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FLAVANOIDS-IV[1]-STEREOCHEMISTRY OF CYANOMACLURIN:

SYNTHESIS OF TRIMETHYL ETHER OF (±) EPICYANOMACLURIN

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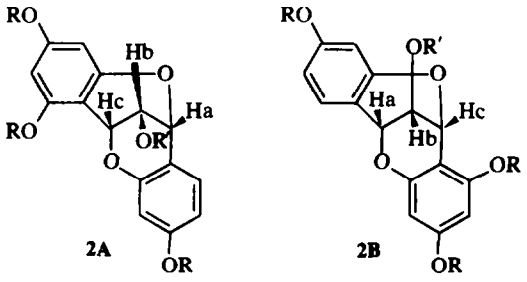
Abstract—Stereochemistry of cyanomaclurin is confirmed by a stereospecific synthesis of (±) epicyanomaclurin trimethyl ether and the solvolysis of its mesylate to the former. The earlier prediction that the dihydropyran protons should have small coupling in both the isomers in this cage structure is also confirmed.

NAIR and Venkataraman had suggested in 1963 that cyanomaclurin has the structure and stereochemistry as shown in **1** and we have recently reported a stereospecific synthesis of its (±) trimethyl ether[1] **3** in which the NMR spectral assignments of H-a and H-c protons are based on the comparison of the H-4 proton signals in flavan-3,4-diols with substitution pattern in ring A as in phloroglucinol and in resorcinol.[2] This is particularly true in cyanomaclurin because depending on how the molecule is looked at both the dihydropyran protons belong to H-4 of a flavan-3,4-diol system, e.g. H-c in 1A or H-a in 1B.

These assignments are reverse to those made by Nair *et al.*[3] who, in a later publication; on the basis of an independent evidence have revised the assignment. By comparing the widths of the H-a and H-c proton signals in the light of the new assignments they have also altered the stereochemistry of H-b and suggested that cyanomaclurin has the stereochemistry **2**.[4] The key argument in both the papers was that $J_{a,c}$ should be larger than $J_{e,e}$. This would be valid in normal flavan-3,4-diols[5] but we have already pointed out that this is not applicable to cyanomaclurin because of its cage conformation. This is also true for the revised stereostructure **2** because, depending on how he drieding model is viewed, the same two protons H-b and H-c which appear axial-equatorial like in **2A** and account for larger J value,[4] appear equatorial-equatorial like when the model is viewed at as in **2B**.

Moreover the revision of stereochemistry based on comparison of the widths of H-a and H-c proton signals raises another pertinent point. Both benzylic protons H-a and H-c have either equatorial-axial like or equatorial-equatorial like relationship with H-b depending on how the model is viewed as in **2A** or **2B**. Therefore both the earlier assignment and the revision of stereochemistry on comparative data is rather unsatisfactory. Even though our stereospecific synthesis is based on sound comparison of physical and spectral properties of the synthetic and natural samples it may be argued that because of

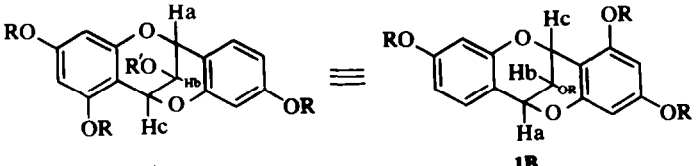


2: R = R' = H
8: R = Me, R' = H
25: R = Me, R' = Ac
26: R = Me, R' = Ms

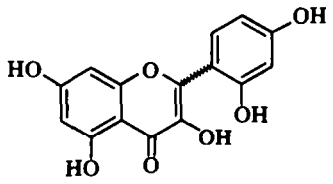
symmetrical conformation the NMR spectra of the isomers **1** and **2** might be indistinguishable and cyanomaclurin might in fact have stereostructure **2**.

Considering the cooccurance of morin **4** and dihydro morin-a trans-3-hydroxyflavanone **5** the possible path of biogenesis of cyanomaclurin might involve the reduction of dihydromorin to a flavan-3,4-diol leucomorindin **6** and subsequent cyclodehydration.[6] Recent isolation of 2',4',5 - trihydroxyflavan - 3,4 - diol - auriculacacidin **7**[7] is pertinent from this point of view and the synthesis of trimethyl ether of cyanomaclurin of Seshadri *et al.*[6] based on these lines is noteworthy. These considerations lead to the stereochemistry of cyanomaclurin as in **3**. However in order to remove the ambiguity regarding the disposition of the OH group at C-3 we have synthesised the stereoisomer **8** and our results clearly show that this is different from the one derived from the natural source, and we regard this as the epicyanomaclurin derivative.

