Experiments on the Synthesis of Tetracycline. Part IV.[1] Ring B Formation through 1,3-Dipolar Additions

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The model compound 4-(2-formylbenzyl)-2-phenylnaphtho[1,8-*bc*]furan-5-one (I; R = CHO) has been converted into the corresponding *N*-phenyl-6aβ,12β-epoxyiminonaphthaceno[1,12-*bc*]furan-6-one (II; R = H) by treatment with *N*-phenylhydroxylamine. Conversion of this intermediate into 6β-acetoxy-12β-anilino-6aα,7,12,12aα-tetrahydro-1-phenyl-6*H*-naphthaceno[1,12-*bc*]furan (X; R^1 = OAc, R^2 = H, R^3 = H) is described. A method for converting certain *N*-arylalkylamines into the corresponding imines has been developed, and the application of this oxidation to the synthetic sequence is elaborated. Finally, the successful application of the cyclisation procedure to produce tetracyclic substances bearing substituents in ring A is described.

HAVING been unsuccessful in applying the Michael reaction of cyanohydrin tetrahydropyranyl ethers to ring A substituted compounds,[1] we studied an alternative type of ring closure, namely the 1,3-dipolar addition reaction,[2,3] as exemplified by Scheme 1. Since earlier

SCHEME 1

studies in this laboratory [4] and elsewhere [5,6] had demonstrated the ease with which nitrones could be added to conjugated double bonds, we sought to apply this reaction in our synthesis. The presence of an aldehyde function in the model ACD compound (I; R = CHO) and also of a conjugated double bond suggested this pathway as a potential means of creating ring B. Although the nitrone [I; R = CH:$\overset{+}{N}$(O$^-$)Ph] derived by condensation of the aldehyde with phenylhydroxylamine, could in principle add to the conjugated double bond in either of two directions, we felt that the desired mode of addition, to provide a linear skeleton, would dominate. Upon treatment of the model aldehyde (I; R = CHO) with phenylhydroxylamine in ethanol two compounds were isolated. One (*ca.* 80% yield) was shown to be the adduct (II; R = H), $\nu_{max.}$ 1680 cm.$^{-1}$ $\lambda_{max.}$ 365, 299, 276, and 243 nm. (indicating reduction of the enone). The 7-methylene protons gave rise to an AB system in the n.m.r. spectrum (τ 6·69—6·17, J_{AB} 18—19 Hz), which also showed singlets occurred at τ 5·56 (1H) and 4·65 (1H). The other product (III; R = H) was obtained in *ca.* 11% yield. These adducts were separated by column chromatography. Each was easily converted, by a reversal of the addition process, into an equilibrium mixture of compounds (II; R = H) and (III; R = H), in proportions not significantly different from those at isolation, by refluxing in ethanol.

Compound (III; R = H) gave rise to an AB system at τ 6·17 and 6·69 (J_{AB} 19 Hz) in the n.m.r. spectrum. Mild acids and bases did not affect the rate of conversion of the starting aldehyde, nor the position of equilibrium. The use of ethan[^{2}H]ol as solvent caused no introduction of deuterium into the products. These observations are consistent with the proposed 1,3-dipolar mechanism, the reversibility of which in nitrone additions has also been noted by other workers.[7]

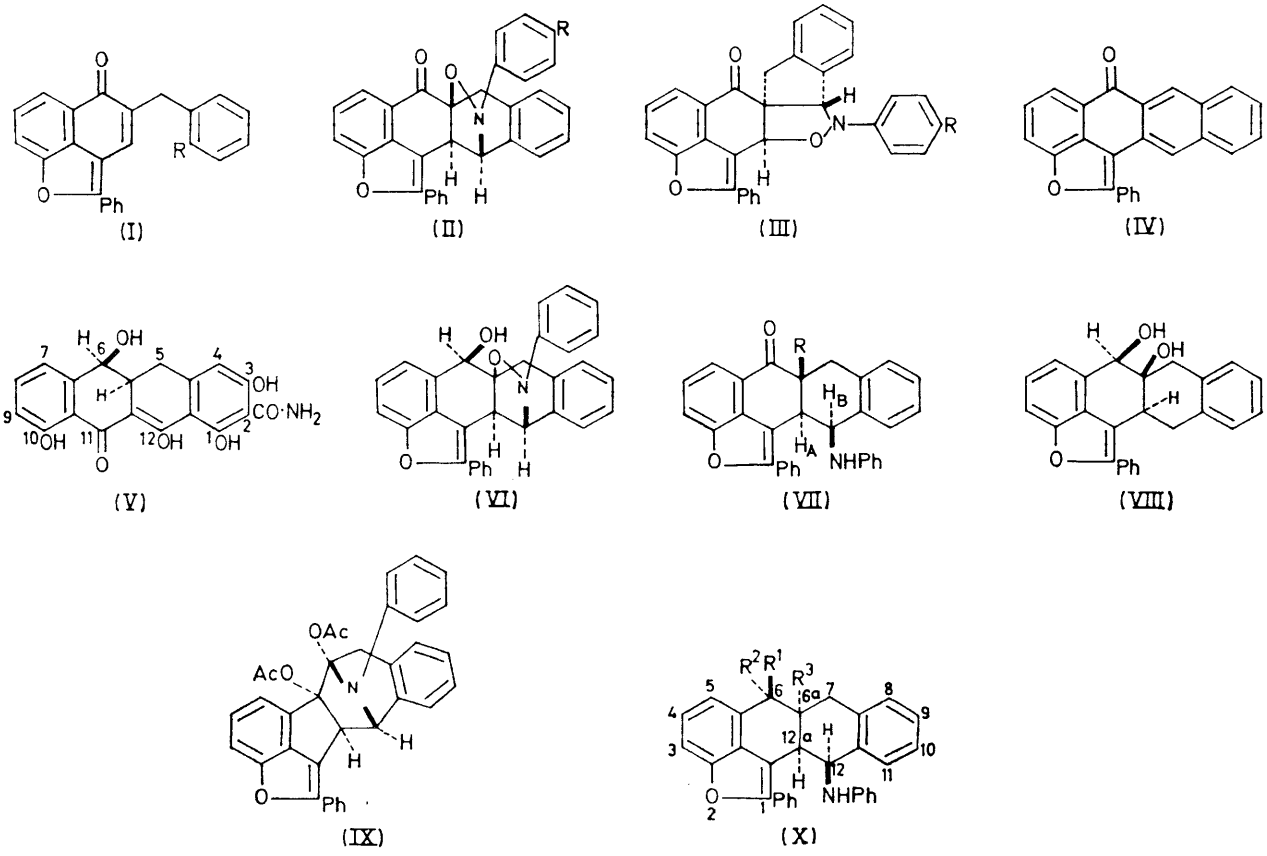
Further evidence for the structural assignments given to compounds (II; R = H) and (III; R = H) was obtained by chemical means (see later). Evidence for the ease of reconversion, even at room temperature, was found in the observation that strong mineral acid caused isomer (II; R = H) to revert to the aldehyde (I; R = CHO), presumably by an irreversible acid hydrolysis. Treatment with acetic anhydride and pyridine converted compound (II; R = H) into the amide (I; R = CO·NHPh),[8] $\nu_{max.}$ 3280, 1650, and 1620 cm.$^{-1}$, $\lambda_{max.}$ 406 and 265 nm., formed as a result of the action of acetic anhydride on the nitrone [I; R = CH:$\overset{+}{N}$(O$^-$)Ph].[9,10] When the isomer (II; R = H), was heated with potassium t-butoxide, aromatisation of ring B occurred to yield the known ketone (IV),[1] by elimination of the elements of phenylhydroxylamine. An attempt at bromination of compound (II; R = H) with *N*-bromosuccinimide led to the monobromo-compound (II; R = Br). No degradation of this derivative was attempted; however, the location of the bromine atom was readily discernible from the n.m.r. spectrum, which revealed an A_2B_2 system (τ 3·27 and 3·88, *J* 9 Hz) characteristic of a *p*-substituted aniline.[10] It may be that this bromination also proceeds through the open, nitrone form, since bromination of some alkyl nitrones occurs in the ring attached to the nitrogen atom.[11]

The structural requirements of the synthetic objective

[1] Part III, E. Aufderhaar, J. E. Baldwin, D. H. R. Barton, D. J. Faulkner, and M. Slaytor, preceding paper.
[2] R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 633.
[3] R. Huisgen, *Proc. Chem. Soc.*, 1961, 357.
[4] H. R. Browning, Ph.D. Thesis, London University, 1961.
[5] N. A. LeBel and J. J. Whang, *J. Amer. Chem. Soc.*, 1959, **81**, 6334; C. W. Brown, K. Marsden, M. A. T. Rogers, C. M. B. Taylor, and R. Wright, *Proc. Chem. Soc.*, 1960, 254.
[6] N. A. LeBel ,M. E. Post, and J. J. Whang, *J. Amer. Chem. Soc.*, 1964, **86**, 3759.
[7] N. A. LeBel and T. A. Lajiness, *Tetrahedron Letters*, 1966, 2173.
[8] O. L. Brady and F. P. Dunn, *J. Chem. Soc.*, 1926, 2411.
[9] F. Kröhnke, *Annalen*, 1957, **604**, 203.
[10] L. M. Jackman, 'Nuclear Magnetic Resonance Spectroscopy,' Pergamon, London, 1959, p. 92.
[11] J. K. Sutherland and D. A. Widdowson, *J. Chem. Soc.*, 1964, 3495.

