Experiments on the Synthesis of Tetracycline. Part XIV.[1] Closure of Ring B by Base-catalysed Photocyclisation

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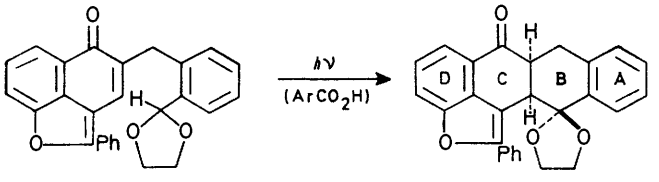
The photocyclisation of 4-[2-(dioxolan-2-yl)benzyl]-2-phenylnaphtho[1,8-*bc*]furan-5-one (I) to the naphthacenofuran (II) is catalysed by strong base. The simpler 2-[2-(dioxolan-2-yl)benzyl]-1,4-naphthoquinone (V) was not efficiently photocyclised to the naphthacenequinone (VI). Extension of the base-catalysed photocyclisation procedure provided an efficient route to the fully substituted linear tetracyclic acetal (IX) from the naphthofuran (VIII). An alternative theory for the photocyclisation of acetals of the type (I) to the linear tetracycline-type acetals (II) is advanced.

PREVIOUS papers [2-6] in this series have described an approach to the synthesis of tetracycline in which an acid-catalysed photocyclisation reaction was used to construct ring B of the linear tetracyclic skeleton (Scheme 1).[3] Tricyclic (ACD) acetals of type (I) were photo-



(I) (II)

SCHEME 1

cyclised in the presence of benzoic acid (1 equiv.) to give tetracyclic acetals of type (II).

The photocyclisation of (I) to (II) has now been studied in the presence of non-nucleophilic bases. Table 1 summarises our results and indicates that potassium t-butoxide is the most promising base. Further experiments (Table 2) with potassium t-butoxide demonstrated that this base, in a 1 : 1 ratio to starting material (I), gave the tetracyclic acetal (II) in 85% yield.

TABLE 1

Conversion of the acetal (I) into the naphthacenofuran (II)

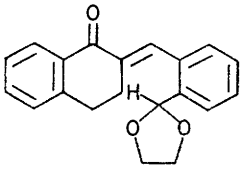
Catalyst	Reaction time (h) *
$KOBu^t$	4.5
$NaN(SiMe_3)_2$	6.5
DABCO †	8
DBN ‡	28 §

*After which no starting material remained. † 1,4-Diazabicyclo[2.2.2]octane. ‡ 1,5-Diazabicyclo[4.3.0]non-5-ene § Incomplete reaction, with by-products.

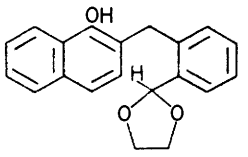
The mono(ethylene acetal) of phthalaldehyde was condensed with α-tetralone under basic conditions to give the benzylidene derivative (III). Treatment of this with potassium t-butoxide gave the naphthol (IV).

[1] Part XIII, D. H. R. Barton, P. D. Magnus, and J. C. Quinney, *J.C.S. Perkin I*, 1975, 1610.
[2] E. Aufderhaar, J. E. Baldwin, D. H. R. Barton, D. J. Faulkner, and M. Slaytor, *J. Chem. Soc.* (*C*), 1971, 2175.
[3] D. H. R. Barton, D. L. J. Clive, P. D. Magnus, and G. Smith, *J. Chem. Soc.* (*C*), 1971, 2193.
[4] D. H. R. Barton, P. D. Magnus, and T. Hase, *J. Chem. Soc.* (*C*), 1971, 2215.
[5] D. H. R. Barton, P. D. Magnus, and M. J. Pearson, *J. Chem. Soc.* (*C*), 1971, 2225.
[6] D. H. R. Barton, J. A. Challis, P. D. Magnus, and J. P. Marshall, *J. Chem. Soc.* (*C*), 1971, 2241.

