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STEREOCHEMISTRY OF FLAVAN-3,4-DIOLS

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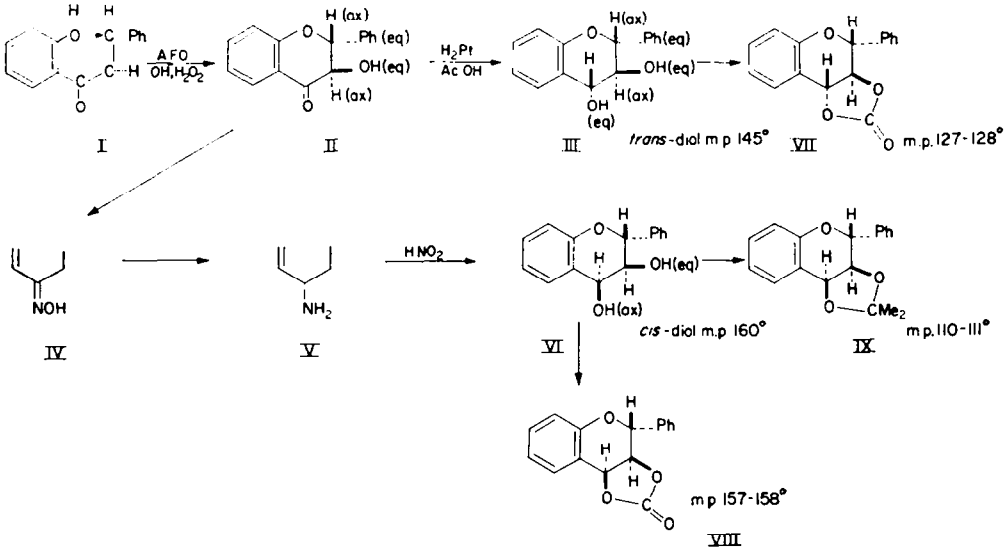
Abstract—Details are given of the preparation and properties of the compounds involved in the nuclear magnetic resonance work previously described.[1] The application of the oxime–amine method[2] to the production of flavan-3,4-diols with an axial 4-OH group is described.

IN 1961 Corey *et al.*[1] showed by application of N.M.R. that the flavan-3,4-diol (m.p. 145°, III) obtained by the catalytic reduction of dihydroflavonol (II)[2] is a *trans*-diol while the isomer (VI) (m.p. 160°) prepared through the oxime (IV) and amine (V)[3]



has the *cis*-configuration. This work also supports the assignment on chemical grounds of the conformation shown in II to dihydroflavonol prepared by the alkaline peroxide oxidation of the chalcone I (AFO reaction).[3–5] Further, Dr. M. A. Vickars

[1] E. J. Corey, E. M. Philbin and T. S. Wheeler, *Tetrahedron Letters* No. 13, 429 (1961).
[2] R. Bognár and M. Rákosi, *Chem. & Ind.* 188 (1956); *Acta Chim. Acad. Sci. Hung.* **14,** 369 (1958),
[3] R. Bognár, M. Rákosi, H. Fletcher, E. M. Philbin and T. S. Wheeler, *Tetrahedron Letters* No. 19, 4 (1959).
[4a] V. B. Mahesh and T. R. Seshadri, *Proc. Indian Acad. Sci.* **41,** 210 (1955); [b] A. B. Kulkarni and C. G. Joshi, *J. Indian Chem. Soc.* **34,** 217 (1957).
[5] T. S. Wheeler, *Records Chem. Progress* **18,** 133 (1957).

(personal communication) found that oxidation by chromium trioxide in pyridine of compounds III and VI gives dihydroflavonol (II) in yields of 50% and 14% respectively.