(V) [1] were such that the isoxazolidine ring system of compound (II) would need to be opened in such a way as to provide a ketone function at C-12. Realising that hydrogenolysis of the weak N–O linkage could provide a 12-anilino-group, which in principle should be convertible into a 12-keto-function we were led to an examination of the reduction of compound (II; R = H).

The use of Adams platinum oxide catalyst, lithium aluminium hydride, or sodium borohydride, all resulted in reduction of the 6-keto-group to give the alcohol (VI), $\nu_{max.}$ 3400 and 3300 cm.$^{-1}$, the suggested



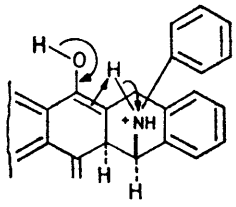
hydroxy-group orientation of which is inferred from the greater accessibility of the α-face, as shown by models. Chromic acid readily converted the alcohol (VI) into the starting ketone (II; R = H). Although a palladium catalyst did yield the required hydrogenolysis product (VII; R = OH), this was not a preparatively attractive route, as the alcohol (VI) and the further hydrogenolysis product (VIII) were formed concomitantly. However, exposure of (II; R = H) to chromium(II) chloride solution for 1 min. gave excellent yields of the hydrogenolysis product (VII; R = OH), $\nu_{max.}$ 3590, 3450, 3110, and 1690 cm.$^{-1}$. N.m.r. signals for H_A and H_B occurred at τ 4·50 and 5·89, respectively, with J_{AB} 5·5 Hz.

The possession of this material now allowed a clear distinction between the isomers (II; R = H) and (III; R = H) to be made, for structure (VII; R = OH) contains an AB system involving C-12a and C-12. This relationship, required by structure (II; R = H), but not by (III; R = H) is compatible with the coupling observed. In fact compound (III; R = H) did not react with chromium(II) chloride; this difference may be attributed to the possibility of preliminary co-ordination of Cr^{2+}, by the 6-carbonyl group in structure (II; R = H), thereby bringing the reducing species into a favourable steric relationship with the O–N bond. Such a situation cannot be achieved in structure (III; R = H).

Cold concentrated sulphuric acid degraded the dihydro-compound (VII; R = OH) to the known ketone (IV).[1] An attempted acetylation with acetyl chloride and pyridine in ether led to a rearrangement product, formulated as (IX). This substance, whilst retaining a reduced naphthofuran-chromophore ($\lambda_{max.}$ 310 nm.) showed only acetate absorption in the i.r. spectrum (1740 cm.$^{-1}$). The presence of two *O*-acetate groups, as required by the analytical figures and the absence of N–H absorption in the i.r. spectrum, suggested that a ketol rearrangement had taken place, with acetylation and final closure of the pyrrolidine ring system.

Although prolonged exposure of the ketone (VII; R = OH) to Cr^{2+} effected a reductive removal of the 6a-hydroxy-group, this could be achieved more efficiently by treatment with zinc in acetic acid for precisely 1 min. The product obtained by direct crystallisation

was the deoxy-compound (VII; R = H), $\nu_{max.}$ 3410, 1684, and 1601 cm., which was quantitatively isomerised to the more stable *cis*-fused isomer (X; R^1R^2 = O, R^3 = H) by chromatography over alumina. The nature of this isomerisation was demonstrated by the observation that compound (X; R^1R^2 = O, R^3 = H) readily incorporated four deuterium atoms attached to carbon, in warm acidic media. Three of these were bound to the *o*- and *p*-positions of the anilino-residue (mass spectrum), and the fourth was incorporated at C-6a, as determined by n.m.r. spectra, which showed the H-12a signal as a clean doublet (*J* 3 Hz), formed by coupling with H-12 only. In the undeuteriated compound this proton exhibited also a 6 Hz coupling with H-6a. We therefore attribute the isomerisation to an epimerisation of the ring junction, and further suggest an explanation of the kinetically controlled production of compound (VII; R = H), having the less stable configuration, during reduction. It is probable that the enol, formed by reductive removal of the C-6a



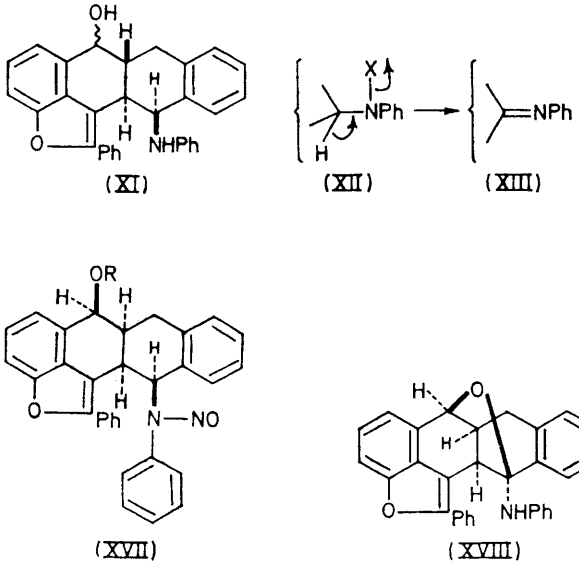
SCHEME 2

hydroxy-group is ketonised by intramolecular transfer of a proton from the nitrogen atom, a process which necessarily produces the less stable *trans* ring junction (*cf.* Scheme 2).

The next step in the sequence, reduction of the C-6 carbonyl group in compound (X; R^1R^2 = O, R^3 = H), could not be achieved by the Meerwein–Ponndorf method, which had been useful in a similar situation.[1] Sodium borohydride reduction led to the *trans*-alcohol (XI), in poor yield. Manganese dioxide oxidation of the *trans*-alcohol (XI) gave back the *trans*-ketone (VII; R = H), proving that the borohydride reduction was preceded by epimerisation. Lithium aluminium hydride reduction, however, provided the required *cis*-alcohol (X; R^1 = OH, R^2 = H, R^3 = H), $\nu_{max.}$ 3590, 3430, and 3380 cm.$^{-1}$, $\lambda_{max.}$ 306, 300, 250, 244, and 235 nm., which could be reoxidised to the *cis*-ketone (X; R^1R^2 = O, R^3 = H). The n.m.r. spectrum of this *cis*-alcohol was useful in the assignment of configuration. Thus the ring-junction protons H-6a and H-12a, were coupled (*J* 5 Hz) in a fashion compatible with their *cis*-relationship,[1,12] and H-6 and H-6a had the usual 3 Hz coupling found [1] in all those compounds exhibiting a *cis*-relationship between these two protons. Finally, the derived acetate (X; R^1 = OAc, R^2 = R^3 = H) showed the acetyl signal at high field (τ 8·65), attributed [1] to shielding by ring A, which can only occur in the assigned geometry.

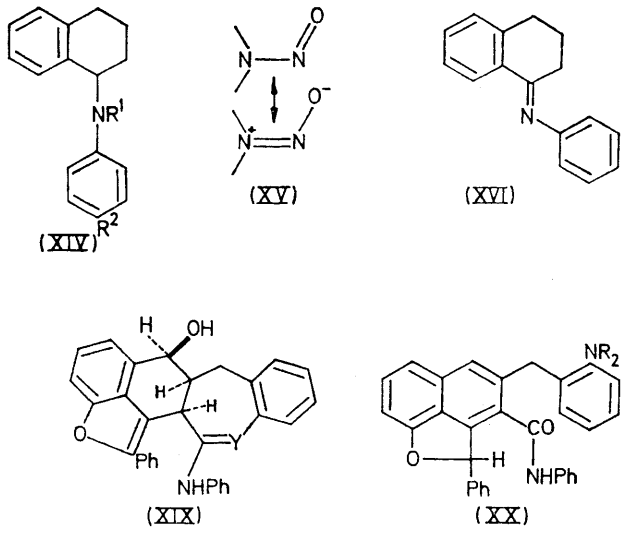
A third isomeric alcohol was obtained during extended reduction of the ketol (VII; R = OH) with zinc. This evidently possessed the stereochemistry shown in (X; R^1 = H, R^2 = OH, R^3 = H), since reoxidation provided the ketone (X; R^1R^2 = O, R^3 = H).

