

A NEW METHOD FOR THE PREPARATION OF 4-HYDROXYFLAVANS

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FLAVANS containing a 4-hydroxyl group are of increasing importance because of a growing interest in flavan-3,4-diols (leucoanthocyanidins, I). Reduction of 4-oxoflavans (II), catalytically or otherwise, has been closely studied and much attention has been directed to the configuration and conformation of the 4-hydroxyl group produced.<sup>1</sup> An alternative approach now described, which contains features of stereochemical interest, involves reduction of a 4-oximinoflavan (III) to the amine (IV) which is then converted into a 4-hydroxyflavan (I).

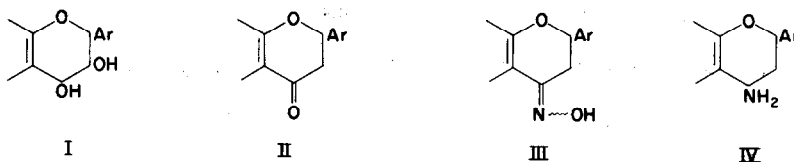
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<sup>1</sup> See, for example, <sup>a</sup> R. Bognar and M. Rakosi, Chem. & Ind. 188 (1956); <sup>b</sup> Acta Chim. Acad. Sci. Hung. 13, 217 (1957); <sup>c</sup> Ibid. 14, 369 (1958); <sup>d</sup> K. Freudenberg and K. Weinges, Ann. 613, 61 (1958); <sup>e</sup> M. D. Kashikar and A. B. Kulkarni, Chem. & Ind. 1084 (1958). Further references are given in these citations.

Previous workers regarded dihydroquercetin as inert to the usual ketonic reagents and attributed this inactivity to the effect of the adjacent hydroxyl group in the 3-position.<sup>2</sup> It has now been found, however, that hindrance by this group is not marked, for with aqueous pyridine as base, dihydroflavonol<sup>3</sup> gives an oxime, m.p. 153-154°, phenylhydrazone, m.p. 173-174°, and semicarbazone, m.p. 270° (decomp.), and 3-hydroxy-4'-methoxy-6-methylflavanone forms the oxime, m.p. 185-187°. Similar derivatives are obtained when the dihydroflavonol is substituted in the 5-position; for example dihydroquercetin phenylhydrazone, m.p. 218° (decomp.), and 3-hydroxy-5,7,3',4'-tetramethoxy-4'-oximinoflavan, m.p. 194°.

The production of oximes suggested a route to the corresponding diols.



<sup>2</sup> H. L. Hergert, P. Coad and A. V. Logan, J. Org. Chem., 21, 304 (1956).

<sup>3</sup> This was prepared from the 2'-hydroxychalcone by oxidation by alkaline hydrogen peroxide (see L. Reichel and J. Steudel, Ann., 553, 83 (1942)). Treatment with sulphuric acid gave flavonol, an indication that the 3-hydroxyl group is equatorial (V. B. Mahesh and T. R. Seshadri, Proc. Indian Acad. Sci., 41, 210 (1955)).

Hydrogenation of the oximes using  $\text{PtO}_2$ ,  $\text{Pd/C}$  or  $\text{LiAlH}_4$  gave the amines which were treated with nitrous acid. The successful experiments to date are outlined below. Some work on 4-oximinoflavan is included.

Flavan-3,4-diol. Reduction of 4-oximinodihydroflavonol catalytically ( $\text{PtO}_2$ ) or with lithium aluminium hydride gave 4-amino-3-hydroxyflavan, m.p.  $172-173^\circ$ , which with nitrous acid yielded a new flavan-3,4-diol, m.p.  $160^\circ$  (dibenzoate, m.p.  $118^\circ$ ). This diol formed an isopropylidene derivative, m.p.  $110-111^\circ$ , and, with phosgene, a carbonate, m.p.  $159^\circ$ .

4'-Methoxy-6-methylflavan-3,4-diol. 3-Hydroxy-4'-methoxy-6-methyl-4-oximinoflavan, gave 4-amino-3-hydroxy-4'-methoxy-6-methylflavan isolated as the acetate with m.p.  $187-188^\circ$ . The amine was converted into 3,4-dihydroxy-4'-methoxy-6-methylflavan, m.p.  $193^\circ$ , identical (mixed m.p. comparison) with the 2-p-C<sub>6</sub>H<sub>4</sub>OMe (e), 3-OH(e), 4-OH (e) diol obtained together with the 4-OH(a) isomer by Joshi and Kulkarni<sup>4</sup> from the corresponding dihydroflavonol and lithium aluminium hydride. The diol with m.p.  $193^\circ$  yielded an isopropylidene derivative, m.p.  $126-127^\circ$ . We are indebted to Dr. Kulkarni for a sample of his compound.

