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FLAVANOIDS—III[a]

A STEREOSPECIFIC SYNTHESIS OF (±) TRIMETHYL CYANOMACLURIN AND ITS ACETATE

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Abstract—A stereospecific synthesis of (±) trimethyl cyanomaclurin has been achieved via 2'-benzyloxy-4',5,7-trimethoxyflav-3-ene and trans-cis-4',5,7-trimethoxy, 2',3,4-trihydroxyflavan. The conformation and stereochemistry at each step is established by NMR.

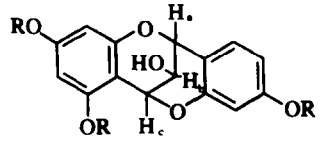
The structure of cyanomaclurin isolated in 1895 has undergone modification thrice.[1] The present structure **1** is based on comparative NMR studies by Nair and Venkataraman[1d] on trimethyl cyanomaclurin and its acetate. A recent synthesis[2] confirmed the presence of two pyran rings without any stereochemical assignment. The assigned stereochemistry[1d] is based on the observed low coupling (less than 6–7 Hz) between proton H-b and H-c requiring these two protons to be diequatorial like. However when a model of cyanomaclurin is examined it is obvious that the same can be viewed in two ways **1a** and **1b**. In **1a** H-b and H-c are diequatorial like and in **1b** the same protons (H-b and H-c) are axial-equatorial like. This makes it clear that assignment of stereochemistry on the basis of coupling constants between H-b and H-c is not satisfactory. We therefore planned to established the stereochemistry through a stereospecific synthesis. In our earlier communication[3] we have reported some stereospecific reactions of a flav-3-ene system. The present communication deals with its utilisation for the synthesis of this moderately complex flavan derivative. Our synthesis clearly shows that the assigned stereochemistry is as in **1** and agrees with that assigned earlier.

Reductive cyclisation of 2-benzyloxy-2'-hydroxy-4,4',6'-trimethoxy chalcone[2] **2** with sodium borohydride in 2-methoxy ethanol and subsequent treatment with acetic acid furnished 2'-benzyloxy-4'-5,7-trimethoxy flav-3-ene **3** (78%). Its structure was confirmed by elemental analysis, and an examination of the NMR spectrum [H-b proton double doublet at 5·43 δ (J = 10 and 4 Hz), H-a proton double doublet at 6·12 δ (J = 4 and 2 Hz), and the H-c proton double doublet at 6·6 δ (J = 10 and 2 Hz)]. The presence of allylic coupling[4] of 2 Hz between H-a and H-c clearly defined a skewed styrene conformation with aromatic ring-B equatorial for flav-3-ene **3**.

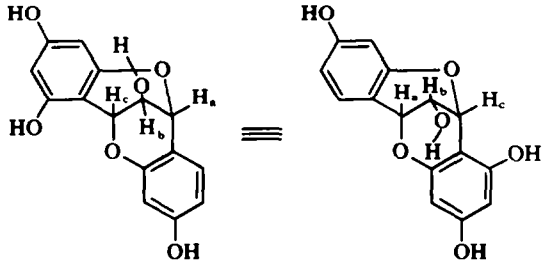
Reaction of molar equantities of flavene **3** and osmium tetroxide furnished the 2,3-trans-3,4-cis diol **4**. The use of barium chlorate-osmium-tetroxide[5] as the oxidizing agent not only facilitated the isolation but also considerably enhanced (from 20 to 87%) the yield.

The IR spectrum (ν-OH 3511 and 3416 cm^{-1}, $\Delta\nu$ = 105 cm^{-1}, cis diol[6]) clearly showed that this product has the expected structure and stereochemistry **4**. The NMR spectrum of its acetate showed the H-b proton as a double doublet at 5·27 δ (J = 9 and 3 Hz), overlapping with H-a proton doublet at 5·4 δ (J = 9 Hz) and H-c proton doublet at 6·2 δ (J = 3 Hz). The overlapping H-a and H-b proton signals were clearly resolved in the NMR spectrum of the diol **4** in pyridine-d_5 showing H-b proton doublet doublet at 4·46 δ (J = 11 and 4 Hz), H-c proton doublet at 5·3 δ (J = 4 Hz), and H-a proton doublet at 6·16 δ (J = 11 Hz). The NMR data, thus, confirmed the assigned stereochemistry.