With the acetate (X; R^1 = OAc, R^2 = H, R^3 = H) of required stereochemistry in hand, we were now in a position to attempt the oxidation of the amino-residue to an imine. In essence, the production, by oxidative means, of some derivative such as (XII), where X is a good leaving group, should allow an elimination to occur, thereby providing the imine (XIII).



(XI) (XII) (XIII)

(XVII) (XVIII)



(XIV) (XV) (XVI)

(XIX) (XX)

A number of examples of this pathway have already been reported (*e.g.* with X = Cl [13] or SO_2Me [14]). However, attempts to make use of either of these methods

[12] H. Conroy, *Adv. Org. Chem.*, 1960, **2**, 265.
[13] W. E. Bachmann, M. P. Cava, and A. S. Dreiding, *J. Amer. Chem. Soc.*, 1954, **76**, 5554.
[14] W. Paterson and G. R. Proctor, *J. Chem. Soc.*, 1965, 485.

were unsuccessful, as also was the use of peracids, mercury(II) acetate,[15] chromium trioxide,[16] quinones,[17] silver(III) picolinate,[18] and the oxygen–platinum black system.[19] As this transformation was found to be more difficult than expected, we decided to examine a suitable model system in order to explore alternative methods. The amine (XIV; $R^1 = R^2 = H$) was prepared by treatment of tetralin with *N*-bromosuccinimide (1 equiv.) and treatment of the resulting benzylic bromide with aniline. Since a possible explanation of our failure to dehydrogenate the amine (X; $R^1 =$ OAc, $R^2 = H$, $R^3 = H$) was the formation, not of the N–X species (XII), but of *ortho*- and *para*-X-substituted derivatives, we chose to study the *N*-nitroso-function. Compounds containing this residue can be prepared under mild conditions, and are relatively stable.

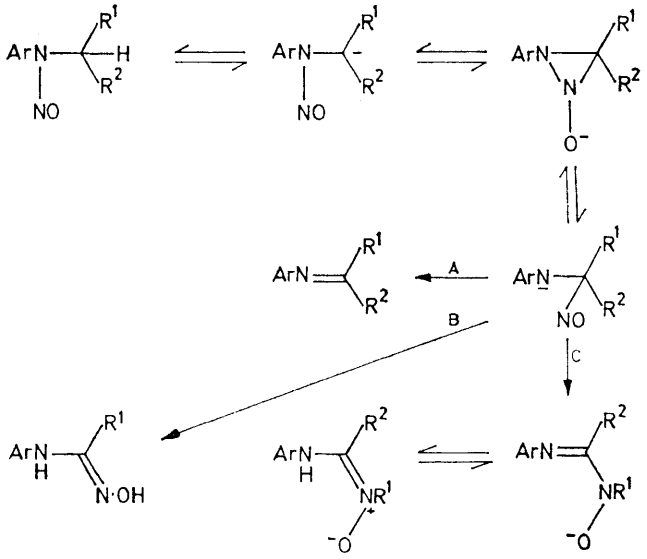
In this case it was felt that the elimination of HNO should be a favourable process. The *N*-nitroso-compound (XIV; $R^1 = NO$, $R^2 = H$) was made by nitrosation in acetic acid. More strongly acidic conditions gave, by rearrangement,[20] the green *p*-nitroso-derivative (XIV; $R^1 = H$, $R^2 = NO$). As indicated by the classical canonical forms (XV), an *N*-nitroso-amine maybe expected to possess some acidity on the α-carbon atom, due to the adjacent positively polarised nitrogen atom. This being so, a base-catalysed elimination was expected to occur. Indeed on treatment of the *N*-nitroso-amine (XIV; $R^1 = NO$, $R^2 = H$) with sodium hydride in dimethylacetamide a smooth elimination reaction occurred to provide the imine (XVI), which was readily hydrolysed to α-tetralone.

With the tetracyclic acetate (X; $R^1 =$ OAc, $R^2 = H$, $R^3 = H$), nitrosation under the successful model conditions gave the *p*-nitroso-derivative. The expedient of changing the solvent to acetic acid–dioxan at 0° gave the desired *N*-nitroso-derivative (XVII; R = Ac). Exposure of this (XVII; R = Ac) to strongly basic conditions (sodium hydride) gave a complex mixture of products. As it seemed likely, on mass spectrometric evidence, that the desired imine had been formed, but had undergone tautomerism to an enamine and subsequent degradation, we reasoned that use of the free hydroxy-compound (XVII; R = H) might improve the reaction by trapping the intermediate imine as the amino-ether (XVIII). The *N*-nitroso-derivative (XVII; R = H) was easily prepared by direct nitrosation of the alcohol (X; $R^1 =$ OH, $R^2 = H$, $R^3 = H$) or by mild base hydrolysis of the acetate (XVII; R = Ac). When treated with base however, it gave a crystalline isomeric product whose spectral properties ($\nu_{max.}$ 3300 cm.$^{-1}$, $\lambda_{max.}$ 325 nm.) confirmed the retention of the CD system. The formulation of this substance as the amino-nitrone (XIX; $Y = \overset{+}{N}–O^-$) is based upon the following evidence.

Reduction with zinc in acetic acid gave a monodeoxy-compound (XIX; Y = N); this was hydrolysed with acid to the amine (XX; R = H), which yielded a diacetyl derivative (XX; R = Ac). The production of the amino-amide (XX; R = H) by hydrolysis of the deoxy-compound is interpreted as the result of fission of a cyclic amidine, itself derived from the nitrone (XIX; $Y = \overset{+}{N}–O^-$) by acceptable mechanisms.

With respect to the mechanisms of these reactions of *N*-nitroso-amines, it seems likely, as has already been suggested,[21] that an intermediate *N*-hydroxyaziridine may be involved (see Scheme 3), which is in equilibrium with the rearranged *C*-nitroso-derivative.

This latter compound has several reaction pathways available to it, depending on its structure. Where R^1 and $R^2 \neq H$ it may undergo elimination to give the imine, as both we and Daeniker[21] have observed (path A). When $R^2 = H \neq R^1$ formation of the amid-oxime is observed[21] (path B), and finally in certain steric and electronic environments a rearrangement may occur, as observed in our own work, to give the amino-nitrone (path C).

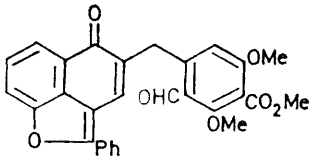


SCHEME 3

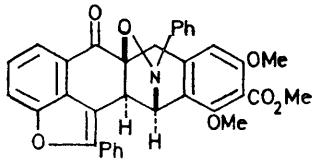
While the investigation of the model series was in progress, we also prepared compounds bearing the substituents in ring A required for the objective (V). Application of the 1,3-dipolar addition reaction to the aldehyde (XXI) [1] provided the cyclised product (XXII) in *ca.* 80% yield. In this case the alternative cyclisation, [*cf.* (III)] was not observed. Reduction with chromium(II) chloride took place as in the model experiments to provide the ketol (XXIII; R = OH), $\nu_{max.}$ 3450, 3390, 1725, and 1680 cm.$^{-1}$ The 6a-deoxygenation

[15] N. J. Leonard, L. A. Millar, and P. D. Thomas, *J. Amer. Chem. Soc.*, 1956, **78**, 3463.
[16] T. Isoda (*Chem. Abs.*, 1960, **54**, 2400d).
[17] L. M. Jackman, *Adv. Org. Chem.*, 1961, **2**, 329.
[18] R. G. R. Bacon and W. J. W. Hanna, *J. Chem. Soc.*, 1965, 4962.
[19] K. Heyns and H. Paulsen, 'Newer Methods of Preparative Organic Chemistry,' ed. K. Foerst, Academic Press, London, 1963, p. 303.
[20] O. Fischer and E. Hepp, *Ber.*, 1886, **19**, 2991.
[21] H. U. Daeniker, *Helv. Chim. Acta*, 1964, **47**, 33.