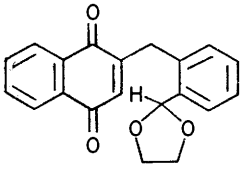
When this naphthol (IV) was subjected to the base-catalysed photocyclisation conditions only thermal degradation was observed. Oxidation of the naphthol



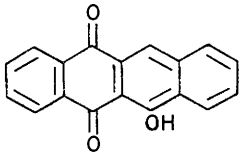
(III)



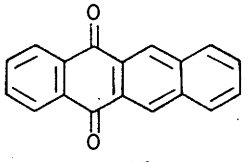
(IV)



(V)



(VI)



(VII)

(IV) with Fremy's salt [7] gave the quinone (V). Irradiation of the quinone (V) under neutral, acidic, or basic

TABLE 2

Conversion of the acetal (I) into the naphthacenofuran (II)

Solvent	KOBu^t (equiv.)	Time (h)	Yield (%)
PhH	0.1	9.5	39
PhH	1.1	4.5	85
PhH	10.0	2	(decomp.)
MeCN	1.1	15	16
$[CH_2]_4O$	1.1	5	69
MeCN (room temp.)	1.1	48	80

TABLE 3

Conversion of the acetal (V) into the naphthacenequinone (VI)

Catalyst	Molar ratio	Time (h)	Yield (%)
$PhCO_2H$	1.1 : 1	65	14.0
KOBu^t	1.1 : 1	15	12.0
None		38	9.5

conditions (Table 3) gave only low yields of photocyclisation product, which was isolated as the naphthacenequinone (VI).

Hydrolysis of the naphthoquinone acetal (V) with methanolic sulphuric acid gave the naphthacenequinone (VII).[8] Presumably this unexpected cyclisation proceeds *via* the mechanism outlined in Scheme 2.

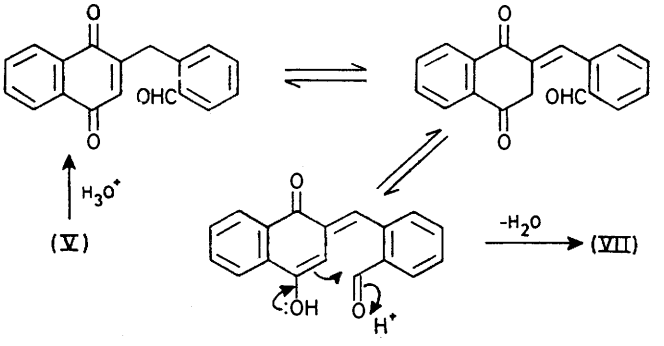
Since the base-catalysed photocyclisation had proved so successful in the model series, the fully substituted series was examined. The acetal [9] (VIII) was irradiated under a variety of conditions, summarised in Table 4. The most satisfactory procedure, utilising potassium t-pentylate (1.1 equiv.) gave the required tetracyclic acetal (IX; X = CO_2Me) (68%). Acid-catalysed photocyclisation was ineffective.

TABLE 4

Photocyclisation of the tricyclic acetal (VIII) to give the tetracyclic acetal (IX; X=CO_2Me)[9]

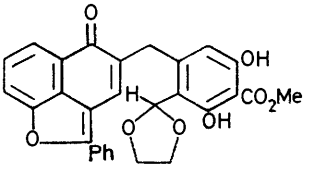
Wt. of acetal (VIII) (mg)	Catalyst (equiv.)	Solvent	Time (h)	Yield (%)
200	KOBu^t (2.5)	PhH	21	41
200	KOBu^t (1.1)	PhH	24	49
200	KOBu^t (0.2)	PhH	24	44
100	KOPe^t * (1.1)	PhH	18	68
100	KOPe^t (1.1)	PhMe	16.5	49
100	KO·CEt$_3$ (1.1)	PhH	16.5	48
100	KO·CEt$_3$ (1.1)	MeCN	28	20
100	NaOPe^t (1.1)	PhH	19	12
100	ArOK † (1.1)	PhH	17	44
100	$PhCO_2H$ (1.1)	MeCN	No reaction	
100	$PhCO_2H$ (1.1) + Et_3N (5)	MeCN	18	27
100	$PhCO_2H$ (1.1) + DABCO (5)	MeCN	14	Deformylation

* Pe^t = t-pentyl. †Ar = 4-methyl-2,6-di-t-butylphenyl.

