

3-Hemiacetals of 3,4-Dihydrospiro[2*H*-1-benzopyran- 2,1'(3'*H*)-isobenzofuran]-3,4-dione

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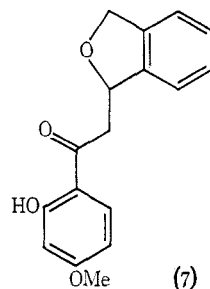
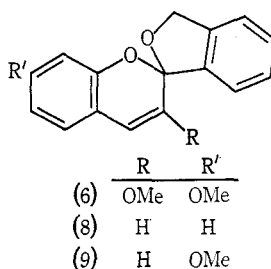
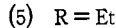
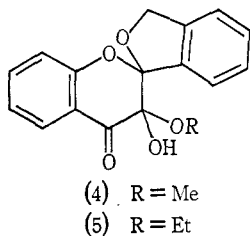
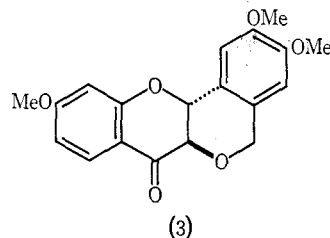
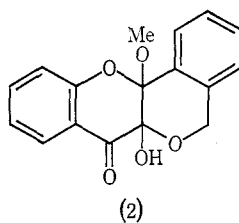
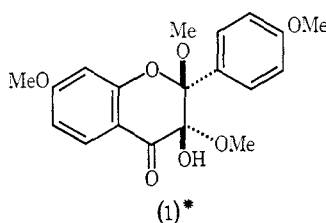
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Abstract

Oxidation of 2'-hydroxymethylflavonol with periodic acid in methanol gives 3,4-dihydro-3-hydroxy-3-methoxyspiro[2*H*-1-benzopyran-2,1'(3'*H*)-isobenzofuran]-4-one.

Oxidation of 7,4'-dimethoxyflavonol with periodic acid in methanol to 3-hydroxy-2,3,7,4'-tetramethoxyflavanone (1)^{1,2} led us to test the possibility that similar oxidation of 2'-hydroxymethylflavonol would give the related flavanone derivative (2)



by intramolecular participation of the hydroxymethyl group in hemiacetal formation at the 3-position of flavanone. Cyclization to such a tetracyclic product (2) would clearly have potential for synthesis³ of peltogynone trimethyl ether (3) and related

* Note: Absolute configuration of one enantiomer of a racemic compound.

¹ Smith, M. A., Webb, R. A., and Cline, L. J., *J. Org. Chem.*, 1965, **30**, 995.

² Clark-Lewis, J. W., Dainis, I., McGarry, E. J., and Baig, M. I., *Aust. J. Chem.*, 1972, **25**, 857.

³ Clark-Lewis, J. W., and Mahandru, M. M., *Aust. J. Chem.*, 1971, **24**, 549.

peltogynan derivatives. However, oxidation of 2'-hydroxymethylflavonol with periodic acid in methanol was found to give the isomeric hemiacetal (4) formed by the alternative cyclization to the 2-position. Recrystallization of the methyl hemiacetal (4) from ethanol gave the corresponding ethyl hemiacetal (5). The hemiacetals melted over a range of temperature, which is attributed to the loss of methanol (commencing at *c.* 133°) or ethanol (at *c.* 150°), and the final m.p. (158° in each case) probably corresponds to the m.p. of the 3,4-dione.

This cyclization to the spirophthalan (4) is analogous to the formation of the spirophthalan (6) in the reduction of methyl 3,7-dimethoxyflavone-2'-carboxylate with lithium aluminium hydride,⁴ and to the formation of a phenacylphthalan (7)⁵ by cyclization of the related 2-hydroxymethylchalcone. Spirophthalans (8) and (9) analogous to the spiran (6) were formed by ring contraction during reduction of isochromenochromone and 7-methoxyisochromenochromone with sodium di(2-methoxyethoxy)aluminium hydride.⁶

The assignment of the structure (4) instead of (2) to the hemiacetal is consistent with the n.m.r. absorption of the methylene protons as a singlet, and rests largely on the very facile conversion of the methyl hemiacetal into the ethyl analogue (5) simply by recrystallization from ethanol, and by the facile elimination of methanol from (4) and ethanol from (5) during melting. Treatment of the hemiacetals (4) and (5) with sodium borohydride in isopropanol led to recovery of 2'-hydroxymethylflavonol (44%), consistent with previous observations on the behaviour of related hemiacetals with metallic hydrides at elevated temperatures.²

Experimental

N.m.r. spectra were recorded with a Varian A60D instrument with SiMe₄ as internal standard. Microanalyses were performed by the Australian Microanalytical Service, Melbourne. Mass spectra were recorded with an A.E.I. MS30.