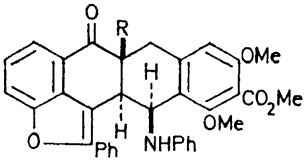
with zinc in acetic acid proceeded rapidly and yielded a mixture. However, by diluting the reaction mixture with dimethylformamide a clean transformation to the deoxy-compound (XXIII; R = H) was achieved. This



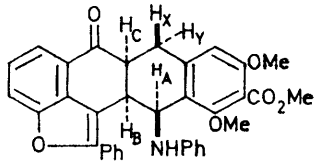
(XXI)



(XXII)



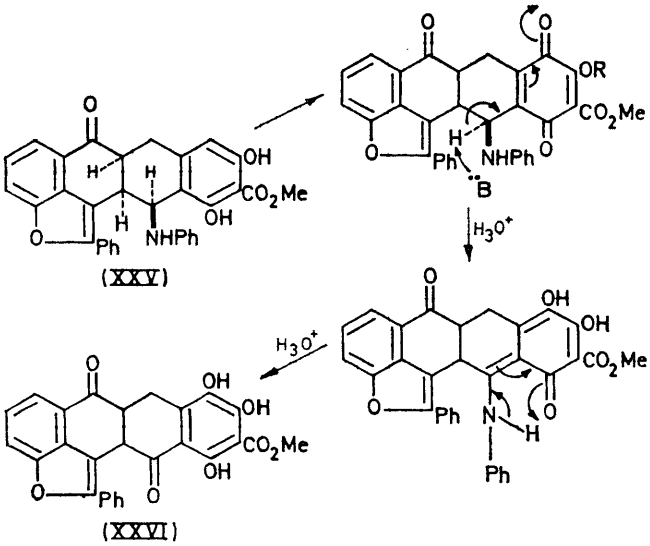
(XXIII)



(XXIV)

trans-deoxy-compound was epimerised by chromatography on alumina to the desired *cis*-ketone (XXIV), τ 5·78 (H_X) and 6·92 (H_Y), (J_{XY} 18, J_{CX} 0, J_{CY} 7·5 Hz), 4·54 (H_A), 5·82 (H_B), and 6·52 (H_C) (J_{AB} 3, J_{BC} 5·5 Hz), 3·30 (ArH), and 6·11, 6·13, and 6·49 (3 × OMe). The 12-anilino-ketone (XXIV) could not, for the reasons already described, be used in the synthesis.

We considered that if the protection of ring A were removed, then the phenol (XXV) could, by oxidation followed by treatment with base, provide the 12-ketone (XXVI) (see Scheme 4). This suggestion was tested



(XXV)

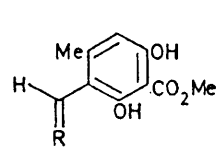
(XXVI)

SCHEME 4

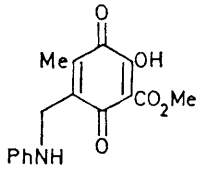
in the following manner. The aldehyde (XXVII; R = O) was condensed with aniline to provide the anil (XXVII; R = NPh), which was hydrogenated over 5% palladium–carbon to yield the *N*-phenylbenzylamine (XXVII; R = H,NHPh). Oxidation of this model compound with Fremy's salt should, in accord with our previous studies, have given the quinone (XXVIII). However, many uncharacterised degradation products were formed, and so the sequence was not pursued further.

At this stage in the work, a new route to ACD tricyclic aldehydes became available,[22] and accordingly the tetracyclic precursor (XXIX; R = H) was treated with phenylhydroxylamine. The isoxazolidine (XXX; R^1 = R^2 = H) was isolated in 61% yield ($\nu_{max.}$ 3440, 1681, 1643, and 1580 cm.$^{-1}$). The reaction was very slow because of the insolubility of the starting aldehyde. However, when the diacetate (XXIX; R = Ac) was treated under the usual 1,3-dipolar reaction conditions a more rapid reaction gave two products. N.m.r. and i.r. spectral evidence demonstrated that these were (XXX; R^1 = R^2 = H) and (XXX; R^1 = H, R^2 = Ac), formed in a ratio of 1 : 2. Treatment of the former (XXX, R^1 = R^2 = H) with basic Fremy's salt rapidly afforded a brown solid whose mass spectral properties were not consistent with a quinone structure for ring A. The compound was not investigated further.

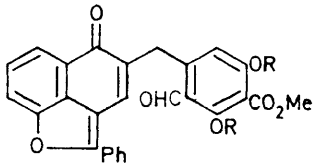
Unfortunately all attempts to utilise the isoxazolidine route have been abortive, but nevertheless they provided



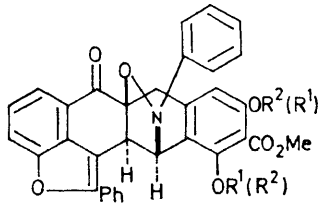
(XXVII)



(XXVIII)



(XXIX)



(XXX)

us with the first ring A substituted linear tetracyclic compounds. In addition a method of converting, in certain cases, an anilino-residue, *via* an imine function into the corresponding ketone derivative was developed.

EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage apparatus. Unless otherwise stated, u.v. spectra were measured for solutions in ethanol and i.r. spectra for Nujol mulls. N.m.r. spectra were run for solutions in deuteriochloroform at 20°, with tetramethylsilane as internal standard.

N-Phenyl-6aβ,12β-epoxyimino-6aα,7,12,12aα-tetrahydro-1-phenylnaphthaceno[1,12-bc]furan-6-one (II; R = H).—The aldehyde (I; R = CHO) (6·25 g.) was stirred in suspension in ethanol (500 ml.) with freshly prepared phenylhydroxylamine (3·0 g.) under nitrogen for 5 days. Further portions of phenylhydroxylamine were added at intervals

[22] Part VII, D. H. R. Barton, P. D. Magnus, and T. Hase, *J. Chem. Soc.* (*C*), 1971, 2215.

of 24 hr. The *isoxazolidine* (II; R = H), which crystallised out (6·82 g., 87%), had m.p. 178—179° (from ethanol), $\lambda_{max.}$ 275 and 360 nm. (ε 19,000 and 14,000), $\nu_{max.}$ ($CHCl_3$) 1680 cm.$^{-1}$, τ 6·69 and 6·17 (2H, ABq, *J* 18·5 Hz), 5·56 (1H, s), 4·65 (1H, s), and 3·33—3·85 (5H, aromatic) (Found: C, 81·75; H, 4·6; N, 2·85. $C_{31}H_{21}NO_3$ requires C, 81·75; H, 4·65; N, 3·1%).

In another experiment the aldehyde (I; R = CHO) (1·5 g.) was heated under reflux with freshly prepared phenylhydroxylamine (600 mg.) in absolute ethanol (150 ml.) for 30 hr. On cooling, the isomer (II; R = H) was obtained (998 mg.). A further crop was collected after concentration (597 mg.). This last crop was chromatographed over alumina (G3) in benzene, and the second isomeric *isoxazolidine* (III; R = H) (207 mg., 11%) was obtained from the first eluates. Solvents were removed at room temperature to avoid isomerisation of this isomer, m.p. (from benzene) 183—184°, $\lambda_{max.}$ 361 and 276 nm. (ε 12,000 and 19,000), $\nu_{max.}$ ($CHCl_3$) 1680 cm.$^{-1}$, τ 6·79 and 6·57 (2H, ABq, *J* 16 Hz), 4·48 (1H, s), and 3·86 (1H, s) (Found: C, 81·9; H, 4·7; N, 3·1%). Azoxybenzene was isolated from the mother liquors.

Attempted Deuterium Exchange with the Isoxazolidine (II; R = H).—The isomer (II; R = H) (100 mg.) was heated under reflux for 15 hr. with ethan[^{2}H]ol (9 ml.) under nitrogen. T.l.c. indicated only the formation of the equilibrium mixture of isomers (II; R = H) and (III; R = H). Removal of the solvent and examination of the product by n.m.r. spectroscopy showed no incorporation of deuterium into either isomer.

2-*Phenyl* 4-(2-*phenylcarbamoylbenzyl*)-*naphtho*[1,8-bc]-*furan*-5-*one* (I; R = CO·NHPh).—The isomer (II; R = H) (500 mg.) in acetic anhydride (5 ml.) and pyridine (10 ml.) was heated at 95° for 16 hr. The cooled mixture was poured into water and extracted with ether; the extract was washed, dried, and evaporated. The oily product was chromatographed over alumina (G3) in benzene. The fractions, in order of elution, were isomer (III; R = H) (103 mg.), isomer (II; R = H) (162 mg.), and the *anilide* (I; R = CO·NHPh) (232 mg., 46%), m.p. 249—250° (from ethanol), $\lambda_{max.}$ 265 and 403 nm. (ε 11,000 and 11,180), $\nu_{max.}$ 3280, 1650, 1620, 1605, and 1590 cm.$^{-1}$, τ 5·87 (2H, s) and −0·51 (1H, s) [Found: C, 81·95; H, 4·9; N, 2·95%; *M*, 455 (mass spectrum). $C_{31}H_{21}NO_3$ requires C, 81·75; H, 4·65; N, 3·1%; *M*, 455].

Treatment of Isomer (II; R = H) *with Acid*.—The isoxazolidine (II; R = H) (50 mg.) in acetic acid (5 ml.) and hydrochloric acid (5 ml.) was stirred at room temperature for 16 hr. The red solution was diluted with water and extracted with chloroform; the extract was evaporated to an oil. Chromatography over alumina gave the aldehyde (I; R = CHO) (18 mg.) identical (m.p. and mixed m.p.) with an authentic specimen.

