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SYNTHESIS OF PTEROCARPAN ANALOGUES: 6a,11a-DEHYDROPTEROCARPAN–COUMESTAN CONVERSION

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Abstract—Synthetic 3,4,8,9-tetramethoxy-6a,11a-dehydropterocarpan undergoes autoxidation to the coumestane analogue, a reaction considered elsewhere to be of significance in coumestan biosynthesis. Nuclear allylation of the methyl ethers of pyrogallol and resorcinol is effected as prelude to the synthesis of more complex natural pterocarpans.

INTRODUCTION

GRISEBACH *et al.*[1] in seeking a chemical analogy for coumestane biosynthesis, found that fusion of 2′,4′,7-trimethoxyisoflavanone with pyridine hydrochloride in the presence of atmospheric oxygen produced low yields of coumestrol (I), whereas in the absence of oxygen only traces of coumestrol could be detected. Hence they inferred that an intermediate (II), although not isolated, must be formed, and postulated its susceptibility to oxidation at the allylic position.

Confirmation of the latter has now been obtained from recent work[2] aimed mainly at the synthesis of folinin (2″,2″:2′,2′-tetramethyl-2,3:5″,6″-chromano-9,10:5′,6′-chromeno-pterocarpan), previously isolated from the root bark of *Neorautanenia ficifolia* by Brink *et al.*[3]

RESULTS AND DISCUSSION

Synthesis of a new pterocarpan analogue, 3,4,8,9-tetramethoxycoumestane (III), was effected according to the procedure of Wanzlick *et al.*,[4] by oxidative coupling of 7,8-dimethoxy-4-hydroxycoumarin with catechol using potassium ferricyanide, followed by immediate methylation of the unstable 8,9-dihydroxy-3,4-dimethoxycoumestane. The fully methylated product (III) was reduced by diborane to 3,4,8,9-tetramethoxy-6a,11a-dehydro-pterocarpan (IV).

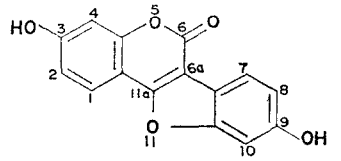
The dehydropterocarpan (IV) when left in acetone solution for 2 days showed *ca.* 90 per cent reversion to the coumestane analogue (III). Such autoxidation confirms Grisebach's recent surmise[1] of the lability of 6a,11a-dehydropterocarpans to oxidation at the 6-position, and indirectly supports their conjecture regarding the position of dehydropterocarpans as intermediates in coumestane biosynthesis from the appropriate isoflavanones. Previously

[1] P. M. DEWICK, W. BARZ and H. GRISEBACH, *Chem. Commun.* 466 (1969).
[2] D. FERREIRA, *Synthesis of Furocoumarins*, M.Sc.Thesis, University of the Orange Free State, Bloemfontein (1969).
[3] C.V.D.M. BRINK, J. P. ENGELBRECHT and D. E. GRAHAM, *J.S. African Chem. Inst.* **23**, 24 (1970).
[4] H. W. WANZLICK, R. GRITZKY and H. HEIDEPRIEM, *Chem. Ber.* **96**, 305 (1963).

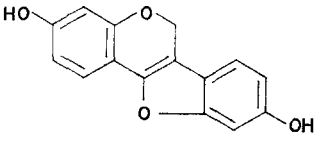
Whalley *et al.*[5] used drastic conditions, namely chromium trioxide in acetic acid, to effect an analogous conversion.

Autoxidation of the above 6a,11a-dehydropterocarpan (IV) at the allylic position is the likely consequence of a free radical mechanism involving hydroperoxide formation,[6] followed by decomposition to the ketone.[7] The low activation energy required must result from resonance stabilization of the allylic radical and the inductive effect of the double bond[8] within a cyclic system.[9]

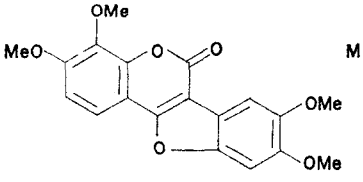
Attempts at selective reduction of the 6a,11a-dehydropterocarpan (IV) to 3,4,8,9-tetramethoxypterocarpan were not successful, presumably due to resonance stabilization of



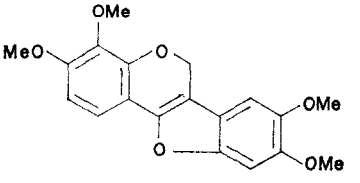
I



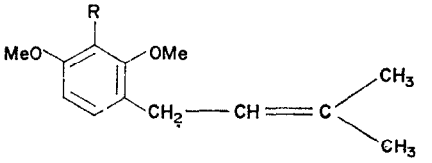
II



III



IV



V R = OMe
VI R = H

the conjugated system. Increasingly drastic conditions, with palladium as catalyst, eventually led to hydrogenation of the benzenoid ring systems, although Brink *et al.*[10] obtained 3,4-dimethoxy-8,9-methylenedioxypterocarpan in exceptionally low yield from the related 6a,11a-dehydropterocarpan under identical conditions.