The obvious route to **8** is the solvolysis of 3-sulphonate ester of **3**. TsCl in pyridine did not react with **3** but MsCl afforded the mesylate **9**. Refluxing with NaOAc/AcOH[8] or AgOAc/DMF did not effect the desired epimerisation and



1: R = R' = H
3: R = Me, R' = H
9: R = Me, R' = Ms



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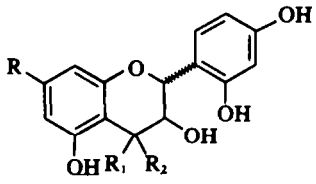
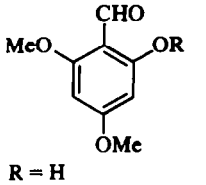


5: $R_1, R_2 = O$, R = OH
6: R_1, R_2 = H, OH, R = OH
7: R_1, R_2 = H, OH, R = H

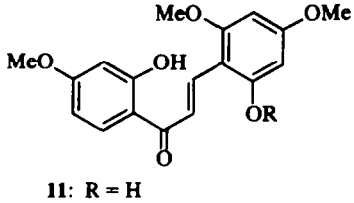
an alternate novel synthetic route was adopted. This involved construction of a *trans-cis* Flavan-3,4-diol with ring A derived from resorcinol and the ring B from phloroglucinol instead of the reverse substitution pattern utilized earlier for the synthesis of **3**.

Condensation of paeonal with 4,6 - dimethoxy - 2 - hydroxy - benzaldehyde **10** using KF/DMSO[9] furnished the 2,2'-dihydroxy chalcone **11** (20%), other condensing agents, NaOH, KOH, $TiCl_4$/THF[10] being unsatisfactory. The corresponding 2'-benzyloxy chalcone **12** was obtained from aldehyde **13** and paeonal (80%), but this could not be debenzylated to **11** by triethyloxoniumfluorborate which was effective in the smooth (70%) conversion of **13** to **10** by hydride abstraction.[11] In order to introduce a more labile protecting group 2-(*p*-methoxy)-benzyloxy aldehyde **15** synthesised for this purpose was converted to chalcone **14**. However, because of the low yield in its preparation the use of this protecting group was not investigated further.

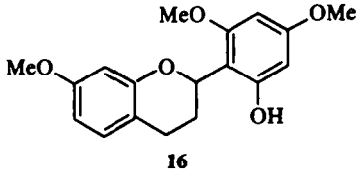
Reductive cyclisation of the 2'-hydroxy chalcone **11** with $NaBH_4$/AcOH furnished, instead of desired flav-3-ene, the corresponding 2'-hydroxyflavan **16** [NMR($CDCl_3$): δ 2·1 (2H, m, H_3), 2·7 (2H, m, H_4), 5·1 (1H, dd, J = 5 and 6 Hz, H_2)]. In contrast the 2-methoxy chalcone **17** prepared from paeonal and aldehyde **18** (80%) under similar conditions gave the flav-3-ene **19** (80%). [NMR(CCl_4): δ 5·5 (1H, dd, $J_{3-2} = 3·5$ and $J_{3-4} = 10$ Hz, H_3), 6·16 (1H, dd, $J_{4-3} = 10$ Hz and $J_{4-2} = 1$ Hz, H_4), 6·48 (1H, dd, $J_{2-3} = 3·5$ Hz, $J_{2-4} = 1$ Hz, H_2)]. Selective demethylation of the 2'-OMe group by $AlBr_3/PhNO_2$[12a] or HCL[12b] did not proceed, but the reductive cyclisation of 2'-hydroxy-2-benzyloxychalcone **12** yielded the 2'-benzyloxy flav-3-ene **20** (70%). Initial experiments at hydrolysis or hydrogenolysis of benzyloxy group in **20** were unsuccessful and it was hoped that the corresponding flavan-3,4-diol would be more amenable. As a model compound the tetramethoxyflav-3-ene **19** when reacted with molar quantity of OsO_4 (pyridine catalysis) and reductive work up (Na_2SO_3) furnished the trans-cis flavan-3, 4-diol **21** (30%) characterised as its diacetate. Use of $Ba(ClO_3)_2$ and OsO_4 (small amount) expedient[1] facilitated the isolation of the diol with enhancement of the yield (80%) and considerable saving of expensive OsO_4. Similarly the flav-3-ene **20** afforded trans-cis 2'-benzyloxy flavan 3–4 diol **22** (90%) NMR ($CDCl_3$) δ 3·8 (1H, masked by Ar–OMe, H_3), 4·7 (1H, bd., J = 4 Hz, H_4)