Reaction of Isomer (II; R = H) *with Base*.—The isoxazolidine (II; R = H) (232 mg.) in dry benzene (25 ml.) was treated with potassium t-butoxide [from potassium (0·3 g.) and t-butyl alcohol (30 ml.)] at room temperature under nitrogen for 48 hr. After addition of glacial acetic acid the red solution was evaporated to dryness. Trituration of the residue with ethanol gave compound (IV), identical with an authentic sample.[1]

N-p-*Bromophenyl*-6aβ,12β-*epoxyimino*-6aα,7,12,12aα-*tetrahydro*-1-*phenylnaphthaceno*[1,12-bc]*furan*-6-*one* (II; R = Br).—The isoxazolidine (II; R = H) (200 mg.) in benzene (20 ml.) and pure *N*-bromosuccinimide (80 mg.) were refluxed for 4 hr. Evaporation of all the solvent and trituration of the colourless gum with ethanol gave a white solid (190 mg.). Recrystallised from ethanol, this gave the *bromo-derivative* (II; R = Br), m.p. 208—209°, $\nu_{max.}$ 1680 cm.$^{-1}$, $\lambda_{max.}$ 357 and 273 nm. (ε 21,300 and 38,100), τ 6·72 and 6·13 (2H, ABq, *J* 19 Hz), 5·55 (1H, s), 4·72 (1H, s), and 3·27 and 3·88 (4H, A_2B_2q, *J* 9 Hz) (Found: C, 69·5; H, 3·95; Br, 15·2; N, 2·45. $C_{31}H_{20}BrNO_3$ requires C, 69·65; H, 3·75; Br, 14·9; N, 2·6%).

N-*Phenyl*-6aβ,12β-*epoxyamino*-6aα,7,12,12aα-*tetrahydro*-1-*phenyl*-6H-*naphthaceno*[1,12-bc]*furan*-6β-*ol* (VI).—The isoxazolidine (II; R = H) (151 mg.) in ether (40 ml.) was added to lithium aluminium hydride (200 mg.) in ether (10 ml.) at room temperature. After 3 hr. the reaction was worked up in the usual way to yield the *alcohol* (VI) (150 mg.), m.p. (from ethanol) 223—224°, $\lambda_{max.}$ 305 and 238 nm. (ε 25,300 and 24,400), $\nu_{max.}$ 3400 and 3300 cm.$^{-1}$, τ 6·69 and 6·08 (2H, ABq, *J* 7 Hz), 5·88 (1H, s), 4·72 (1H, s), and 4·92 (1H, s, 6α-H) (Found: C, 81·7; H, 5·35; N, 2·9. $C_{31}H_{23}NO_3$ requires C, 81·4; H, 5·05, N, 3·05%).

This alcohol (VI) was further characterised as the *monoacetate*, obtained by treatment with acetic anhydride containing a few drops of concentrated hydrochloric acid at room temperature; m.p. 211—212° (from ethanol), $\lambda_{max.}$ 310 and 235 nm. (ε 22,600 and 19,800), $\nu_{max.}$ 1750 cm.$^{-1}$, τ 6·72 and 6·53 (2H, ABq, *J* 18 Hz), 5·80 (1H, s), 4·95 (1H, s), and 7·55 (3H, s) (Found: C, 79·45, H, 5·3; N, 2·65. $C_{33}H_{25}NO_4$ requires C, 79·35; H, 5·05; N, 2·8%).

Oxidation of the Alcohol (VI).—The alcohol (VI) (190 mg.) in pyridine (5 ml.) was treated with chromium trioxide (50 mg.) in pyridine (3 ml.) at room temperature. The pale brown product, obtained after trituration with ethanol, was extracted with acetone; the solution was filtered and evaporated. Recrystallisation of the product from ethanol gave the isoxazolidine (II; R = H) (90 mg.), identical (m.p. and mixed m.p.) with an authentic sample.

6aα,7,12,12aα-*Tetrahydro*-1-*phenyl*-6H-*naphthaceno*[1,12-bc]*furan*-6β,6aβ-*diol* (VIII).—The isoxazolidine (II; R = H) (500 mg.) was reduced in ethanol (250 ml.) with 5% palladium–carbon. After 2·3 hr, 3 equiv. of hydrogen had been taken up. The catalyst was filtered off and the product isolated by chromatography on alumina (G3), gave the *diol* (VIII) (187 mg., 46%), m.p. 189—190 [from light petroleum (b.p. 30—40°)], $\lambda_{max.}$ 301, 275, and 234 nm. (ε 17,000, 10,600, and 12,300), $\nu_{max.}$ 3500 cm.$^{-1}$, τ 7·72 (2H), 6·22—7·29 (3H), 6·69 (2H), and 5·12 (1H, s) (Found: C, 81·5; H, 5·6. $C_{25}H_{20}O_3$ requires C, 81·55; H, 5·45%].

This compound, on treatment with pyridine and acetic anhydride for 18 hr. at room temperature, gave a *monoacetate*, m.p. (from chloroform) 193—194°, $\lambda_{max.}$ 298, 273, 232, and 210 nm. (ε 21,000, 13,000, 15,500, and 29,000), $\nu_{max.}$ 3610 and 1742 cm.$^{-1}$, τ 7·61 (3H, s), 6·10—7·10 (3H), and 3·61 (1H, s) (Found: C, 79·0; H, 5·4. $C_{27}H_{22}O_4$ requires C, 79·45; H, 5·65%).

12β-*Anilino*-6aα,7,12,12aα-*tetrahydro*-6aβ-*hydroxy*-1-*phenylnaphthaceno*[1,12-bc]*furan*-6-*one* (VII; R = OH).—The isoxazolidine (II; R = H) (341 mg.) in glacial acetic acid (25 ml.) and concentrated hydrochloric acid (0·51 ml.) was treated with M-chromium(II) chloride solution (20 ml.) under nitrogen. After being stirred vigorously for 1 min. the solution was added to water and extracted with chloroform; the extract was evaporated to give the crystalline *ketone* (VII; R = OH). Dried in vacuum at 80° for 3

days (yield 301 mg., 88%), this had m.p. (from chloroform) 229—230°, $\lambda_{max.}$ 345 and 247 nm. (ε 14,000 and 22,500), $\nu_{max.}$ 3590, 3450, 3110, and 1690 cm.$^{-1}$, τ 6·64 and 6·48 (2H, ABq, *J* 19 Hz), 5·90 and 4·45 (2H, d, *J* 5 Hz), and 6·02 (2H, exchangeable with D_2O) (Found: C, 81·1; H, 5·2. $C_{31}H_{23}NO_3$ requires C, 81·4; H, 5·0%).

Acetylation of the Alcohol (VII; R = OH).—The dihydro-derivative (VII; R = OH) in dry ether was treated with acetyl chloride and pyridine (a slight excess) at room temperature. The mixture was added to ice–water and the ethereal layer was washed with dilute acid and evaporated. Chromatography over alumina gave, besides some starting material, the *epimino-derivative* (IX), m.p. (from ethanol) 215°, $\nu_{max.}$ 1740 and 1230 cm^{-1} (Found: C, 78·75; H, 4·85; N, 2·65; active hydrogen, 0. $C_{35}H_{27}NO_5$ requires C, 77·7; H, 5·0; N, 2·6; active hydrogen 0%).

12β-*Anilino*-6aβ,7,12,12aα-*tetrahydro*-1-*phenylnaphthaceno*[1,12-bc]*furan*-6-*one* (VII; R = H).—The ketol (VII; R = OH) (100 mg.) in acetic acid (30 ml.) and concentrated hydrochloric acid (0·2 ml.) was stirred under nitrogen at room temperature. Zinc dust (500 mg.) was added and the mixture was stirred for 1 min., filtered through Celite, diluted with water, and extracted with chloroform. The extract was evaporated; trituration of the residue with ethanol gave the *ketone* (VII; R = H) (65 mg., 67%), m.p. 192—194° (from ethanol), $\nu_{max.}$ ($CHCl_3$) 3410, 1684, and 1601 cm.$^{-1}$, τ 7·09—6·27 (3H, m), 6·20—5·75 (1H), and 4·59 (1H, d, H-12) (Found: C, 81·75; H, 5·6; N, 3·4. $C_{31}H_{23}NO_3$,EtOH requires C, 81·6; H, 5·6; N, 2·9%).