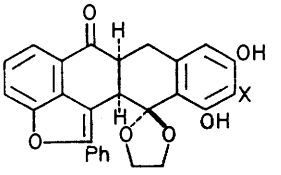


SCHEME 2

Treatment of the tetracyclic acetal (IX; X = CO_2Me) with aqueous ammonia (*d* 0.880) in tetrahydrofuran gave the amide (IX; X = CO·NH_2).



(VIII)

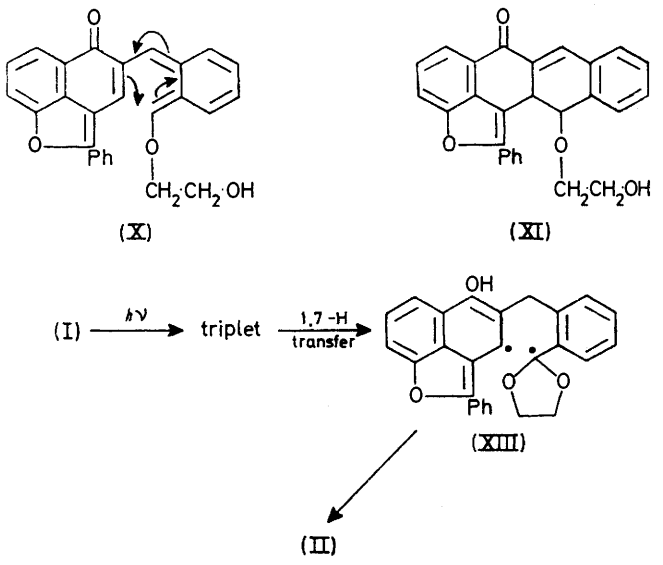


(IX)

The foregoing results have considerable implications for the mechanism whereby photocyclisation to complete ring B takes place. When we discussed [3] the acid-catalysed cyclisation of acetals such as (I) we suggested that an intermediate triene (X) was involved. Many analogies are available for the photocyclisation of such trienes. An alternative mechanism, which has been considered,[10] is outlined in Scheme 3. However, this does not explain why benzoic (or an equivalent) acid has such beneficial effects on the cyclisation.

[7] R. P. Singh, *Canad. J. Chem.*, 1966, **44**, 1994.
[8] L. F. Fieser, *J. Amer. Chem. Soc.*, 1931, **53**, 2329.
[9] D. H. R. Barton, C. C. Dawes, and P. D. Magnus, *J.C.S. Chem. Comm.*, 1975, 432.
[10] J. Wirz, *Helv. Chim. Acta*, 1974 **57** 1283.

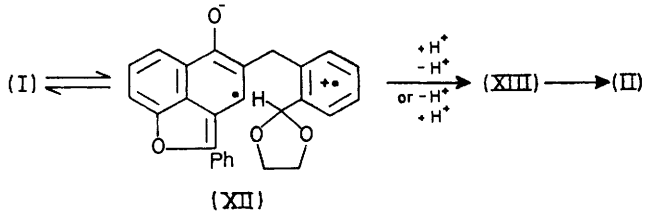
It is conceivable that the photocyclisation induced by strong base could also involve the triene intermediate (X). However it is difficult to see how the cyclisation product (XI) could be isomerised to (II). We therefore



SCHEME 3

propose an alternative explanation for the photochemical phenomena observed.

We consider that the first step after excited state formation is electron transfer [11] to give the radical cation–radical anion (XII). Protonation of the radical anion and loss of a proton from the radical cation would then give the diradical (XIII), whose cyclisation to product is conventional. In the absence of a proton source the intermediate (XII) would collapse to starting material (I). The catalytic effect of a proton source would thus be explained.



In the presence of base the radical cation would be deprotonated to the benzyl radical which, by further protonation would furnish the diradical (XIII) and thence (II). Similar considerations apply to the phenolic substrate (VIII), although here it is no doubt the anion of the phenol which is the electron donor.