10: R = H
13: R = —CH_2Ph
15: R = —CH_2Ph–OMe(P)
18: R = Me



11: R = H
12: R = —CH_2Ph
14: R = —CH_2Ph–OMe(*P*)
17: R = Me



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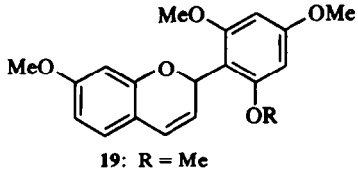
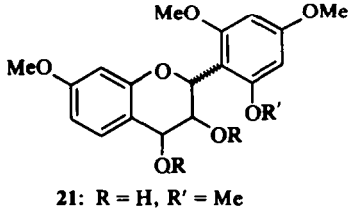


19: R = Me
20: R = —CH_2Ph



21: R = H, R' = Me
22: R = H, R' = —CH_2Ph
23: R = Ac, R'—CH_2Ph
24: R = Ac, R' = H.

5·73 (1H, d, J = 10 Hz, H_2). Hydrogenolysis of its diacetate **23** proceeded smoothly giving the 2'-hydroxy flavan-3,4-diol diacetate **24**.

Having the flavan-3,4-diol of the desired stereochemistry in hand the final cyclisation was achieved by aq. EtOH/H_3BO_3. The resulting compound **25** m.p. 152° has the same R_f value in different solvents as that of the acetate of trimethylether of cyanomaclurin, natural and synthetic, but NMR spectra of the two were quite different. In contrast with the spectrum of the natural product in which H-a, H-b and H-c proton signals lie between 5·2–5·6 δ in the synthetic sample **25** they are well separated at δ 5·66 (1H, t, $J_{c,b} = J_{c,a(w)} = 2·5$ Hz, H-c) 5·23 (1H, t, J = 2·5 Hz, H-b or H-a), 5·07 (1H, dd, J = 2 and 3 Hz, H-a or H-b), indicating the nonidentity of the two.

Eventhough spectral data agrees with the epicyanomaclurin structure **25** for the compound m.p. 152° the possibility of the formation of a 5-membered ring during cyclisation is also likely. Comparison of NMR spectrum of the product m.p. 152° with that of the alcohol m.p. 88° **2** obtained by its hydrolysis clearly showed the presence of two benzylic protons in both the compounds **25** and **2** and of the OH group attached to a non benzylic methine proton which shifted up field in the spectrum of latter. The small upfield shift of H-a and H-c proton signals in the spectrum of **25** observed on acylation of H-b is due to oxygen atom proximity effect in accordance with the observation of Coxon *et al.* in steroid system.[13]

Final confirmation of the stereochemistry of epicyanomaclurin trimethyl ether and also that of cyanomaclurin was obtained when the former was converted to its mesylate **26** and was smoothly solvolysed by KOH/EtOH to cyanomaclurin trimethyl ether which in turn was converted to its acetate m.p. 168–69°.

Thus these results clearly established the stereochemistry of cyanomaclurin as in **1**. Moreover the observed low coupling between the three protons of the pyran ring in both the isomer confirm our earlier prediction[1] that the inequality $J_{a,c} > J_{c,e}$ cannot be relied on in this particular system.

In a slightly strained symmetrical model of cyanomaclurin in sofa conformation with C-3 out of plane H-b makes a dihedral angle of 60° with H-a and H-c in cyanomaclurin and its epimer and should have the same J value for both the protons in both the isomers. The observed difference of cf 1 Hz[4] could be attributed to the slight distortion in the fused dihydropyran system. Comparison of the dihedral angles between H-b and H-c in the models **1** and **2** indicates larger dihedral angle in the former suggesting a smaller J value for H-c proton in cyanomaclurin as compared to its epimer which is not observed.