In order to achieve the synthesis of trimethylcyanomaclurin, the 2'-benzyloxy flavan-3,4-diol **4** was debenzylated by catalytic hydrogenation over Pd/c to yield 2'-hydroxy-4',5,7-trimethoxy flavan-3,4-diol **5** (59%). Its NMR spectrum in pyridine-d_5 [H-b proton double doublet at 4·4 δ (J = 11 and 3 Hz), H-c proton doublet at 5·41 δ

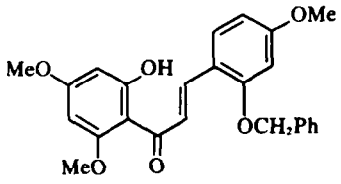


1: R = H
6: R = Me

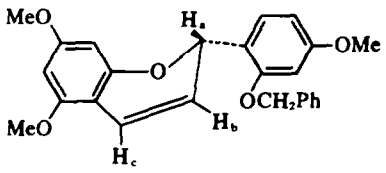


1a **1b**

[a] Flavanoids II: K. G. Marathe, M. J. Byrne and R. N. Vidwans, *Tetrahedron* **22**, 1789 (1966).



2



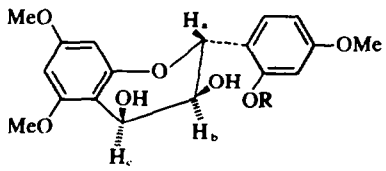
3

(J = 4 Hz), and H-a proton doublet masked with OH protons (clearly visible on D_2O exchange) at 6·05 δ (J = 11 Hz)] proved that the triol **5** is a *trans-cis* isomer and there is no change in the stereochemistry during hydrogenolysis of **4**.

The final cyclisation of the triol to trimethylcyanomaclurin was accomplished by refluxing with boric acid in aqueous ethanol. The resulting product **6** melted at 82–85°, while the reported melting point of trimethyl cyanomaclurin from natural sources is 75–85°[8]. Seshadri and coworkers report a m.p. of 158–59° for the racemic trimethyl ether. In view of the identity in spectral properties of our sample with that reported, the large difference in m.p. of our sample from that of Seshadri *et al.* could be due to polymorphism. The compound m.p. 82–85° analysed for $C_{18}H_{18}O_6$ and its NMR spectrum showed OH proton at 2·1 δ (D_2O exchange), H-b proton triplet at 4·33 δ (J = 3 and 3 Hz), and two benzylic protons at 5·1 and 5·37 δ. In trans-cis-flavan-3,4-diols[7] the equatorial H-c proton adjacent to phloroglucinol nucleus appears downfield as compared to the one adjacent to resorcinol nucleus. Accordingly the signal at 5·37 δ can be assigned to H-c proton and the one at 5·1 δ to H-a. The reported values for the three protons of the pyran nucleus of trimethyl cyanomaclurin are 4·33, 5·12 and 5·43 δ respectively.

The low coupling constant between H-a and H-b in **6** (J_{ab} = 3 Hz) compared to the one observed for these protons in the triol **5** (Jab = 11 Hz) clearly shows conformational inversion in the final cyclisation. Moreover while H-b proton signal shows equatorial-equatorial (as in **1a**) or equatorial-axial (as in **1b**) relation of H-b and H-c; H-a and H-c proton signals appear as ill resolved double doublets (J = 2 and 3 Hz) indicating W-coupling between H-a and H-c.