This identity with Joshi and Kulkarni's product suggests that flavan-3,4-diol (m.p.  $160^\circ$ ) obtained from the amine as described above also has the larger groups - 2e,3e,4e. On the other hand Bognar and Rakosi,<sup>1 a,c</sup> isolated a diol, m.p.  $145^\circ$ , from dihydroflavonol using catalytic hydrogenation,  $\text{LiAlH}_4$ , or  $\text{NaBH}_4$ , and assigned to it the same conformation - 2e,3e,4e.

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<sup>4</sup> C. G. Joshi and A. B. Kulkarni, J. Indian Chem. Soc. **34**, 753 (1957).

These results require further study since a trans-flavan-3e,4e,-diol would not be expected to yield a cyclic compound.<sup>5</sup> The formation of such derivatives merits consideration in the light of Philbin and Wheeler's<sup>6</sup> suggestion that five atoms of the dihydropyran ring in flavans are coplanar. Also recent investigations reduce confidence in the application of stereochemical rules.<sup>1 a,7</sup>

$\alpha$ -4-Hydroxyflavan, 4-Oximinoflavan, m.p. 170-171<sup>o</sup>, on controlled catalytic reduction (Pd/C or PtO<sub>2</sub>) formed 4-aminoflavan m.p. 112<sup>o</sup>, (acetate, m.p. 157-159<sup>o</sup>; hydrochloride, m.p. 268-273<sup>o</sup>); this with nitrous acid gave in good yield only  $\alpha$ -4-hydroxyflavan, m.p. 118-119<sup>o</sup> (acetate, m.p. 85-87<sup>o</sup>).<sup>8</sup> The conversion with nitrous acid appears to be stereospecific.

Hydrogenation (Pd/C) of flavanone oxime until 3 moles of hydrogen had been absorbed yielded 1-amino-1- $o$ -hydroxyphenyl-3-phenylpropane, m.p. 203-206<sup>o</sup>, identical (mixed m.p.) with an authentic specimen prepared by reduction of  $o$ -hydroxy- $\beta$ -phenylpropiophenone oxime, m.p. 117-118<sup>o</sup>.<sup>1 b,9</sup> Many examples of such reductive decyclizations have been observed.<sup>8 c,9</sup>

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<sup>5</sup> D. H. R. Barton and R. C. Cookson, Quart. Rev. 10, 82 (1956).

<sup>6</sup> E. M. Philbin and T. S. Wheeler, Proc. Chem. Soc. 167 (1958); cf. H. Hart and C. R. Wagner, Ibid. 284 (1958).

<sup>7</sup> W. Huckel, M. Maier, E. Jordan and W. Seeger, Ann. 616, 46 (1958), K. D. Hardy and R. J. Wicker, J. Amer. Chem. Soc. 80, 640 (1958).

<sup>8</sup> For previous work on  $\alpha$ - and  $\beta$ -4-hydroxyflavans see: <sup>a</sup> K. Freudenberg and L. Orthner, Ber. 55, 1748 (1922); <sup>b</sup> P. Karrer, Y. Yen and I. Reichstein, Helv. Chim. Acta 13, 1308 (1930); <sup>c</sup> R. Mazingo and H. Adkins, J. Amer. Chem. Soc. 60, 669 (1938); <sup>d</sup> T. A. Geissman and R. O. Clinton, J. Amer. Chem. Soc. 68, 700 (1946); <sup>e</sup> V. N. Gupta, A. C. Jain and T. R. Seshadri, Proc. Indian Acad. Sci. 38, 470 (1953); <sup>f</sup> J. E. Gowan, S. P. MacGiolla Riogh, G. J. MacMahon, S. O'Cleirigh, E. M. Philbin and T. S. Wheeler, Tetrahedron 2, 116 (1958).

<sup>9</sup> T. Tasaki, Acta Phytochim. 3, 259 (1927); Chem. Abstr. 23, 125 (1929).

Satisfactory analyses have been obtained for new compounds.

Work is in hand on the use of 3-aminoflavanones (from 3-isonitrosoflavanones) for the synthesis of derivatives of flavan-3-ol.<sup>10</sup>

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<sup>10</sup> Immediately before this paper was submitted for publication information was received that similar work on 3-aminoflavanones was independently in progress in the Institute of Science, Bombay, under the direction of Dr. A. B. Kulkarni.