

Experiments on the Synthesis of Tetracyclines. Part XII.¹ Extension of the Acetal Photocyclisation Process

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In analogy to earlier work, the acid-catalysed photocyclisation of 3-[2-(dioxolan-2-yl)benzyl]chromone (II; XX = O·CH₂·CH₂·O) to give 6,6-ethylenedioxy-5a α ,6,11,11a α -tetrahydro-12*H*-benzo[*b*]xanthen-12-one (III) and its *trans*-(5a α *H*,11a β *H*) isomer (IV) has been effected. It is suggested that this photocyclisation process will be of general synthetic utility.

In Part V² we described an acid-catalysed photochemical reaction for forming the C(11a)–C(12) bond in our projected tetracycline synthesis. This photochemical reaction in a generalised form should lend itself to the creation of linear carbocyclic structures that would

¹ Part XI, D. H. R. Barton, P. D. Magnus, G. Smith, G. Streckert, and D. Zurr, *J.C.S. Perkin I*, 1972, 542.

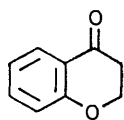
² Part V, D. H. R. Barton, D. L. J. Clive, P. D. Magnus, and G. Smith, *J. Chem. Soc. (C)*, 1971, 2193.

otherwise require circuitous procedures. A further example of the application of this reaction is now described.

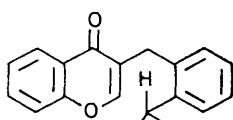
Chroman-4-one (I)³ was condensed with *o*-phthalaldehyde in ethanol at reflux with triethylamine as

³ (a) G. B. Bachman and H. A. Lavine, *J. Amer. Chem. Soc.*, 1948, **70**, 599; (b) O. Dann and H. Hofmann, *Chem. Ber.*, 1962, **95**, 1446; (c) W. E. Parkhan and A. D. Huestis, *J. Amer. Chem. Soc.*, 1962, **84**, 813.

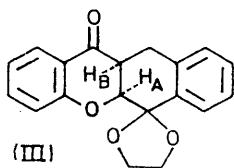
catalyst. To obtain reproducible yields it was necessary to complete the reaction by evaporating off the solvent and heating the mixture to 140–170°. The product (II; XX = O) was identified as the endocyclic double-bond isomer of the benzylidenechromanone by the u.v. spectrum [λ_{\max} 305, 298, 245, 227, and 207 nm (ϵ 8680, 9230, 20,480, 28,850, and 33,700)]; cf. chromone,⁴ λ_{\max} 297 and 245 nm (ϵ 6600 and 9770). In the n.m.r. spectrum the benzylic protons gave a singlet at τ 5.75; the olefinic proton resonated at τ 2.20, the aldehyde proton at -0.3 , and the aromatic proton *peri* to the carbonyl group at 1.8 (dd, J 2 and 8 Hz). The aldehyde



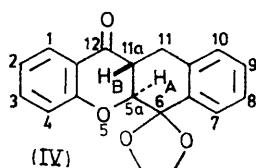
(I)



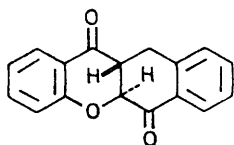
(II)



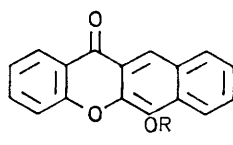
(III)



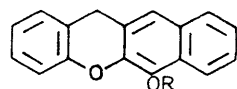
(IV)



(V)



(VI)



(VII)

was converted into its acetal (II; XX = O·CH₂·CH₂·O) by standard procedures. Photolysis of the product in benzene containing *o*-chlorobenzoic acid (medium-pressure mercury lamp) proceeded rapidly and in reasonable yield (65%). The first-formed product was the *cis*-isomer (III) which under the acidic reaction conditions was epimerised to the *trans*-isomer (IV). The *trans*-isomer (IV) was isolated by chromatography; λ_{\max} (EtOH) 320, 254, and 214 nm (ϵ 2360, 6640, and 25,300). The n.m.r. spectrum of compound (IV) was complex and was deciphered with the aid of spin decoupling. The proton H_A gave rise to a doublet by coupling to H_B (J_{AB} 14 Hz); H_B is coupled to both benzylic protons (J 6 and 12.5 Hz) and the benzylic protons are coupled to one another (J 18.5 Hz). The *cis*-isomer was isolated by preparative t.l.c. and was

⁴ B. K. Ganguly and P. Bagchi, *J. Org. Chem.*, 1956, 1415.