Such a theory of photocyclisation would require that the potential CD system be electrophilic and the potential ring D be nucleophilic. This would explain the failure to photocyclise the acetal (IV).

[11] R. A. Neunteufel and D. R. Arnold, *J. Amer. Chem. Soc.*, 1973, **95**, 4080; J. Libman, *ibid.*, 1975, **97**, 4141; Y. Shigemitsu and D. R. Arnold, *J.C.S. Chem. Comm.*, 1975, 407, and references cited therein.

EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage apparatus. Unless stated otherwise, i.r. spectra were recorded for Nujol mulls and u.v. spectra for solutions in ethanol. N.m.r. spectra were determined for solutions in deuteriochloroform (unless stated to the contrary) with Varian T60 and HA100 instruments (tetramethylsilane as internal standard). Mass spectra were run with an A.E.I. MS9 spectrometer. Benzene was dried over sodium metal and distilled. Chloroform was dried over calcium chloride, passed down a column of alumina (Gl) and distilled prior to use. Solutions were dried over sodium sulphate. Light petroleum refers to the fraction of b.p. 40—60°. T.l.c. and p.l.c. were carried out on layers of silica gel (0.5 mm and 1 mm thick, respectively). Fluorescences quoted are for excitation at 253.7 nm. A 500 W tungsten lamp, housed in a reflecting enclosure, was employed in the photochemical reactions. The reaction flask was suspended in the enclosure, collinear with the axis of the lamp, and at a distance such as to maintain the solvent at reflux temperature.

Base-catalysed Photocylisation of the Model Acetal (I).—(i) *Variation of the base.*—The tricyclic acetal (40 mg) in anhydrous benzene (50 ml) was irradiated in the presence of base (1.1 equiv.) at reflux temperature in nitrogen. The reactions were monitored (t.l.c. analysis; elution with chloroform) for the disappearance of the starting material (R_F 0.5) and the appearance of the tetracyclic acetal (II) (R_F 0.75; pale-blue fluorescence), with the results recorded in Table 1.

Experiments in which the amount of catalyst was varied for the case of the most favourable base ($KOBu^t$) were carried out similarly. The reaction mixture was washed with water and dried, and the residue purified by p.l.c. Crystallisation from chloroform–diethyl ether gave material, m.p. 225—227°, identical (i.r., u.v., and n.m.r. spectra) with samples of the tetracyclic acetal (II) previously prepared [3] by acid-catalysed photocyclisation. The results are summarised in Table 2.

(ii) *Variation of the solvent.* Yields for reactions carried out as described above, with potassium t-butoxide (13 mg, 1.1 equiv.) as catalyst and anhydrous acetonitrile and tetrahydrofuran as solvents, are also recorded in Table 2.

2-[2-(*Dioxolan-2-yl*)*benzylidene*]*tetralin-1-one* (III) (with J. I. OKOGUN).—α-Tetralone (2.6 g) and phthalaldehyde mono(ethylene acetal) (1.6 g) were heated in ethanol (12 ml) in the presence of saturated methanolic potassium hydroxide (10 drops) at gentle reflux for 15 min. When cool, the mixture was poured into iced water, the product was extracted with benzene, and the extracts were washed with water until the washings were neutral. Recovery, followed by crystallisation from methanol, afforded the benzylidene derivative (III) as needles (1.3 g), m.p. 129—130°, $\nu_{max.}$ 1 665, 1 615, and 1 594 cm^{-1}, $\lambda_{max.}$ 225 and 285 nm (ε 10 000 and 14 500), τ 7.2 (4 H, m), 6.0 (4 H, m), and 4.18 (1 H, s), *m/e* 306 (M^+).