[5] W. J. BOWYER, J. N. CHATTERJEA, S. P. DHOUBHADEL, B. O. HANDFORD and W. B. WHALLEY, *J. Chem. Soc.* 4212 (1964).
[6] R. CRIEGEE, H. PILZ and H. FLYGARE, *Chem. Ber.* **72,** 1799 (1939).
[7] A. I. KAMNEVA and Y. S. PANIFILOVA, in *The Oxidation of Hydrocarbons in the Liquid Phase* (edited by N. M. EMANUEL), p. 219, Pergamon Press, Oxford (1965).
[8] E. H. FARMER, G. F. BLOOMFIELD, A. SUNDRALINGHAM and D. A. SUTTON, *Trans. Faraday Soc.* **38,** 348 (1942).
[9] J. L. BOLLAND, *Trans. Faraday Soc.* **46,** 358 (1950).
[10] D. BOUWER, C.V.D.M. BRINK, J. P. ENGELBRECHT and G. J. H. RALL, *J.S. African Chem. Inst.* **21,** 159 (1968).

Similarly attempts at introduction of γ,γ-dimethylallyl groups into the 3,4,8,9-tetramethoxy-6a,11a-dehydropterocarpan (IV) were expectedly unsuccessful. However, the dehydropterocarpan (IV) was again oxidized quantitatively to the coumestane analogue (III) in the presence of phenyl lithium and γ,γ-dimethylallyl bromide during the course of these attempts.

As model substances for the eventual nuclear allylation of pterocarpans, *O*-trimethylpyrogallol and *O*-dimethylresorcinol readily afford substitution at their respective 4-positions (V and VI). Boltze and Dell[11] previously claimed 2-substitution for resorcinol.

EXPERIMENTAL

M.ps are uncorrected. I.r. spectra were recorded using the KBr disc method, and NMR spectra on a Varian HA-100 spectrometer using tetramethylsilane as internal standard. Mass spectra were recorded on an AEI MS9 spectrometer.

The purity of compounds was assessed by NMR spectrometry, and their structures by both mass and NMR spectrometry.

3,4,8,9-*Tetramethoxycoumestan* (*III*)

The synthetic sequence was similar to that used by Brink *et al.*[10] for 3,4-dimethoxy-8,9-methylenedioxypterocarpan. 7,8-Dimethoxy-4-hydroxycoumarin, m.p. 237–238°, was prepared from pyrogallol by a von Pechmann synthesis according to the method of Shah *et al.*[12] followed by methylation with Me_2SO_4. $K_3Fe(CN)_6$ was used as oxidant in the oxidative coupling of 7,8-dimethoxy-4-hydroxycoumarin with catechol in the Wanzlick procedure[4] to give 3,4-dihydroxy,8,9-dimethoxycoumestan, m.p. 350°.[10]

The unstable dihydroxycoumestan (1·2 g) was methylated immediately with Me_2SO_4 (0·8 g) and K_2CO_3 (12 g) in acetone (500 ml) by refluxing at 100° for 5 hr. After filtration the acetone was removed under vacuum and the residue taken up in $CHCl_3$. The $CHCl_3$ was washed successively with 5% NaOH and H_2O, and dried (Na_2SO_4.) Removal of the solvent under vacuum afforded a pale yellow solid which was purified on activated alumina using acetone as eluant. Crystallization from acetone gave pale yellow *needles* (900 mg), m.p. 199–200°.

The i.r. spectrum showed ν_{max} 1730 cm^{-1} due to an α,β-unsaturated lactone.

The mass spectrum [*m/e* 356 (100), 341 (33) 313 (9·1), 298 (8·0), 285 (10·2), 236 (12·5)] was consistent with the above structure.

The NMR spectrum [τ2·42 (H_1, doublet), 2·52 (H_7, singlet), 2·87 (H_{10}, singlet), 3·06 (H_2, doublet), 5·94, 6·00, 6·02, 6·04 (methoxyl, singlets); $J_{1,2}$ 8·4, $J_{7,10} < 1$ Hz] confirms the above structure.