12β-*Anilino*-6aα,7,12,12aα-*tetrahydro*-1-*phenylnaphthaceno*[1,12-bc]*furan*-6-*one* (X; R^1R^2 = O, R^3 = H).—When the previously described experiment was repeated and the crude product was directly chromatographed over alumina (G3) in benzene, the main fraction was found to be the cis-*ketone* (X; R^1R^2 = O, R^3 = H) (83 mg., 86%), m.p. (from benzene) 224—227°, $\lambda_{max.}$ 348, 295, and 254 nm. (ε 7700, 12,800, and 17,200), $\gamma_{max.}$ 3440 and 1685 cm.$^{-1}$, τ 7·13 (1H, NH), 6·30—6·80 (2H, m), 5·76 (1H, d, *J* 18 Hz), 5·60 (1H, dd, *J* 6 and 3 Hz), and 4·95 (1H, d, *J* 3 Hz) (Found: C, 84·35; H, 5·4; N, 3·25. $C_{31}H_{23}NO_2$ requires C, 84·35; H, 5·25; N, 3·15%).

Deuteriation of the cis-*Ketone* (X; R^1R^2 = O, R^3 = H).—The *cis*-ketone (266 mg.) in dry tetrahydrofuran (40 ml.) was treated with deuterium chloride in deuterium oxide [from thionyl chloride (1 ml.) in deuterium oxide (6 ml.)]. The solution was refluxed under dry nitrogen for 3 hr. and neutralised with solid sodium carbonate. After filtration, the solvent was removed in vacuum to give an oil which crystallised from chloroform–light petroleum (b.p. 30—40) as the *tetradeuteriated* cis-*ketone* (see Discussion section) (X; R^1 = R^2 = O, R^3 = D), m.p. 230—232°, $\lambda_{max.}$ 347, 295, and 253 nm., $\nu_{max.}$ 3450, 3100, and 2940 cm.$^{-1}$, τ 7·12 (1H, NH), 6·87—5·79 (2H, ABq, *J* 19 Hz), 5·60 (1H, d, *J* 3 Hz), and 4·91 (1H, d, *J* 3 Hz) (Found: M^+, 445. $C_{31}H_{19}D_4NO_2$ requires *M*, 445).

Reduction of the cis-*Ketone* (X; R^1R^2 = O, R^3 = H) *with Sodium Borohydride*.—The *cis*-ketone (22 mg.) in ethanol (30 ml.) was treated with sodium borohydride (1·9 mg.) and stirred at room temperature overnight. Chromatography of the product on alumina (G3) gave some starting ketone (6 mg.) and another compound (10 mg.) shown to be the *trans*-alcohol (XI), by oxidation with manganese dioxide in benzene at room temperature to the *trans*-ketone (VII; R = H).

Reduction of the cis-*Ketone* (X; R^1R^2 = O, R^3 = H) *with Lithium Aluminium Hydride*.—The *cis*-ketone (104 mg.) in ether (40 ml.) was added to a suspension of lithium aluminium hydride (100 mg.) in the same solvent (20 ml.). The mixture was stirred for 10 min. and then ethyl acetate was added dropwise. The product, obtained in the usual way, crystallised from light petroleum (b.p. 30—40°) as 12β-*anilino*-6aα,7,12,12aα-*tetrahydro*-1-*phenyl*-6H-*naphthaceno*-[1,12-bc]*furan*-6β-*ol* (X; R^1 = OH, R^2 = R^3 = H) (96 mg., 92%), m.p. 207—208°, $\lambda_{max.}$ 306, 300, 250, 244, and 235 nm. (ε 31,000, 30,600, 26,600, and 26,200), $\nu_{max.}$ 3590, 3430, and 3380 cm.$^{-1}$, τ 7·18br (1H, m,), 6·78—6·38 (2H, m), 5·84br (1H, t, *J* *ca.* 5 Hz), 4·87 (1H, d, *J* 3 Hz), and 4·95 (1H, d) (Found: C, 83·8; H, 5·7; N, 3·35. $C_{31}H_{25}NO_2$ requires C, 83·95; H, 5·7; N, 3·15%).

When oxidised with manganese dioxide in benzene this alcohol was cleanly reconverted into the *cis*-ketone (X; R^1R^2 = O, R^3 = H).

Acetylation of the cis-*Alcohol* (X; R^1 = OH, R^2 = R^3 = H).—The alcohol (X; R^1 = OH, R^2 = R^3 = H) (511 mg.) was warmed with pyridine (6 ml.) and acetic anhydride (4 ml.) at 95° for 2 hr. Work-up in the usual way gave a solid that crystallised from ether–light petroleum b.p. 30—40°) to give 6β-*acetoxy*-12β-*anilino*-6aα,7,12,12aα-*tetrahydro*-1-*phenyl*-6H-*naphthaceno*[1,12-bc]*furan* (X; R^1 = OAc, R^2 = R^3 = H) (475 mg., 85%), m.p. 176—177°, $\lambda_{max.}$ 324, 309, 294, 281, 251, and 235 nm. (ε 13,800, 21,200, 18,300, 15,400, 19,600, and 17,000), $\nu_{max.}$ 3490 and 1742 cm.$^{-1}$, τ 8·65 (3H, s), 7·17br (1H, m, H-6a), 6·78br (2H, s), 5·82 (1H, t, J_1 = J_2 = 7 Hz), 5·61 (1 H, d, *J* 7 Hz, H-12a), and 4·73 (1H, d, *J* 7 Hz, H-6α) (Found: C, 81·6; H, 5·75; N, 2·85. $C_{33}H_{27}NO_3$ requires C, 81·6; H, 5·6; N, 2·9%).

Prolonged Reduction of the Ketol (VII; R = OH) *with Zinc in Acetic Acid*.—The ketol (VII; R = OH) (518 mg.) in dimethylformamide (50 ml.) and acetic acid (30 ml.) was stirred with an excess of zinc dust at room temperature for 18 hr. The mixture was filtered through Celite, poured into water, and extracted with chloroform. The dried extract was evaporated and chromatographed over alumina (G3) to yield an *alcohol* (X; R^1 = H, R^2 = OH, R^3 = H) (147 mg.), m.p. 208—209°, $\lambda_{max.}$ 322, 308, 299, 249, 241, and 234 nm. (ε 15,700, 23,800, 23,600, 21,900, 21,400, and 20,900), $\nu_{max.}$ 3550 and 3395 cm.$^{-1}$, τ 7·52br (1H, m, H-6a), 7·15—6·22 (2H, m), 5·92 (1H, t, J_1 = J_2 = 4·5 Hz), 4·95 (1H, d, *J* 4·5 Hz), and 4·85 (1H, s).

Oxidation of this compound with manganese dioxide in benzene gave the known *cis*-ketone (X; R^1R^2 = O, R^3 = H).

1-*Anilino*-1,2,3,4-*tetrahydronaphthalene* (XIV; R^1 = R^2 = H).—Tetralin (1·32 g.) in redistilled carbon tetrachloride (50 ml.) was treated with freshly crystallised *N*-bromosuccinimide (1·96 g.) at reflux for 45 min. The cooled solution was filtered and evaporated at room temperature to an oil, which was immediately treated with aniline (4·6 g.) in benzene (4 ml.) at room temperature for 1 hr. The solution was concentrated, the aniline hydrobromide was filtered off, and the residue was chromatographed over alumina (G3) in benzene. The first fraction, a colourless oil, was crystallised from light petroleum (b.p. 30—40°) to give the *anilino-derivative* (XIV; R^1 = R^2 = H) (888 mg., 38%), m.p. 59—60°, $\lambda_{max.}$ 299, 253, and 209 nm. (ε 2000, 16,400, and 24,200), $\nu_{max.}$ 3390 and 1603 cm.$^{-1}$, τ 8·19 (4H, m), 7·28 (2H, m), 6·30 (1H), 5·44 (1H), and 3·04 (9H, m) (Found: C, 86·05; H, 7·35; N, 6·55. $C_{16}H_{17}N$ requires C, 86·05; H, 7·65; N, 6·25%); the *hydrochloride* had m.p. (from ether) 120—135° (decomp.)

(Found: C, 74·0; H, 7·25; Cl, 13·95; N, 5·25. $C_{16}H_{18}ClN$ requires C, 74·0; H, 6·95; Cl, 13·7; N, 5·4%).

The second fraction gave 1,4-*dianilino*-1,2,3,4-*tetrahydronaphthalene*, m.p. (from light petroleum) 147—148° (399 mg., 13%), $\lambda_{max.}$ 296, 253, and 209 nm. (ε 4700, 31,400, and 37,800), τ 8·07 (4H, m), 6·29 (2H), 5·40 (2H), and 3·36—2·77 (10H, m) (Found: C, 83·8; H, 7·15; N, 9·15. $C_{22}H_{22}N_2$ requires C, 84·05; H, 7·05; N, 8·9%).

A large-scale preparation was conveniently separated into its components by fractional distillation.