EXPERIMENTAL

All mps 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 and varian HA-100. Chemical shifts are expressed in PPM down field from TMS.

2,2'-Dihydroxy-4,4',6-trimethoxychalcone **11**. KF (4 g) was added to a soln of **10** (1 g) and paeonal (0·9 g) in dry DMSO (15 ml) and the mixture was refluxed for 2 hr. The dark red soln was decanted and poured in water, extracted with ether, washed with H_2O, dried (Na_2SO_4) and evaporated. The viscuous gum was chromatographed on SiO_2. Elution with C_6H_6–MeOH (95:5) gave a compound (20%), crystallised from EtOH m.p. 169; ν_{max} 3400 cm^{-1} (2X-OH), 1650 (x − χ = 0) (Found: C, 65·1; H, 6·15. $C_{18}H_{18}O_6$ requires: C, 65·44; H, 5·77%).

2-Benzyloxy-4,6-dimethoxybenzaldehyde **13**. A mixture of **10** (1 g), DMF (15 ml) anhyd K_2CO_3 (3 g) and benzyl bromide (1·5 g) was refluxed on sand bath for 45 min. Pouring on ice H_2O, and triturating with glass rod afforded a solid, crystallised from EtOH, m.p. 99° (90%) (Found: C, 70·69; H, 5·81. $C_{16}H_{16}O_4$ requires: C, 70·57; H, 5·92%).

2-Benzyloxy-2'-hydroxy 4,4',6-trimethoxychalcone **12**. A mixture of paeonal (1·66 g) and **13** (2·82 g) in EtOH (30 ml) was treated with KOH (10 ml, 10 N), the mixture was allowed to stand at room temp. for 16 hr. It was neutralised in cold with dil HCl, which gave a yellow solid, filtered and washed with H_2O, MeOH, crystallisation from EtOH gave yellow needles, m.p. 170–72° (80%) (Found: C, 71·47; H, 6·09. $C_{25}H_{24}O_6$ requires: C, 71·41; H, 5·75%).

4,6-Dimethoxy-2-hydroxbenzaldehyde **10**. 2-benzyloxy aldehyde **13** (0·5 g) and triethyl-oxoniumfluobroate (1 g) in dichloromethane (25 ml) was refluxed for 3 hr. Poured into water, extracted with CH_2Cl_2, the CH_2Cl_2 layer after washing with water was extracted with 2N NaOH. NaOH layer on acidification with dil HCl in cold gave the debenzylated **10**, crystallised from MeOH, m.p. 71° (70%) (lit.[14] 11°).

2-(p-Methoxy)benzyloxy - 4,6 - dimethoxybenzaldehyde **15**. A mixture of **10** (1 g) DMF (15 ml), anhyd K_2CO_3 (3 g) and *p*-methoxybenzyl bromide (1·5 g) was refluxed on sand bath for 1 hr. Poured on ice H_2O, and extracted with $CHCl_3$. The $CHCl_3$ layer on washing with H_2O was dried and evaporated. The residue obtained was chromatographed on SiO_2. C_6H_6 eluates on evaporation afforded a solid, crystallised from EtOH, m.p. 75 (40%) (Found: C, 67·09; H, 6·18. $C_{17}H_{18}O$ requires: C, 67·44; H, 6·0%).

2-(p-Methoxy)benzyloxy - 2' - hydroxy - 4,4',6 - trimethoxy chalcone **14**. A mixture of **15** (1·5 g) and pacenal (0·83 g) was condensed as for **12**. The solid obtained was purified by chromatography on SiO_2. $CHCl_3$ eluates on evaporation afforded **14**, crystallised in to yellow prisms from EtOH, m.p. 181–82° (30%) (Found: C, 69·43; H, 5·81. $C_{26}H_{26}O_7$ requires: C, 69·32; H, 5·82%).

2'-Hydroxy-2,4,4',6-tetramethoxychalcone **17**. Paeonal (1·66 g) aldehyde **18** (1·96 g) reacted with KOH (10%, 10 ml), EtOH (10 ml) as in **12**. The product was crystallised from EtOH to give yellow needles, m.p. 164° (80%), ν_{max} 1640 cm^{-1} (x − χ = 0) (Found: C, 65·92; H, 5·16. $C_{19}H_{20}O_6$ requires: C, 66·27; H, 5·16%).