3,4-Dihydro-3-hydroxy-3-methoxyspiro[2H-1-benzopyran-2,1'(3'H)-isobenzofuran]-4-one (4)

A suspension of 2'-hydroxymethylflavonol⁷ (5 g) in methanol (400 ml) was stirred at room temperature with periodic acid (6 g) for 2 h. The clear solution was passed through a bed of Amberlite IRA 400 resin (acetate form) to remove the oxidant, and the yellow solution was concentrated to *c.* 70 ml under reduced pressure, and kept for 48 h. The crystalline deposit (2.1 g, 38%) was redissolved in methanol and crystallization gave *3,4-dihydro-3-hydroxy-3-methoxyspiro[2H-1-benzopyran-2,1'(3'H)-isobenzofuran]-4-one* in prisms (1.6 g, 29%), m.p. 133–158° (with loss of methanol from *c.* 133°) (Found: C, 68.7; H, 4.8; *m/e*, 298. C₁₇H₁₄O₅ requires C, 68.5; H, 4.7%; mol. wt, 298). N.m.r. (CDCl₃): δ 3.24 (s, 3H, OMe), 4.66 (br s, 1H, OH; removed by exchange with D₂O), 5.20 (s, 2H, ArCH₂O), and 6.80–8.10 (m, 8H, ArH).

3,4-Dihydro-3-ethoxy-3-hydroxyspiro[2H-1-benzopyran-2,1'(3'H)-isobenzofuran]-4-one (5)

Recrystallization of the foregoing hemiacetal from ethanol gave the *ethyl hemiacetal* in prisms, m.p. 150–158° (with loss of ethanol from *c.* 150°) (Found: C, 69.1; H, 5.3; *m/e*, 312. C₁₈H₁₆O₅ requires C, 69.2; H, 5.2%; mol. wt, 312). N.m.r. (CDCl₃): δ 1.16 (t, 3H, OCH₂CH₃), 2.97–3.97 (m, 2H, OCH₂CH₃), 4.65 (br s, 1H, OH; removed by exchange with D₂O), 5.18 (s, 2H, ArCH₂O),

⁴ Clark-Lewis, J. W., and Skingle, D. C., *Aust. J. Chem.*, 1967, **20**, 2169.

⁵ Clark-Lewis, J. W., and Mahandru, M. M., *Aust. J. Chem.*, 1974, **27**, 2689.

⁶ Clark-Lewis, J. W., and Mahandru, M. M., *Aust. J. Chem.*, 1971, **24**, 563.

⁷ Clark-Lewis, J. W., Della, E. W., and Mahandru, M. M., *Aust. J. Chem.*, 1969, **22**, 2389.

and 6.90–8.00 (m, 8H, ArH). Computation (LAOCN3)⁸ of the ethoxyl proton signals (ABX₃) gave the following parameters: δ_A 3.72; δ_B 3.26; δ_X 1.16; J_{AB} 9.4, $J_{AX} = J_{BX} = 7.2$ Hz.

2'-Hydroxymethylflavonol from the Hemiacetals (4) and (5)

The foregoing methyl hemiacetal (1 g) was boiled under reflux with sodium borohydride (0.5 g) in isopropanol (50 ml) containing a little ethanol for 3 h before being added to ice-water (200 ml) and acetic acid (3 ml). The solution was extracted with ether, and the ethereal extract was washed with aqueous sodium hydrogen carbonate and water, and dried (MgSO₄) before evaporation under reduced pressure. Crystallization of the gummy residue from carbon tetrachloride gave 2'-hydroxymethylflavonol in needles (0.39 g, 44%), m.p. 162° (lit.⁷ 162°).

Acknowledgment

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⁸ Castellano, S., and Bothner-By, A. A., *J. Chem. Phys.*, 1964, **41**, 3863; Castellano, S. M., in 'Computer Programs for Chemistry' (Ed. D. F. DeTar) Vol. 1, p. 10 (Benjamin: New York 1968).