3,4,8,9-*Tetramethoxy*-6a,11a-*dehydropterocarpan* (*IV*)

3,4,8,9-Tetramethoxycoumestan (750 mg) was dissolved in dry tetrahydrofuran (300 ml) and diborane passed through the solution at 0° over 4 hr. Diborane was led through the solution for a further 36 hr at room temperature. The white jelly-like complex was treated with 10% H_2SO_4 (30 ml). After evaporation of the tetrahydrofuran the aqueous solution was extracted with benzene.

The benzene extract was washed with H_2O, dried, and the compound purified by column chromatography on activated alumina with benzene as eluant. The pale yellow solid was recrystallized from methanol as *needles* (620 mg), m.p. 190–191°.

The i.r. spectrum showed the complete absence of carbonyl function.

The mass spectrum [*m/e* 342 (100), 341 (13·2), 328 (10·3), 327 (42·7), 299 (5·6), 171 (15·0)] was consistent with the above structure.

The NMR spectrum provided further confirmation of structure [τ2·84 (H_1, doublet), 2·93 (H_7, doublet), 3·21 (H_{10}, singlet), 3·47 (H_2, doublet), 4·40 (methylene H, singlet), 6·04 (6H), 6·07(3H), 6·10 (3H) (methoxyl H, singlets), $J_{1,2}$ 8·4, $J_{7,10} < 1$ Hz].

Autoxidation of 3,4,8,9-*Tetramethoxy*-6a,11a-*dehydropterocarpan* (*IV*) *to* 2,3,8,9-*Tetramethoxycoumestan* (*III*)

A solution of the dehydropterocarpan in acetone kept at room temperature for 48 hr showed *ca.* 90 per cent conversion to the coumestane analogue. The latter was isolated by TLC on Kieselgel H (Merck) with $CHCl_3$ as solvent. The product, m.p. 199°, gave a mixed m.p. 199–200°, and an i.r. spectrum identical to synthetic III.

The dehydropterocarpan in anhydrous ether in the presence of phenyl lithium and γ,γ-dimethylallyl bromide, underwent the same autoxidation at room temperature during attempted nuclear allylation.

[11] K. H. Boltze and H. D. Dell, *Angew. Chem.* **5**, 415 (1966).
[12] V. R. Shah, J. L. Bose and R. C. Shah, *J. Org. Chem.* **25**, 677 (1960).

Attempted Reduction of 3,4,8,9-*Tetramethoxy*-6a,11a-*dehydropterocarpan* (*IV*)

Conditions were those previously applied for an analagous reduction.[10] With 5 and 10% Pd on charcoal no hydrogenation occurred using a variety of solvent media. With 30% Pd/C in ethyl acetate–HOAc at 6 atm pressure hydrogenation occurred at 60° after 30 min, yielding a product of low polarity (thin layer chromatography).

I.r. and NMR spectra showed that hydrogenation of the aromatic ring systems had occurred. Brink *et al.*[10] under identical conditions obtained a mixture of seven products of which one was the desired pterocarpan.

Nuclear Allylation of Simple Phenols

(i) 4-(*γ,γ-Dimethylallyl*)-*O-dimethylresorcinol* (*VI*). Resorcinol dimethylether was metallated with phenyl lithium and the product treated with γ,γ-dimethylallyl bromide according to the method of Boltze and Dell.[11] The NMR spectrum of the resultant oil showed substitution at the 4-position [τ 3·0 H_5, doublet), 3·57 (H_2, doublet), 3·60 (H_6, quartet), 4·73 (olefinic H, triplet), 6·77 (methylene H, doublet), 6·22, 6·24 (methoxyl H, singlets), 8·30 (methyl H, broad singlet); $J_{5,6}$ 8·5, $J_{2,6}$ 2·5, $J_{\alpha,\beta}$ 6·5 Hz).

(ii) 4-(*γ,γ-Dimethylallyl*)-*O-trimethylpyrogallol* (*V*). Synthesis was carried out as above and the resultant oil examined by NMR spectroscopy. The spectrum was consistent with 4-substitution [τ2·42 (H_5, doublet), 3·30 (H_6, doublet), 3·40 (olefinic H, triplet), 6·20 (methylene H, doublet), 6·00, 6·13, 7·19 (methoxyl H, singlets), 8·72 (methyl H, broad singlet: $J_{5,6}$ 9·0, $J_{\alpha,\beta}$ 6·5 Hz).

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