1,2,3,4-*Tetrahydro*-1-N-*nitrosoanilinonaphthalene* (XIV; R^1 = NO, R^2 = H).—1-Anilino-1,2,3,4-tetrahydronaphthalene (500 mg.) in acetic acid (100 ml.) and water (11 ml.) was treated with sodium nitrite (235 mg., 1·5 mol.). The mixture was stirred for 30 min. at room temperature, poured into water, and then extracted with chloroform. The *nitroso-derivative* was an oil which crystallised from light petroleum (b.p. 30—40°) (507 mg., 90%), m.p. 65—66°, $\lambda_{max.}$ 273, 258, and 210 nm. (ε 6400, 7500, and 19,900), $\nu_{max.}$ 1600 and 1500 cm.$^{-1}$, τ 8·19 (4H, m), 7·31 (2H, m), 3·13 (10H, m) [Found: C, 76·4; H, 6·25; N, 11·15. $C_{16}H_{16}N_2O$ requires C, 76·15; H, 6·4; N, 11·1%).

1,2,3,4-*Tetrahydro*-1-p-*nitrosoanilinonaphthalene* (XIV; R^1 = H, R^2 = NO).—The *N*-nitroso-compound (XIV; R^1 = NO, R^2 = H) (23 mg.) in absolute ethanol (20 ml.) was treated with dry hydrogen chloride for 1 hr. The product, obtained by extraction of the diluted reaction mixture with chloroform, was chromatographed on alumina to yield the p-*nitroso-derivative* (XIV; R^1 = H, R^2 = NO), m.p. 130—131° [from light petroleum (b.p. 30—40°)], $\lambda_{max.}$ 424, 306, 272, 237, and 207 nm. (ε 34,200, 1300, 6500, 9500, and 16,800), τ 8·08 (4H, m), 7·22 (2H, m), 5·24 (1H), and 4·70 (1H) (Found: C, 76,35; H, 6·45; N, 10·9. $C_{16}H_{16}N_2O$ requires C, 76·15; H, 6·5; N, 11·1%).

The same compound could be obtained by treatment of the amine with sodium nitrite and concentrated hydrochloric acid in acetic acid.

Reaction of the N-*Nitroso-compound* (XIV; R^1 = NO, R^2 = H) *with Sodium Hydride*.—The *N*-nitroso-derivative (2·0 g.) in dimethylformamide (200 ml.) was treated with sodium hydride (455 mg.) and warmed at 95° for 5 hr. After filtration (Celite) the solution was diluted with water and extracted with chloroform. The washed extract was evaporated to an oil, which was chromatographed over alumina (G3) to give 1,2,3,4-*tetrahydro*-1-*phenyliminonaphthalene* (XVI) (703 mg., 40%), m.p. (from benzene) 72—74°, $\lambda_{max.}$ 327, 296, 255, and 211 nm. (ε 3000, 4000, 23,800, and 34,000), τ 8·16 (2H), 7·56 (2H), and 7·21 (2H) (Found: C, 86·75; H, 6·85; N, 6·3. $C_{16}H_{15}N$ requires C, 86·85; H, 6·85; N, 6·35%).

When dry dimethylacetamide was used as solvent the reaction was complete after 6 hr. at room temperature, with an improved yield (63%).

Hydrolysis of the Imine (XVI).—The imine (50 mg.) was shaken with dilute hydrochloric acid (5 ml.) and ether (10 ml.) for 15 min. Evaporation of the organic phase gave an oil (25 mg.), shown by its spectral properties to be α-tetralone (confirmed by the preparation of the benzylidene derivative, m.p. 106°; mixed m.p. with an authentic sample showed no depression).

6aα,7,12,12aα-*Tetrahydro*-12β-N-*nitrosoanilino*-1-*phenyl*-6H-*naphthaceno*[1,12-bc]*furan*-6β-*yl Acetate* (XVII; R = Ac).—The anilino-derivative (X; R^1 = OAc, R^2 = H, R^3 = H) (676 mg.) in dry dioxan (100 ml.) and glacial acetic acid (35 ml.) at 0° was treated with sodium nitrite (500 mg.). The mixture was stirred for 5 hr., and poured into water. The precipitate was filtered off and recrystallised from chloroform–light petroleum (b.p. 40—60°) to give the N-*nitroso-derivative* (XVII; R = Ac) (600 mg., 84%), m.p. 183—185°, $\nu_{max.}$ 1730, 1601, 1502, 1478, and 1455 cm.$^{-1}$, τ 8·22 (3H, s), 7·15br (1H, m), 6·69 (2H, m), 6·28 (1H, m), and 5·60 (1H, m), *m/e* 514 (M^+, $C_{33}H_{26}N_2O_4$), with ready loss of NO.

6aα,7,12,12aα-*Tetrahydro*-12β-N-*nitrosoanilino*-1-*phenyl*-6H-*naphthaceno*[1,12-bc]*furan*-6β-*ol* (XVII; R = H).—The hydroxy-anilino-derivative (X; R^1 = OH, R^2 = H, R^3 = H) (128 mg.) in glacial acetic acid (35 ml.) and water (15 ml.) was treated with sodium nitrite (140 mg.) at 0° for 15 min. (t.l.c. control). The solution was poured into water and the product was recrystallised from chloroform–light petroleum (b.p. 30—40°) to give the N-*nitroso-derivative* (XVII; R = H) (128 mg., 80%), m.p. 160—163°, $\nu_{max.}$ 3440, 1596, 1470, 1460, and 1152 cm.$^{-1}$, *m/e* 472 ($C_{31}H_{24}N_2O_3$ requires 472); ready loss of NO was exhibited.

This product was identical with the compound formed by treatment of the corresponding acetoxy-derivative (XVII; R = Ac) with ethanolic sodium hydroxide.

Reaction of the Hydroxy-N-*nitroso-compound* (XVII; R = H) *with Sodium Hydride*.—The *N*-nitroso-derivative (XVII; R = H) (203 mg.) in dry dimethylacetamide (30 ml.) was stirred at room temperature, under nitrogen, with sodium hydride (267 mg.) for 16 hr. After filtration through Celite into water, the mixture was extracted with ether and the dried extract was evaporated at room temperature to a semisolid. Crystallisation from ether–chloroform gave the *amidine* N-*oxide* (XIX; Y = $\overset{+}{N}$–O^-) (107 mg., 53%), m.p. 280—283°, $\lambda_{max.}$ 325, 310, 298, 281, 267, 249, 240, 235, and 207 nm. (ε 14,900, 22,100, 20,700, 18,200, 16,700, 17,400, 17,700, 17,600, and 30,400), $\nu_{max.}$ ($CHCl_3$) 3300, 1614, and 1600 cm.$^{-1}$, τ 7·13 (1H), 6·98 (1H), 6·46—6·21 (2H), 5·28 (1H), 4·80 (1H), and 3·41—3·13 (5H) [Found: C, 78·2; H, 5·3; N, 5·9%; *M* (mass spectrum), 472. $C_{31}H_{24}N_2O_3$ requires C, 78·8; H, 5·1; N, 5·95%; *M*, 472].

Reduction of the Amidine N-*Oxide* (XIX; Y = $\overset{+}{N}$–O^-).—The *N*-oxide (55 mg.) in acetic acid (15 ml.) was treated with zinc powder (120 mg.) at room temperature. The mixture was stirred for 2 hr. and filtered through Celite; the filtrate was carefully neutralised with sodium hydrogen carbonate solution and extracted with chloroform. The oily product was crystallised by treatment with ether–light petroleum (b.p. 40—60°) to give the *amidine* (XIX; Y = N) (40 mg., 75%), m.p. 255—256°, $\lambda_{max.}$ 325, 410, 298, 282, 246, 240, 234, and 208 nm. (ε 15,800, 22,300, 19,200, 14,200, 13,600, 16,300, 18,900, and 38,000), $\nu_{max.}$ 3440, 1623, and 1591 cm.$^{-1}$, τ 7·32 (1H), 7·12 (1H), 6·45—6·26 (1H, m), 6·06 (2H), 5·34 (1H), and 5·25 (1H) [Found: C, 81·45; H, 5·2%; *M* (mass spectrum), 456. $C_{31}H_{24}N_2O_2$ requires C, 81·55; H, 5·35%; *M*, 456].

Acid Hydrolysis of the Amidine (XIX; Y = N).—The alcohol (XIX; Y = N) (117 mg.) in acetic acid (15 ml.) was heated at 95° for 3 hr. with hydrochloric acid (6N; 10 ml.). The solution was neutralised (aqueous sodium hydrogen carbonate) and extracted with chloroform. The extract was evaporated and the residue was crystallised from chloroform–light petroleum (b.p. 30—40°) to give the *amide* (XX; R = H) (95 mg., 56%), m.p. 136—139°, $\lambda_{max.}$ 332, 278, 243, and 213 nm. (ε 3200, 23,100, 43,400, and 45,900) $\nu_{max.}$ 3480, 3390, 1665, 1633, and 1599 cm.$^{-1}$.