The stereochemical results described in our preliminary communication[1] ("received" June 17, 1961) agree with those of Bokadia *et al.*[6] ("received" May 25, 1961). We now describe the preparation and properties of the compounds which formed the basis of the N.M.R. work[1] and a similar study of the corresponding 4'-methoxy-6-methylflavan-3,4-diols. Details are given of the application of the oxime-amine method (IV; V; VI)[3] to the production of flavan-3,4-diols with an axial 4-hydroxyl group. As mentioned previously[1,3] and observed by Bokadia *et al.*[6] the production of a cyclic carbonate by a 3,4-diol is not diagnostic for a *cis*-configuration.[7] Formation of an isopropylidene derivative is a more reliable test.[6]

Bognár *et al.*[8] following Hückel *et al.*[9] assumed that hydrogenation of a cyclic ketone in acetic acid with a platinum catalyst affords the axial alcohol and tentatively assigned configurations to some flavan-4-ols on this basis. Application of N.M.R. to this problem[10] has shown that catalytic reduction of flavanones in acid solution yields as with dihydroflavonols[1,6] the equatorial 4-alcohol. The oxime–amine method (IV, V, VI) affords correspondingly axial 4-alcohols. The tentative assignments made by Bognár *et al*[8] have therefore to be reversed.

If one assumes that catalytic reduction of the oxime (IV) to the amine (V) follows the same course as reduction of the corresponding ketone under similar conditions,[11] then compound V is an equatorial amine and formation of VI occurs with inversion. It is not possible, however, to generalize in regard to the course of deamination reactions.[12]

EXPERIMENTAL

Flavan-3,4-diols

2,3-Trans-*Flavan*-3,4-trans-*diol* (III). Dihydroflavonol (0·5 g, II) which had been prepared by the AFO reaction[6] was hydrogenated (PtO_2, AcOH, 1 mol H) in the warm, and catalyst and solvent removed (red. press.). The solid residue separated from ethanol in needles (0·2 g), m.p. 145.[2] The compound gave a deep violet colour with sulphuric acid (Found: C, 74·6; H, 5·8. Calc. for $C_{15}H_{14}O_3$: C, 74·4; H, 5·8%).

The *dibenzoate* (pyridine-benzoyl chloride) crystallized from ethanol in needles, m.p. 156–157° (Found: C, 77·5; H, 4·8. $C_{29}H_{22}O_5$ requires: C, 77·3; H, 4·9%).

Cyclic carbonate (VII).[1] A solution of the *trans*-diol (0·3 g) in dioxan (1 ml) and benzene (9 ml) was treated dropwise with phosgene in toluene (12·5%; 1·5 ml) and, after 1 hr, triethylamine (2 ml) and additional phosgene solution (4 ml) were added. The mixture was kept for 2 hr and was extracted with ether, after addition of water.[13] The cyclic carbonate (Found: C, 72·0; H, 4·7. Calc. for $C_{16}H_{12}O_4$: C, 71·6; H, 4·5%) thus obtained, separated from ligroin in needles (0·2 g), m.p. 127–128° (lit. 129–130·5° [6]).

[6] M. M. Bokadia, B. R. Brown, P. L. Kolker, C. W. Love, J. Newbould, G. A. Somerfield and P. M. Wood, *J. Chem. Soc.* 4663 (1961).

[7] H. Kwart and G. C. Gatos, *J. Amer. Chem. Soc.* **80,** 881 (1958); S. J. Angyal and C. G. Macdonald, *J. Chem. Soc.* 686 (1952).

[8] R. Bognár, M. Rákosi, H. Fletcher, D. Kehoe, E. M. Philbin and T. S. Wheeler, *Tetrahedron* **18,** 135 (1962).

[9] W. Hückel, M. Maier, E. Jordan and W. Seeger, *Liebig's Ann.* **616,** 46 (1958).

[10] C. P. Lillya, D. Kehoe, Eva M. Philbin, M. A. Vickars and T. S. Wheeler, *Chem. & Ind.* (in press).

[11] D. H. R. Barton, *J. Chem. Soc.* 1027 (1953).

[12] D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10,** 44 (1956); C. W. Shoppee, S. K. Roy and B. S. Goodrich, *J. Chem. Soc.* 1583 (1961) and references there cited.

[13] F. E. King and J. W. Clark-Lewis, *J. Chem. Soc.* 3384 (1955).