2',4',6',7-Tetramethoxyflav-3-ene **19**. Compound **17** (1 g) in -2 methoxy-ethanol (20 ml) was stirred with $NaBH_4$ (0·1 g) at 90° for 0·5 hr. After 12 hr at room temp the faint yellow soln of the complex was boiled with $CHCl_3$ (20 ml) for 10 min and then reflux with a soln of ACOH in $CHCl_3$ (10%, 20 ml) for 2 hr. Excess $NaHCO_3$ was added, the mixture was poured in H_2O, 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 benzene eluates afforded a solid on trituration with light petroleum, crystallised from Et_2O, m.p. 96–97° (80%). NMR (CCl_4), δ 3·6, 3·66, 3·7 (6H, 3H, 3H each, S, 4x-OMe), 5·3 (1H, dd, $J_{3-2} = 3·5$ Hz, $J_{3-4} = 10$ Hz, H_3), 6·0 (2H, bs, H_5', H_5'), 6·11 (1H, bs., $Jw_{1/2} = 1·5$ Hz, H_8), 6·16 (1H, dd, $J_{4-3} = 10$ Hz, $J_{4-2} = 1$ Hz, H_4) 6·18 (1H, d, $J_o = 8$ Hz, H_6), 6·48 (1H, dd, $J_{2-3} = 3·5$ Hz, $J_{2-4} = 1$ Hz, H_2), 6·7 (1H, d, $J_o = 8$ Hz, H_5) (Found: C, 69·47; H, 6·46. $C_{19}H_{20}O_5$ requires: C, 69·5; H, 6·14%).

2'-Hydroxy-4',6',7'-trimethoxyflavan **16**. The chalcone **11** (1 g), in 2-methoxy ethanol (20 ml) was treated with NaB_4 (0·1 g), $CHCl_3$, ACOH/$CHCl_3$ as above. The product was purified by chromatography on SiO_2, eluated first with benzene then with C_6H_6–MeOH (98:2) mixture, which gave on evaporation a solid crystallised from $CHCl_3$-light petroleum, m.p. 120–21° (40%); ν_{max} 3450 cm^{-1} (1X-OH); NMR($CDCl_3$) δ 2·1 (2H, m, H_3), 2·7 (2H, m, H_4), 3·73 (9H, s, 3X-OMe), 5·1 (1H, dd, J = 5 and 6 Hz, H_2), 6·07 (2H, s, H_5', H_5'), 6·5 (2H, two d, $J_m = 2$ Hz, H_6, H_8), 6·9 (1H, bs-OH, D_2O exchange), 7 (1H, d, $J_o = 10$ Hz, H_5) (Found: C, 68·28; H, 6·60. $C_{18}H_{20}O_5$ requires: C, 68·24; H, 6·37%).

2'-Benzloxy-4',6',7-trimethoxyflav-3-ene **20**. The chalcone **12** (1 g) in 2-methoxy-ethanol (20 ml) was reductively cyclised to **20** as above. The product was purified by chromatography on SiO_2. C_6H_6 eluates on evaporation and triturating with light petroleum afforded a solid, crystallised from ACOEt-light petroleum, m.p. 92° (70%); NMR (CCl_4), δ 3·63 (9H, S, 3X-OMe), 4·86 (2H, S,

X-OCH_2), 5·33 (1H, dd, J_{3-4} = 10 Hz, J_{3-2} = 3 Hz, H_3, 6 (2H, S, H'_3, H'_5), 6·07 (1H, bs. $J_{w1/2}$ = 1·5 Hz, H_8), 6·10 (1H, dd, J_o = 8 Hz, $J_{w1/2}$ = 1·5 Hz, H_6), 6·16 (1H, dd, J_{4-3} = 10 Hz, J_{ally} = 3 Hz, H_4), 6·43 (1H, dd, J_{2-4} = 3 Hz, J_{2-3} = 3 Hz, H_2), 6·63 (1H, d, J_o = 8 Hz, H_5), 7·2 (5H, S, -Ph) (Found: C, 74·04; H, 6·27. $C_{25}H_{24}O_6$ requires: C, 74·24; H, 5·98%).

trans-cis-2',4',6',7-Tetramethoxyflavan-3,4-diol **21**. A suspension of **19** (1 g) in aq. THF (1:1·40 ml) was stirred with OsO_4 (0·05 g) and Ba $(ClO_3)_2$ (1 g) for 24 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 and crystallisation from $CHCl_3$-light petroleum gave white prisms m.p. 154–55° (70%), ν_{max} 3550, 3450 cm^{-1} (2X-OH) (Found: C, 62·55; H, 6·16. $C_{19}H_{20}O_7$ requires: C, 62·97; H, 6·12%).