The above trimethyl cyanomaclurin gave an acetate m.p. 168–69°. Its identity was established by direct comparison (m.m.p., TLC, IR) with an authentic sample prepared from the natural product. Its NMR spectrum is identical with that reported by Nair and Venkataraman[1d] for trimethylcyanomaclurin acetate (Fig. 1).



4: R = CH_2Ph
5: R = H

Thus these results confirm the stereochemistry of cyanomaclurin and its acetate as in **1**. However we believe that the epimeric alcohol trimethylepicyanomaclurin will also show small coupling between protons H-b, H-a and H-c. Experiments to verify this are in progress.

EXPERIMENTAL

All m.ps were taken on a Kaufler hot stage and are uncorrected. IR spectra were measured as nujol mulls, on Perkin-Elmer 337, UV on Beckman DK-2 in methanol, and NMR on Varian T-60. Chemical shifts are expressed in ppm downfield from TMS.

2'-Benzyloxy-4',5,7-trimethoxyflav-3-ene **3**. Compound **2** (1 g) in 2-methoxy ethanol (20 ml) was stirred with $NaBH_4$ (0·1 g) at 90° for ½ hr. After 12 hr at room temp the colourless soln of the complex was boiled with $CHCl_3$ (20 ml) for 10 min and then refluxed with a soln of AcOH in $CHCl_3$ (10% 20 ml) for 2 hr. Excess $NaHCO_3$ was added, the mixture was poured in water, and extracted with $CHCl_3$. The $CHCl_3$ extract on washing, drying (Na_2SO_4), and removal of the solvent furnished an oily residue which was chromatographed on SiO_2. The viscous gum obtained in the benzene eluates afforded a solid on trituration with light petroleum, which gave prisms from EtOAc-light petroleum, m.p. 75° (78%); NMR (CCl_4), δ 3·69 and 3·75 (6 H and 3 H each, s, 3 X–OMe), 5·03 (2 H, s, $=OCH_2Ph$), 5·43 (1 H, dd, J = 10 and 4 Hz, H-b), 5·87 (2 H, s, H-3', H-6), 6·12 (1 H, dd, J = 4 and 2 Hz, H-a), 6·37 (2 H, s, H-5', H-8), 6·6 (1 H, dd, J = 10 and 2 Hz, H-c), 7·3 (6 H, bs, H-6', Ph) (Found: C, 74·59; H, 6·23. $C_{25}H_{24}O_5$ requires: C, 74·24; H, 5·98%).

trans - cis - *2' - Benzyloxy - 4',5,7 - trimethoxyflavan - 3,4 - diol* **4**. A suspension of **3** (0·8 g) in aq. THF (1:1, 50 ml) was stirred with OsO_4 (0·05 g) and $BaClO_4$ (0·6 g) for 22 hr. At the end of this period the pale yellow soln was extracted with $CHCl_3$. The $CHCl_3$ layer was washed thoroughly with sat. Na_2SO_3, brine, and finally with water, and dried. Removal of the solvent gave a gummy mass which was crystallised from $CHCl_3$-light petroleum, m.p. 163–64° (87%); ν_{max} 3511, 3416 cm^{-1} (2x–OH) (Found: C, 68·28; H, 6·08, $C_{25}H_{26}O_7$ requires; C, 68·48; H, 5·98%).

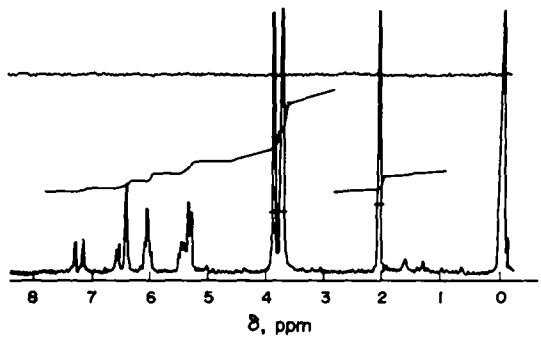


Fig. 1. NMR spectra of cyanomaclurin trimethyl ether acetate (synthetic).