The diol was recovered unchanged in attempts to prepare an isopropylidene derivative by the method described below in relation to the *cis*-diol.[13] Bokadia *et al.*[6] obtained the isopropylidene derivative (IX) of the *cis*-diol from the *trans*-isomer by application of copper sulphate and acetone.

2,3-Trans-*Flavan*-3,4-cis-*diol* (VI).[3] 3-Hydroxy-4-oximinoflavan (IV) (Found: C, 70·6; H, 5·2; N, 5·6; $C_{15}H_{13}NO_3$ requires: C, 70·6; H, 5·1; N, 5·5%) which was prepared from dihydroflavonol (AFO product) and hydroxylamine hydrochloride in aqueous pyridine, separated from benzene in needles, m.p. 153–154°.

4-*Amino*-3-*hydroxyflavan* (V). (a). The oxime was hydrogenated (PtO_2, AcOH; 2 mol H) at atm. press. in warm aqueous (80%) acetic acid. An ethereal solution of the residue from removal of the catalyst and solvent (red. press.) was washed with aqueous sodium hydrogen carbonate and with water. Evaporation of the solvent yielded 4-*amino*-3-*hydroxyflavan* (Found: C, 74·2; H, 6·5; N, 6·5. $C_{15}H_{15}NO_2$ requires: C, 74·7; H, 6·3; N, 5·8%), m.p. 172–173° (needles from ethanol).

(b). A mixture of 3-hydroxy-4-oximinoflavan (1 g) in tetrahydrofuran (30 ml) and of lithium aluminium hydride (1 g) in ether (250 ml) was refluxed for 2 hr. Next day the product was poured on hydrochloric acid and crushed ice. The acid solution with further acid washings of the ethereal layer was treated with base and the liberated amine recovered by ether and crystallized from ethanol (mixed m.p. confirmation).

2,3-Trans-*Flavan*-cis-3,4-*diol* (VI).[3] The aminohydroxyflavan (0·5 g) when treated with sodium nitrite and acid as previously described for the preparation of flavan-4α-ol,[8] yielded the diol (0·2 g), m.p. 160° (from methanol) (Found: C, 73·9; H, 5·8. Calc. for $C_{15}H_{14}O_3$: C, 74·4; H, 5·8%). Bokadia *et al.*[6] found it more convenient to reduce the ketone (II) by lithium aluminium hydride and aluminium chloride. The *dibenzoate* (pyridine–benzoyl chloride) separated from methanol in needles, m.p. 121–122° (Found: C, 77·5; H, 4·9. $C_{29}H_{22}O_5$ requires: C, 77·3; H, 4·9%).

Isopropylidene derivative (IX).[3] A mixture of the *cis*-diol (0·1 g), acetone (6 ml) and conc. hydrochloric acid (1 drop) was kept for 7 days at room temp. and treated with triethylamine (2 drops) and water.[13] The precipitate (Found: C, 76·8; H, 6·4. Calc. for $C_{18}H_{18}O_3$: C, 76·6; H, 6·4%) formed needles from methanol (0·06 g), m.p. 110–111° (lit. 112·5–113·5°).[6]

Cyclic carbonate (VIII).[3] This compound (Found: C, 71·7; H, 4·2. Calc. for $C_{16}H_{12}O_4$: C, 71·6; H, 4·5%) was prepared as was the carbonate of the *trans*-diol. It separated from ethanol in needles, m.p. 157–158° (lit. 134·5–135° [6] since corrected to m.p. 159°—personal communication).

4-*Hydroxy*-3-*methoxyflavan*. Flavonol was methylated (dimethyl sulphate, potassium carbonate, acetone) to yield 3-methoxyflavone, m.p. 114° (needles from ethanol). Oyamada[14] who used diazomethane reports m.p. 114°. Hydrogenation (PtO_2, AcOH; 2 mol H) afforded the *hydroxymethoxyflavan* (Found: C, 74·8; H, 6·3; OMe, 12·8. $C_{16}H_{16}O_3$ requires: C, 75·0; H, 6·3; OMe, 12·1%), m.p. 151–152° (needles from light petroleum, b.p. 60–80°). It was not possible to assign a configuration to the methyl ether.