2-[2-(*Dioxolan-2-yl*)*benzyl*]-1-*naphthol* (IV).—The benzylidene compound (III) (1.2 g) in t-butyl alcohol (60 ml) was heated in the presence of potassium t-butoxide (1.2 g, 2.7 equiv.) at 50—55 °C in nitrogen for 18 h. The solvent was removed *in vacuo* and the residue was acidified with saturated aqueous potassium dihydrogen phosphate at 0 °C. Recovery with benzene gave a gum which was chromatographed on a column of silica gel. Elution with benzene, followed by crystallisation from warm light petroleum (b.p. 60—80°),

yielded the *naphthol* (IV) as needles (0.75 g), m.p. 125°, $\nu_{max.}$ 3 400, 1 600, 1 580, and 800 cm^{-1}, $\lambda_{max.}$ ($CHCl_3$) 237, 267, 274, 287, 313, and 327 nm (ε 10 100, 14 300, 8 300, 9 200, 6 500, and 4 800), τ 5.84 (4 H, m), 5.54 (2 H, s), 3.97 (1 H, s), 1.9—2.7 (10 H, m), and −0.06 (1 H, s, exchangeable with D_2O) (Found: C, 78.0; H, 5.7%; *m/e*, 306. $C_{20}H_{18}O_3$ requires C, 78.4; H, 5.9%; *M*, 306).

Irradiation of the Naphthol (IV).—The naphthol (30 mg) in refluxing benzene (50 ml) was irradiated in the presence of potassium t-butoxide (30 mg, 2.7 equiv.). After 24 h, t.l.c. showed the presence of many components. A control experiment, carried out under dark conditions, gave rise to the same mixture of products (t.l.c.), none of which exhibited fluorescence characteristic of a tetracyclic chromophore. When the irradiation was carried out at room temperature no naphthol was consumed.

2-[2-(*Dioxolan-2-yl*)*benzyl*]-1,4-*naphthoquinone* (V).—The naphthol (IV) (1.5 g) in methanol (400 ml) was treated with freshly prepared [7] Fremy's salt (8.0 g) in aqueous sodium acetate (1M; 10 ml). The mixture was shaken vigorously for 15 min, and the violet solution allowed to stand at room temperature for a further 30 min (pH remained in the range 6—8). The solution was diluted with water, extracted with chloroform, and the extract washed with water and dried. Recovery, followed by crystallisation from methanol afforded the *quinone* (V) as yellow needles (1.2 g), m.p. 86°, $\nu_{max.}$ 1 670, 1 620, and 1 590 cm^{-1}, $\lambda_{max.}$ ($CHCl_3$) 252, 260, 266, and 335 nm (ε 19 400, 15 200, 14 100, and 3 000), τ 6.00 (6 H, m, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$ and benzyl CH_2), 4.10 (1 H, s), 3.60 (1 H, t, *J ca.* 1 Hz), and 1.9—2.9 (8 H) (Found: C: 74.7; H, 5.15%; *m/e*, 320. $C_{20}H_{16}O_4$ requires C, 75.0; H, 5.0%; M^+, 320).

Photocyclisation of the Quinone Acetal (V).—The acetal (50 mg) in benzene (70 ml) was irradiated as previously described under conditions of acid and base catalysis; also in the absence of any catalyst. These reactions produced small amounts of yellow, fluorescent hydroxynaphthacenequinone (VI), which was isolated by p.l.c. (yields given in Table 3); m.p. 268—270°, $\nu_{max.}$ 3 140, 1 680, 1 620, 1 585, 1 210, 765, and 725 cm^{-1}, $\lambda_{max.}$ ($CHCl_3$) 255, 275, 283, 298, 312, and 442 nm (ε 22 400, 9 200, 9 000, 6 600, 2 600, and 4 000), τ 1.9—3.0 (m) (Found: C, 78.7; H, 3.7. $C_{18}H_{10}O_3$ requires C, 78.8; H, 3.7%), *m/e* 274 (M^+, base peak), 246, and 218.

A control experiment, carried out with the exclusion of light and with potassium t-butoxide as catalyst, produced only uncyclised (t.l.c.) decomposition products.