⁵ K. R. Huffman, M. Loy, and E. F. Ullman, *J. Amer. Chem. Soc.*, 1965, 87, 5417.

readily epimerised to the *trans*-isomer by treatment with triethylamine in ethanol.

The acetal (IV) was converted into the diketone (V) by treatment with trityl fluoroborate¹ in dichloromethane followed by water, since direct acid hydrolysis gave complex mixtures. Compound (V) was isolated in high yield (ν_{\max} 1695, 1685, and 1610 cm⁻¹). When it was treated with aqueous sodium hydroxide solution, the xanthone (VI; R = H) was formed (ν_{\max} 3330, 1650, 1635, and 1603 cm⁻¹), presumably through autoxidation of the enolate anion. No product corresponding to the naphthalene formed by β -elimination of phenolate anion from compound (V) was isolated. The hydroxyxanthone (VI; R = H) was characterised as the acetate (VI; R = Ac) and the methyl ether (VI; R = Me). Zinc dust-acetic acid reduction of the acetate (VI; R = Ac) gave the xanthen (VII; R = Ac), τ 5.8 (benzylic proton). Comparison of the u.v. spectrum of the xanthone (VI; R = H) with that of the known 11-hydroxy-isomer^{5,6} confirmed the structure.

EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage apparatus. I.r. spectra were measured for Nujol mulls and u.v. spectra for solutions in ethanol unless stated otherwise. N.m.r. spectra were taken for solutions in deuteriochloroform at room temperature with Varian A60 and HA100 spectrometers. Mass spectra were determined with an A.E.I. MS9 high resolution spectrometer. Light petroleum refers to the fraction of b.p. 40–60°.

3-(2-Formylbenzyl)chromone (II; XX = O).—Chroman-4-one (2.53 g) and *o*-phthalaldehyde (2.45 g) in absolute ethanol (15 ml) and triethylamine (15 ml) were heated at reflux for 20 h. The mixture was then kept under a stream of nitrogen while being heated in an oil-bath at 140–170°. After 1 h a 1:1 mixture (10 ml) of ethanol and triethylamine was added and the resulting mixture was kept at 140–170° for a further 5 h. It was then evaporated and the residue was chromatographed in benzene over alumina to give the *chromone* (II; XX = O) (4.1 g), m.p. (from benzene–light petroleum) 131–134°, ν_{\max} 2760, 1695, and 1635 cm⁻¹; for u.v. and n.m.r. spectra see Discussion section (Found: C, 77.2; H, 4.7. C₁₇H₁₂O₃ requires C, 77.3; H, 4.6%).

3-[2-(Dioxolan-2-yl)benzyl]chromone (II; XX = O·CH₂·CH₂·O).—The *chromone* aldehyde (II; XX = O) (2.8 g) in dry benzene (350 ml) and ethylene glycol (10 ml) containing toluene-*p*-sulphonic acid monohydrate (29 mg) was heated at reflux for 18 h. The vapour was allowed to percolate through a thimble containing calcium hydride. The cooled solution was added to aqueous sodium carbonate (10%; 250 ml). The aqueous layer was extracted with benzene (100 ml). The combined benzene extracts were dried (Na₂SO₄) and evaporated to yield the *acetal* (II; XX = O·CH₂·CH₂·O) (3.2 g), m.p. (from benzene–light petroleum) 106–108°, ν_{\max} 1645 and 1615 cm⁻¹, λ_{\max} 320, 300, 227, and 205 nm (ϵ 7765, 7560, 27,650, and 21,760), τ 6.0 (6H, m), 4.0 (1H, s), 2.5 (8H, m), and 2.7 (1H, dd, J 2 and 8 Hz) (Found: C, 73.9; H, 5.3. C₁₉H₁₆O₄ requires C, 74.0; H, 5.2%).

⁶ W. A. Henderson, jun., and E. F. Ullman, *J. Amer. Chem. Soc.*, 1965, 87, 5424.

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