4′-*Methoxy*-6-*methylflavan*-3,4-*diols*. The *trans*-diol (prepared by catalytic reduction of the dihydroflavonol), m.p. 169°,[6,15] did not form an isopropylidene derivative when kept for 9 days at room temp. in acetone solution containing a trace of hydrochloric acid.[13] Bokadia *et al.*[6] found that more vigorous conditions promoted formation of the isopropylidene derivative of the *cis*-diol.

4′-*Methoxy*-6-*methyl*-2,3-trans-*flavan*-3,4-cis-*diol* (*through the* 4-*oximino*-3-*hydroxyflavan*)[3]

3-*Hydroxy*-4′-*methoxy*-6-*methyl*-4-*oximinoflavan*. The parent dihydroflavonol[4,16] was refluxed for 3½ hr in aqueous pyridine with hydroxylamine hydrochloride. The *oxime* separated from benzene in needles, m.p. 185–187° (Found: C, 68·5; H, 5·9; N, 4·8. $C_{17}H_{17}NO_4$ requires: C, 68·2; H, 5·7; N, 4·7%).

4-*Amino*-3-*hydroxy*-4′-*methoxy*-6-*methylflavan*. The oximinoflavan was hydrogenated at atm. press. (PtO_2, AcOH, 2 mol H) and catalyst and solvent removed (red. press.). The *aminoflavan acetate* crystallized from methanol in needles, m.p. 187–188° (Found: C, 66·0; H, 6·7; N, 4·4. $C_{17}H_{19}NO_3.CH_3COOH$ requires: C, 66·1; H, 6·7; N, 4·1%).

4′-*Methoxy*-6-*methylflavan*-cis-3,4-*diol*. The aminoflavan acetate on treatment with nitrous acid[8] formed the *cis*-3,4-diol, m.p. 193° (needles from methanol). The diacetate had m.p. 95° (needles from methanol). These m.p.'s agree with those given in the literature[3,6,15a] for these compounds. The isopropylidene derivative[3] (acetone–hydrochloric acid)[13] (Found: C, 73·9; H, 6·7; OMe, 9·8. Calc.

[14] T. Oyamada, *J. Chem. Soc. Japan* **55**, 1256 (1934); *Chem. Abstr.* **29**, 4358 (1935).

[15] C. G. Joshi and A. B. Kulkarni; [a] *Chem. & Ind.* 1421 (1954); [b] *J. Indian Chem. Soc.* **34**, 753 (1957).

[16] K. G. Marathe, Ph.D. Thesis, Poona, 67 (1953).

for $C_{20}H_{22}O_4$: C, 73·6; H, 6·8; OMe, 9·7%) crystallized from aqueous ethanol in needles, m.p. 126–127° (lit. 129–130°).[6]

3-*Hydroxy*-5,7,3′,4′-*tetramethoxy*-4-*oximinoflavan* which was prepared from the corresponding dihydroflavonol[17] crystallized from acetone in needles, m.p. 194°. (Found: C, 61·0; H, 5·5; N, 3·9. $C_{19}H_{21}NO_7$ requires: C, 60·8; H, 5·6; N, 3·7%).

4-*Amino*-3-*hydroxy*-5,7,3′,4′-*tetramethoxyflavan*.[18] Catalytic hydrogenation (H_2, PtO_2, AcOH) or reduction of the oxime by lithium aluminium hydride afforded this *amine* (Found: C, 62·9; H, 6·7; N, 3·3; OMe, 34·5. $C_{19}H_{23}NO_6$ requires: C, 63·1; H, 6·4; N, 3·9; OMe, 34·2%), m.p. 182–185° (needles from ethanol). No useful result was obtained in attempts at deamination using nitrous acid.

[17] H. L. Hergert, P. Coad and A. V. Logan, *J. Org. Chem.* **21**, 304 (1956).
[18] D. Kehoe. Personal communication.