Acid Hydrolysis of the Quinone Acetal (V).—The acetal (500 mg) in methanol (60 ml) and water (40 ml) was heated in the presence of concentrated sulphuric acid (5 ml) at 100 °C for 2 h. During the reaction, yellow needles separated. The mixture was cooled and the product collected at the pump and washed with water. Recrystallisation from chloroform–methanol gave the naphthacenequinone (VII) (300 mg), m.p. 283—285°, mixed m.p. (see below) 280—285°, $\nu_{max.}$ 1 685, 1 622, 1 595, 770, and 730 cm^{-1}, $\lambda_{max.}$ ($CHCl_3$) 249, 278, 295, 316, and 296 nm (ε 20 500, 19 900, 21 300, 4 800, and 3 200), *m/e* 258 (M^+), 230, and 202, identical with a sample prepared by the method of Fieser.[8] Both samples gave a characteristic violet colour with concentrated sulphuric acid.

4-[2-(*Dioxolan-2-yl*)-3,5-*dihydroxy*-4-*methoxycarbonylbenzyl*]-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (VIII) (with C. C. Dawes).—(i) *With toluene*-p-*sulphonic acid as catalyst.* A suspension of the corresponding aldehyde (200 mg), prepared as previously described,[4] in anhydrous chloroform (10 ml) was stirred with an excess of diethylene orthocarbonate [9] (400 mg, 7.5 equiv.). Toluene-*p*-sulphonic acid (2 mg) was added, and the solution stirred at room temperature for 4 h. Triethylamine (20 μl) was added, and stirring was continued for a further 15 min. The yellow solution was washed with saturated aqueous sodium hydrogen carbonate, and the aqueous washings were extracted with more chloroform. The combined organic solutions were dried and evaporated to give a yellow solid (205 mg). Crystallisation from chloroform–benzene gave the *tricyclic acetal* (VIII) as yellow microcystals (185 mg), m.p. 220—224°, $\nu_{max.}$ 3 380, 1 662, and 1 641 cm^{-1}, $\lambda_{max.}$ 222, 264, 327, and 404 nm (ε 24 600, 8 100, 23 800, and 28 800), τ *ca.* 5.85 (4 H, m, $W_{\frac{1}{2}}$ 10 Hz), 5.83 (3 H, s), 5.70 (2 H, s), 3.55 (1 H, s), 3.45 (1 H, s), 1.8—2.5 (9 H, m), and 0.37 and −0.42 (each 1 H, D_2O-exchangeable) (Found: C, 69.8; H, 4.6%; *m/e*, 498. $C_{29}H_{22}O_8$ requires C, 69.9; H, 4.45%; *M*, 498).

(ii) *With boron trifluoride–ether complex as catalyst.* To a suspension of the corresponding aldehyde (700 mg) in anhydrous chloroform (30 ml) was added diethylene orthocarbonate [9] (1.1 g, 6 equiv.), together with a solution made by addition of water (5% v/v) to redistilled boron trifluoride–ether complex (35 μl). The dark orange solution was stirred at room temperature. After 4.5 h, n.m.r. analysis indicated the complete disappearance of starting materials; triethylamine (35 μl) was added and stirring continued for 15 min to give a clear, yellow solution. Evaporation at room temperature, followed by the removal of excess of reagent and the reagent by-products by sublimation (10^{-4} mmHg; 80 °C; 3 h) gave a yellow solid (770 mg). Trituration of this material with dichloromethane–benzene (1 : 1), followed by filtration, gave the acetal (VIII) (731 mg), m.p. 212—216°, identical (i.r., u.v., and n.m.r. spectra) with the previous sample. Reactions in which freshly distilled, anhydrous boron trifluoride–ether was employed as catalyst led to quantitative recovery of starting material.