τ 6·06—5·89 (2H), 3·97 (3H), and 3·60—2·30 (19H), M^+ 456 ($C_{31}H_{24}N_2O_2$ requires 456).

The amide (XX; R = H) (35 mg.) in acetic anhydride (5 ml.) was stirred at room temperature for 18 hr. The product, obtained in the usual way, was chromatographed over alumina (G3) to yield the *diacetylamide* (XX; R = Ac) (4 mg.), $\lambda_{max.}$ 3480, 1706, 1668, 1645, and 1600 cm.$^{-1}$, M^+ 540 ($C_{35}H_{28}N_2O_4$ requires 540). *NN*-Diacetyl-*o*-toluidine[23] shows $\nu_{max.}$ 1707 cm.$^{-1}$ (film).

Methyl N-*Phenyl*-6aβ,12β-*epoxyimino*-6aα,7,12,aα-*tetrahydro*-9,11-*dimethoxy*-6-*oxo*-1-*phenyl*-6H-*naphthaceno*[1,12-bc]*furan*-10-*carboxylate* (XXII) (with D. J. Faulkner).—The aldehyde (XXI)[1] (109 mg.) and freshly prepared phenylhydroxylamine (45 mg.) were stirred under nitrogen in absolute ethanol (25 ml.) for 6 days. The precipitate was recrystallised from chloroform and ethanol to yield the *adduct* (XXII) (90 mg., 80%), m.p. 213—214°, $\lambda_{max.}$ 365 and 277 nm. (ε 10,900 and 20,600), $\nu_{max.}$ 1730 and 1692 cm.$^{-1}$, τ 6·75 (1H), 6·24 (1H), 6·21 (3H), 6·16 (3H), 6·08 (3H), 5·70 (1H), 4·05 (1H), and 3·32 (1H) (Found: C, 73·55; H, 4·85; N, 2·4. $C_{35}H_{27}NO_7$ requires C, 73·3; H, 4·7; N, 2·45%).

Methyl 12β-*Anilino*-6aα,7,12,12aα-*tetrahydro*-6aβ-*hydroxy*-9,11-*dimethoxy*-6-*oxo*-1-*phenyl*-6H-*naphthaceno*[1,12-bc]-*furan*-10-*carboxylate* (XXIII; R = OH) (with D. J. Faulkner).—The isoxazolidine (XXII) (52 mg.) in acetic acid (10 ml.) and concentrated hydrochloric acid (2 drops) was treated with M-chromium(II) chloride (2·5 ml.) under nitrogen. After 5 min. the solution was added to water and extracted with chloroform. The product was crystallised from chloroform–ether to give the *amino-ketol* (XXIII; R = OH) (38 mg., 73%), m.p. 180—182°, $\nu_{max.}$ 3450, 3390, 1730, and 1680 cm.$^{-1}$ (Found: C, 73·4; H, 5·45; N, 2·5. $C_{35}H_{29}NO_7$ requires C, 73·05; H, 5·1; N, 2·45%).

Methyl 12β-*Anilino*-6aβ,7,12,12aα-*tetrahydro*-9,11-*dimethoxy*-6-*oxo*-1-*phenyl*-6H-*naphthaceno*[1,12-bc]*furan*-10-*carboxylate* (XXIII; R = H) (with D. J. Faulkner).—The amino-ketol (XXIII; R = OH) (50 mg.) in dimethylformamide (11·5 ml.) and glacial acetic acid (4·5 ml.) was treated with zinc dust (60 mg.). The mixture was swirled for 1 min. and *quickly* filtered into sodium hydrogen carbonate solution. The *ketone* (XXIII; R = H), extracted with chloroform, crystallised from chloroform–ether as pale yellow needles (28 mg., 57·5%), m.p. 193—196°, $\nu_{max.}$ 3380, 1725, and 1680 cm.$^{-1}$ (Found: M^+, 559. $C_{35}H_{29}NO_6$ requires *M*, 559).

Methyl 12β-*Anilino*-6aα,7,12,12aα-*tetrahydro*-9,11-*dimethoxy*-6-*oxo*-1-*phenylnaphthaceno*[1,12-bc]*furan*-10-*carboxylate* (XXIV) (with D. J. Faulkner).—When the previous experiment was repeated and the crude product was directly chromatographed on alumina (G3) there was obtained the isomeric cis-*amino-ketone* (XXIV) (34 mg., 70%), m.p. (from chloroform–ethanol) 229—232°, $\lambda_{max.}$ 347, 292, and 246 nm. (ε 10,200, 21,300, and 31,100), $\nu_{max.}$ 3400, 1725, and 1680 cm.$^{-1}$, τ 7·28 (1H, NH), 6·49 (3H, s), 6·12, (6H, s), 5·78 and 6·92 (2H, ABq, *J* 18 Hz), 6·52 (1H, m, H-6a), 5·82 (1H, q, *J* 5·5 and 3 Hz, H-12a), and 4·54 (1H, d, *J* 3 Hz) (Found: C, 75·1; H, 5·2; N, 2·7. $C_{35}H_{29}NO_6$ requires C, 74·95; H, 5·55; N, 2·5%).

Methyl 2,6-*Dihydroxy*-4-*methyl*-3-*phenyliminomethylbenzoate* (XXVII; R = NPh).—Methyl 3-formyl-2,6-dihydroxy-4-methylbenzoate (1·0 g.) in methanol (40 ml.) was heated under reflux with aniline (0·490 ml., 1·1 equiv.) for 3 min. The orange solution was evaporated until two thirds of the solvent had been removed, and cooled to 0°. Pale yellow crystals separated (1·332 g., 98%) of the *anil* (XXVII; R = NPh), m.p. 144—145°, $\nu_{max.}$ 1640 and 1595 cm.$^{-1}$, $\lambda_{max.}$ 412, 328, 296, 285, 250, 228, 224, and 203 nm. (ε 19,400, 12,400, 6700, 6500, 16,700, 16,500, 17,200, and 18,400), τ 7·66 (3H), 6·00 (3H), 3·87 (1H), 2·56—2·84 (5H), 1·57 (1H), −2·98 (1H), and −6·18 (1H) (Found C, 67·6; H, 5·45; N, 4·95. $C_{16}H_{15}NO_4$ requires C, 67·35; H, 5·3; N, 4·9%).

Methyl 3-*Anilinomethyl*-2,6-*dihydroxy*-4-*methylbenzoate* (XXVII; R = H,NHPh).—The imine (XXVII; R = NPh) (1·20 g.) in dry benzene (100 ml.) was hydrogenated over 5% palladium–carbon. After 30 min., when there was no further uptake of hydrogen, the solution was filtered through Celite. Evaporation left an oil which yielded the *amine* (XXVII; R = NHPh) on trituration with ether (yield 1·08 g., 88%), m.p. 116—117°, $\nu_{max.}$ 3430 3170, 1671, 1635, and 1609 cm.$^{-1}$, $\lambda_{max.}$ 325, 286, 253, 223, and 206 nm. (ε 3500, 5900, 25,400, 25,300, and 28,100), τ 7·67 (3H), 5·97 (3H), 5·79 (2H), 3·64 (1H), and 2·70—3·50 (5H) (Found: C, 66·95; H, 5·8; N, 5·0. $C_{16}H_{17}NO_4$ requires C, 66·9; H, 5·95; N, 4·9%).

Methyl N-*Phenyl*-6aβ,12β-*epoxyimino*-6aα,7,12,12aα-*tetrahydro*-9,11-*dihydroxy*-6-*oxo*-1-*phenyl*-6H-*naphthaceno*-[1,12-bc]*furan*-10-*carboxylate* (XXX; $R^1 = R^2 = H$).—The aldehyde (XXIX; R = H) (100 mg.) was suspended in absolute ethanol (20 ml.) containing phenylhydroxylamine (200 mg.). The mixture was heated at 95° for 0·5 hr. and then stirred at room temperature under nitrogen. Further quantities of phenylhydroxylamine (100 mg) were added after 2 and 4 days. The reaction was stopped after 8 days when t.l.c. had shown there was about 80% conversion into a new compound. Crystallisation from ether–chloroform gave the *ketone* (XXX; $R^1 = R^2 = H$) (73 mg., 61%), m.p. 217—218°, $\nu_{max.}$ 3440, 1681, 1643, and 1580 cm.$^{-1}$, $\lambda_{max.}$ 361, 336, 295, 278, and 263 nm. (ε 12,400, 10,700, 17,900, 25,300, and 35,000), τ 6·26, 6·72 (ABq, 2H, J_{AB} 18 Hz), 5·91 (3H), 3·90 (1H), 3·34—3·82 (5H), 2·40—2·67 (8H), and 0·04 (1H) (molecular formula by mass spectrometry $C_{33}H_{23}NO_7$).

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[23] J. J. Sudborough, *J. Chem. Soc.*, 1901, 533.