonate [(LXXIX), R = R = CO, R^1 = PhCO]. Methylation of the aldehyde [(LXXIX), R = H, R^1 = PhCO] under standard conditions gave the dimethyl ether [(LXXIX), R = Me, R^1 = PhCO] which with sodium methoxide afforded the desired phenol [(LXXIX), R = Me, R^1 = H] in good yield.



(LXXXVI) (LXXXVII)



(LXXXVIII)



(LXXXIX)

This phenol was then condensed with the standard ring C/D component (XIII) under acid conditions to furnish, after further isomerization with triethylamine, the desired ketone [(LXXX), R = H]. This was smoothly formylated by $CHCl_2$—OMe in the presence of aluminium chloride to the aldehyde [(LXXXIX), X = O, R = H]. We were unable to prepare the ethylene acetal of this compound under the usual conditions. However, treatment with methanesulphonyl chloride in pyridine gave the corresponding methanesulphonate [(LXXXIX), X = O, R = $MeSO_2$] and this compound could be converted smoothly into its ethylene acetal [(LXXXIX), X = O—CH_2—CH_2—O, R = $MeSO_2$] in the usual way. Acid catalysed photocyclization gave the desired ketone [(LXXXI), R = $MeSO_2$] in reasonable yield and we hope soon to convert this into the key compound (LXXXII).

In the meantime we have been investigating methods for the specific *ortho*-hydroxylation of phenols in order to effect the conversion of (LXXXII) into (LXXXIII). In principle, the reaction of a phenolate anion with a

suitable diaryl peroxide appears to be promising. We have already published a preliminary account of our work[13].

The work described above was carried out during the last thirteen years in collaboration with the following colleagues: Dr E. Aufderhaar, Dr J. E. Baldwin, Dr L. Bould, Dr (Mrs) J. A. Challis, Dr D. L. J. Clive, Dr D. J. Collins, Mr D. H. Davies, Dr S. D. Djokič, Dr D. J. Faulkner, Dr N. J. A. Gutteridge, Dr B. Halpern, Dr T. Hase, Mr J. P. Marshall, Dr R. J. Martin, Dr J. I. Okogun, Dr M. J. Pearson, Dr Q. N. Porter, Dr M. Slaytor, Dr G. Smith and Mr D. Zurr. Thanks are due to all these colleagues for their contributions and especially to Dr P. G. Magnus who not only made important contributions to the experimental side of the work, but also participated very significantly in the conception and direction of the work during the last five years.

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