Methyl 12-*Ethylenedioxy*-6aα,7,12,12aα-*tetrahydro*-9,11-*dihydroxy*-6-*oxo*-1-*phenyl*-6H-*naphthaceno*[1,12-bc]*furan*-10-*carboxylate* (IX; X = CO_2Me).—Anhydrous benzene (500 ml) was deoxygenated by passage of a stream of dry, oxygen-free argon at reflux temperature for 30 min. The tricyclic acetal (VIII) and potassium t-pentylate (90 mg, 1.1 equiv.) were added and the stirred solution was irradicated under gentle reflux in argon. After 20 h, t.l.c. (elution with ethyl acetate–dichloromethane, 3 : 17) showed complete consumption of the tricyclic acetal (R_F 0.6) and a single product (R_F 0.8; pale blue fluorescence). The cooled solution was washed with saturated aqueous potassium dihydrogen phosphate (NaCl addition). The aqueous layer was extracted with dichloromethane, and the combined organic extracts were dried and evaporated at 40 °C. The orange-brown residue (350 mg) in dichloromethane was chromatographed on a column of silica gel (14 × 2.5 cm). Elution with ethyl acetate–dichloromethane (1 : 19), followed by crystallisation from chloroform–ethyl acetate, gave the *tetracyclic acetal* (IX; X = CO_2Me) (184 mg), m.p. 242—245°, $\nu_{max.}$ 3 420, 1 686, 1 662, and 1 617 cm^{-1}, $\lambda_{max.}$ 228, 267, 295, 307, and 344 nm (ε 31 000, 26 000, 12 000, 11 000, and 13 500), τ 6.06 (3 H, s), 5.8—7.5 (7 H, complex m), 5.65 (1 H, d, *J* 6 Hz), 3.64 (1 H, s), 1.8—2.85 (8 H, m), and 0.78 and −0.80 (each 1 H, s, D_2O-exchangeable) (Found: C, 69.9; H, 4.45. $C_{29}H_{22}O_8$ requires C, 69.9; H, 4.45%), *m/e* 498 (M^+, 3%), 252 (100), and 220 (60).

Smaller-scale photocyclisation reactions employing alternative bases and different solvents are summarised in Table 4. A typical experiment is as follows. The tricyclic acetal (VIII) (100 mg) in anhydrous, oxygen-free benzene (200 ml) was irradiated in the presence of the potassium salt of 2,6-di-t-butyl-*p*-cresol (57 mg, 1.1 equiv.) as described in the previous experiment. After 17 h the mixture was worked-up as before and the product purified by p.l.c. Elution with ethyl acetate–dichloromethane (3 : 17) gave the tetracyclic acetal (IX; X = CO_2Me) (44 mg) as the least polar band, identified by its i.r. spectrum.

12-*Ethylenedioxy*-6aα,7,12,12aα-*tetrahydro*-9,11-*dihydroxy*-6-*oxo*-1-*phenyl*-6H-*naphthaceno*[1,12-bc]*furan*-10-*carboxamide* (IX; X = $CO{\cdot}NH_2$).—The methyl ester (IX; X = CO_2Me) (100 mg) was added to a mixture of tetrahydrofuran and aqueous ammonia (*d* 0.88) (1 : 1; 10 ml) which had previoulsy been saturated with ammonia gas. The solution was stirred at room temperature in ammonia gas for 16 h. After the removal of the tetrahydrofuran and the excess of gaseous ammonia *in vacuo* at room temperature, saturated aqueous potassium dihydrogen phosphate (10 ml) was added, and the solution was extracted repeatedly with ethyl acetate. Recovery afforded a brown gum (124 mg). P.l.c., followed by crystallisation from ethyl acetate–light petroleum, gave the *amide* (IX; X = $CO{\cdot}NH_2$) as off-white, felted needles, m.p. 225—226° (decomp.), $\nu_{max.}$ 3 460, 3 320, 3 180, 1 695, 1 680sh, 1 650, and 1 610 cm^{-1}, $\lambda_{max.}$ 225, 256sh, 265, 275, 295, 307, and 348 nm (ε 30 400, 23 000, 23 300, 19 500, 13 000, 12 500, and 13 000), τ [$(CD_3)_2SO$] 5.54 (1 H, d, *J* 6 Hz), 3.77 (1 H, s), and 1.7—2.8 (7 H, m) (Found: C, 69.4; H, 4.5; N, 2.9. $C_{28}H_{21}NO_7$ requires C, 69.6; H, 4.4; N, 2.9%), *m/e* 483 (M^+, 4%), 467 (2), 439 (10), 247 (36), and 237 (100).

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