Acetate. Ac_2O/pyridine, m.p. 136° (60%); ν_{max} 1725 cm^{-1} (X-$OCOCH_3$), NMR 100 MHz (CCl_4), δ 1·75, 2·02 (3H each, S, 2X-$OCOH_3$), 3·66, 3·74 (3H, 6H each, S, 3X-OMe), 5·66 (1H, dd, J = 12 and 2 Hz, H_3), 5·94–6·1 (4H, m, H'_3, H'_5, H_8, H_2) 6·2 (1H, d, J = 2 Hz, H_4), 6·32 (1H, dd, J = 8 and 2 Hz, H_6), 7·04 (1H, d, J_o = 8 Hz, H_5) (Found: C, 61·87; H, 5·87. $C_{23}H_{26}O_9$ requires: C, 61·95; H, 6·0%).

trans-cis 2' - Benzyloxy - 4',6',7 - trimethoxyflavan - 3,4 - diol **22**. The compd **20** (1 g) in aq. THF (1:1 50 ml) with OsO_4 (0·05 g) and Ba (ClO_3) (0·6 g) and stirring (30 hr) was converted as above into diol **22** crystallised from MeOH, m.p. 82° (70%), ν_{max} 3490, 3400 cm^{-1} (2X-OH), NMR ($CDCl_3$), δ 2·27 (2H, bs. 2X-OH, D_2O exchange), 3·8–3·93 (10 H, m, 3X-OMe, H_3), 4·7 (1h, d, J = 2 Hz, H_4), 5·06 (2H, S, -OCH_2), 5·77 (1H, d, J = 10 Hz, H_2), 6·16 (2H, S, H'_3, H'_5), 6·4 (1H, bs, H_8) 6·5 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, H_6), 7·23 (1H, d, J_o = 8 Hz, H_5), 7·27 (5H, S, -Ph) (Found : C, 68·61; H, 6·23. $C_{25}H_{26}O_7$ requires: C, 68·48; H, 5·98%).

Acetate **23**. Ac_2O/Pyridine, m.p. 58–59° (65%); ν_{max} 1720 cm^{-1} (X-$OCOCH_3$), NMR 100 MHz (CCl_4), δ 1·78, 1·96 (3H each, S, 2X-$OCOCH_3$), 3·64, 3·66, 3·7 (3H each, S, 3X-OMe), 4·98 (2H, S, -OCH_2), 5·82 (1H, dd, J = 12 and 3 Hz, H_3), 5·9–6·06 (4H, m, H'_3, H'_5, H_8, H_2), 6·2 (1H, d, J = 3 Hz, H_4), 6·32 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, H_6), 7 (1H, d, J_o = 8 Hz, H_5), 7·1–7·34 (5H, bs, -Ph) (Found: C, 66·74; H, 5·98. $C_{29}H_{30}O_9$ requires C, 66·65; H, 5·79%).

trans - cis - 2' - Hydroxy - 4',6',7 - trimethoxyflavan - 3,4 - diol diacetate **24**. A soln of **23** (0·4 g) in EtOAc (20 ml) and few drops of NEt_3 was stirred with 10% Pd/C (0·25 g) in an atmosphere of H_2 for 1/2 hr. The catalyst was filtered off and the solvent removed. The residual gum was crystallised from EtOAc-light petroleum, m.p. 79–80° (55%), ν_{max} 3420 cm^{-1} (X-OH), 1710 (2X-$OCOCH_3$), NMR ($CDCl_3$), δ 1·83, 2·13 (3H each, S, 2X-$OCOCH_3$), 3·7 (9H, S, 3X-OMe), 5·84 (1H, dd, J = 8 and 2 Hz, H_3) 6·06 (3H, bs, H'_3, H'_5, H_8) 6·15 (1H, d, J = 8 Hz, H_2), 6·5 (1H, bs, H_4), 6·6 (1H, dd, J = 8 and 2 Hz, H_6), 7·2 (1H, d, J_o = 8 Hz, H_5) (Found: C, 61·15; H, 6·03. $C_{22}H_{24}O_9$ requires: C, 61·1; H, 5·59%).