Acetate. Ac_2O-pyridine, m.p. 60–62° (50%); ν_{max} 1720 cm^{-1} (X–$OCOCH_3$); NMR (CCL_4), δ 1·73 and 1·9 (3 H each, s, 2X–$OCOCH_3$), 3·66, 3·78, 3·8 (3 H each, s, 3X-OMe), 5·02 (2 H, s, –OCH_2Ph), 5·27 (1 H, dd, J = 9 and 3 Hz, H-b), 5·4 (1 H, d, J = 9 Hz, H-a), 5·9 (1 H, s, H-3'), 6·1 (1 H, d, J_o = 10 Hz, H-5'), 6·2 (1 H, d, J = 3 Hz, H-c), 6·4 (1 H, d, J_m = 2 Hz, H-6'), 6·5 (1 H, d, J_m = 2 Hz, H-8), 7·37 (6 H, bs, H-2 and Ph) (Found: C, 66·31; H, 5·54. $C_{29}H_{30}O_9$ requires: C, 66·65; H, 5·41).

trans - cis - 2' - *Hydroxy* - 4',5,7 - *trimethoxyflavan* - 3,4 - *diol.* **5**. A soln of **4** (0·3 g) in EtOAc (10 ml) and THF (5 ml) and few drops of NEt_3 was stirred with 10% Pd/C (0·2 g) in an atm. of H_2 for 1 hr. The catalyst was filtered off and the solvent removed. The residual solid was crystallised from $CHCl_3$-light petroleum m.p. 148° (59%); ν_{max} 3425, 3290, 3125 cm^{-1} (3X–OH); (Found: C, 62·24; H, 5·95. $C_{18}H_{20}O_7$ requires: C, 62·06; H, 5·79%).

(±) *Trimethylcyanomaclurin* **1**. A mixture of **5** (0·2 g) aq EtOH (1:1 20 ml) and H_3BO_3 (0·5 g) was refluxed for 5 hr, cooled, and extracted with $CHCl_3$. Solvent removal under vacuum furnished a solid which was purified by chromatography on SiO_2. The C_6H_6–EtOAc (49:1) eluate furnished a solid m.p. 82–85° ($CHCl_3$-light petroleum), lit.[8] m.p. 75–85; ν_{max} 3470 cm^{-1} (–OH): NMR ($CDCl_3$), δ 2·1 (1 H, s, –OH, D_2O exchange), 3·7, 3·84 (6 H, 3 H each, s, 3X–OMe), 4·33 (1 H, t, J = 3 Hz, H-b), 5·1 (1 H, dd ill resolved, J = 3 and 2 Hz, H-a), 5·37 (1 H, dd ill resolved, J = 3 and 2 Hz, H-c), 6·0 (2 H, dd, J_m = 2 Hz, H_6 and H_8); 6·4 (1 H, s, H–3'), 6·5 (1 H, d, J_o = 8 Hz, H-5'), 7·2 (1 H, d, J_o = 8 Hz, H_6') (Found: C, 65·73; H, 5·79. $C_{18}H_{18}O_6$ requires: C, 65·44; H, 5·49%).

Acetate. Ac_2O-pyridine, m.p. 168–69° (55%) ν_{max} 1725 cm^{-1} (–$OCOCH_3$); λ_{max} 278 and 284 nm (log ϵ 3·9, 3·96); NMR($CDCl_3$), δ 2·1 (3 H, s, –$OCOCH_3$), 3·7, 3·86 (6 H, 3 H, s, 3X–OMe), 5·27–5·66 (3 H, m, H-a, H-b, H-c), 6·0 (2 H, dd, J = 2 Hz, H_6 and H_8), 6·4 (1 H, s, H–3'), 6·5 (1 H, d, J_o = 8 Hz, H–5'), 7·2 (1 H, d, J_o = 8 Hz, H_6') (Found: C, 64·13; H, 5·67. $C_{20}H_{20}O_7$ requires: C, 64·41; H, 5·41%).

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