(±) *Trimethylepicyanomaclurin acetate* **25**. A mixture of **24** (0·2 g) aq. EtOH (1:1, 20 ml) and H_3BO_3 (0·5 g) was refluxed for 15 hr, cooled and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with NaOH, H_2O, dried and evaporated. Removal of the solvent furnished a solid, purified by chromatography on SiO_2. C_6/C_6/EtOAc (49:1) eluate afforded a solid, m.p. 152° (50%). ν_{max} 1725 cm^{-1} (X-$OCOCH_3$); λ_{max} 276, 284 nm (log ϵ 3·58, 3·53); NMR ($CDCl_3$) δ 2·1 (3H, S, X-$OCOCH_3$), 3·7, 3·84 (6H, 3H each, S, 3X-OMe), 5·07 (1H, dd, J = 2 and 3 Hz, Ha or H-b), 5·23 (1H, t, J = 2·5 Hz, H-b or H-a), 5·66 (1H, t, $J_{b,c}$ = $J_{c,a}$ = 2·5 Hz, H-c), 5·97 (2H, dd, J = 2 Hz, H'_3, H'_5), 6·46 (1H, S, H_8), 6·56 (1H, d, J = 8, H_6), 7·2 (1H, d, J = 8 Hz, H_5) (Found: C, 64·76; H, 5·56. $C_{20}H_{20}O_7$ requires: C, 64·41; H, 5·41%).

(±) *Trimethylepicyanomaclurin* **8**. A mixture of **25** (120 mg) and 1N methanolic KOH (10 ml) was stirred at room temp for 12 hr under N_2. It was concentrated on a stream bath and diluted with water, and extracted with $CHCl_3$. The residue obtained after removal of solvent was purified by chromatography on SiO_2. The C_6H_6/EtOAc (49:1) eluate furnished a solid, m.p. 87–88° (50%) ν_{max}-3450 cm^{-1} (X-OH); NMR ($CDCl_3$), δ 2·1 (1H, S, -OH, D_2O exchange), 3·73, 3·9 (6H, 3H each, S, 3X-OMe), 4·2 (1H, t, J = 3 Hz, H-b), 4·93 (1H, dd unresolved, J = 3 and 2 Hz, H-c), 5·46 (1H, dd, unresolved, J = 3 and 2 Hz, H-a), 6 (2H, dd, J_m = 2 Hz, H'_3, H'_5), 6·46 (1H, S, H_8), 6·56 (1H, d, J_o = 8 Hz, H_6), 7·23 (1H, d, J_o = 8 Hz, H_5) (Found: C, 65·54; H, 5·21. $C_{18}H_{18}O_6$ requires: C, 65·44; H, 5·49%).

Trimethylcyanomaclurin mesylate **9**. Cyanomaclurin trimethyl ether (0·1 g) in dry pyridine (1 ml) was cooled at 0°. To a cooled soln was added mesylchloride (0·12 g) in pyridine (0·5 ml). It was kept at 0° for 1 hr then at room temp for 12 hr. After pouring into ice cold HCl, a solid separated and was filtered off and crystallised from MeOH to give white plates, m.p. 181–182° (60%); (Found: C, 55·59; H, 4·7. $C_{19}H_{20}O_8S$ requires: C, 55·8; H, 4·93%).

Trimethyl epicyanomaclurin mesylate **26**. The compound **2** (0·1 g) in dry pyridine was treated with mesylchloride as above. The product was crystallised from MeOH to give white shining plates, m.p. 172° (60%). (Found: C, 55·80; H, 5·03. $C_{19}H_{20}O_8S$ requires: C, 55·8; H, 4·93%).

Cyanomaclurin trimethylether (epimerisation) **3**. Mesylate **26** (50 mg) was refluxed with methanolic KOH for 12 hr. It was concentrated on a water bath, diluted with water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried and evaporated. The solid obtained was crystallised from $CHCl_3$-light petroleum m.p. 81–85° (lit.[1] 82–85°) (40%). IR superimposible with that of synthetic cyanomaclurin trimethyl ether. (Found: C, 65·71; H, 5·60. $C_{18}H_{18}O_6$ requires: C, 65·44; H, 5·49%).

Acetate. Ac_2/pyridine, m.p. 168–69° (lit.[1] 168–69).

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