Hemiketals Related to Peltogynol: Synthesis of the Robinsons' Hemiketal

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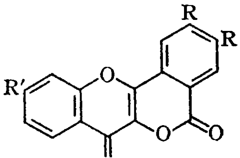
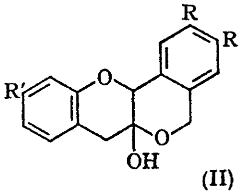
THE products obtained from the flavonol lactones (I) by reduction with lithium aluminium hydride are now to be shown to be hemiketals (II). The trimethoxyhemiketal (IIc), m.p. 201·5—202°, was originally formulated by Bryant, Hassall, and Weatherston[1] as a diastereiosomer of peltogynol trimethyl ether (III; R=R′=OMe),[2] but both this formulation and our recently suggested spiroketal structure (IVc)[3] are invalidated by mass spectra of the hemiketals (II). The hemiketal (IIc) is the trimethyl ether of the structure originally suggested by Robinson and Robinson[4] for peltogynol (III; R=R′=OH),[2] and it shows the expected properties, including rapid conversion into the peltogynidin trimethyl ether cation (Vc) by acids in the presence of air. The hemiketals (IIa), m.p. 171—172°, and (IIb), m.p. 169—170°, similarly yield yellow (Va) and orange (Vb) cations.

Each hemiketal (II) was obtained as a mixture of *cis*- and *trans*-isomers (2-H and 3-OH *cis* or *trans*), and their structures were elucidated largely from spectroscopic evidence. The n.m.r. spectrum ($CDCl_3$) of the hemiketal (IIa) revealed a methylene quartet at high field ($Ar{\cdot}CH_2{\cdot}C$), a methylene quartet at low field ($Ar{\cdot}CH_2{\cdot}O$), and a low-field one-proton singlet ($C{\cdot}CHAr{\cdot}O$); the absence of spin–spin coupling between the high- and low-field protons was confirmed by double irradiation. The spectra are complicated by the *cis–trans*-isomerism of the hemiketals (II) which is discussed below, and the n.m.r. data are consistent also with the spiroketal structures (IV).[3] Mass spectra confirmed the molecular formulae, and the main fragmentation occurred by retro-Diels–Alder fission of the chroman heterocyclic nucleus in the hemiketals (II) and could not be rationalised on the basis of the alternative spiroketal formulation (IV). The absence of significant $M - 17$ peaks corresponding to benzyl carbonium ions also militates against the spiroketal structures (IV), as do failures of attempted acetylation, hydrogenolysis, and oxidation with manganese dioxide. The hemiketal (IIb) was converted by methanol and toluene-*p*-sulphonic acid into the methyl ether (ketal), m.p. 106—106·5°. Chemically convincing proof of the hemiketal structures (II) was obtained by reduction of the hemiketal (IIa) with sodium borohydride which gave racemic *trans*-2′-hydroxymethylflavan-3-ol (VI), m.p. 140—141° ($J_{2,3}$ = 9·0; $J_{3ax,4ax}$ = 10·45; $J_{3ax,4eq}$ = 5·05; $J_{4ax,4eq}$ = 16·0 c./sec.; 2-H, τ 4·98; 3-H τ 6·00; 4*eq*-H, τ 6·91; 4*ax*-H, τ 7·10; these values are consistent with data for analogous compounds[5]); the methylene protons of the hydroxymethyl group are in an asymmetric environment, and absorbed as an AB quartet (J_{AB}= 12·3 c./sec.; A, τ 5·25; B, τ 5·51).

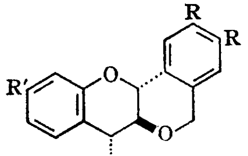
The unsubstituted hemiketal (IIa) was obtained as a mixture of *cis*- (83%) and *trans*-isomers (17%), and equilibration of a solution in deuterochloroform (sealed, evacuated n.m.r. tube) at 56° gave in 3 days an equilibrium mixture of *cis*- (63%) and *trans*-isomers (37%), which was unchanged after a further 3 days. The position of equilibrium was determined by integration of the 2-H signals (*cis* τ 5·03; *trans* τ 5·23). After 12 days (total time) at 56° the mixture had been converted entirely into the flav-2-ene (VIIa) identified by two-proton singlets at τ 6·38 ($Ar{\cdot}CH_2{\cdot}C{=}C$) and 4·95 ($Ar{\cdot}CH_2{\cdot}O$) and by its immediate conversion into



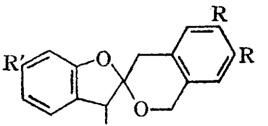
(I)



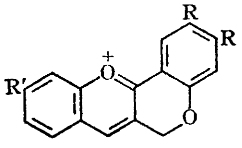
(II)



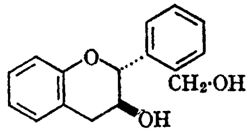
(III)



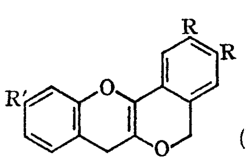
(IV)



(V)



(VI)



(VII)

(a) R = R′ = H; (b) R = H, R′ = OMe;
(c) R = R′ = OMe

the flavylium salt (Va) by cold acid in the presence of air. The monomethoxyhemiketal (IIb) was obtained predominantly (*ca.* 95%) in the *cis*-form and was similarly isomerised to a mixture of *cis*- (58%) (2-H, τ 5·01) and *trans*-isomers (42%) (2-H, τ 5·22), and after a further 29 hr. at 56° was entirely converted into the flav-2-ene (VIIb). The trimethoxyhemiketal (IIc) was obtained as a mixture of isomers (80 : 20), and the proportion of these was conveniently determined by integration of methoxyl signals. The predominant isomer was assigned the *trans*-configuration from the occurrence of a 2-H signal at τ 5·30 which integrated for 80% of one proton. By analogy with the hemiketals (IIa and IIb) the 2-H signal of the *cis*-isomer is expected to occur at lower field (*ca.* τ 5·00—5·05) in the region obscured in this instance by the two-proton singlet ($Ar\cdot CH_2\cdot O$) at τ 5·07. After heating the hemiketal (IIc) in deuterochloroform at 56° for 18 hr., the isomer ratio became 60% *cis* to 40% *trans*, and during a further 18 hr. the mixture was converted into the flav-2-ene (VIIc) (66%). Continued heating of the flav-2-ene over a period of days apparently led to the disproportionation envisaged by Robinson,[4] but none of the isomeric flav-3-ene was detected. The flav-2-ene (VIIc) immediately gave the peltogynidin trimethyl ether cation (Vc) when treated in air with cold acid.

The 2-H signal of the *cis*-hemiketals occurs at lower field than in the *trans*-isomers, although this consistency with data for other flavan derivatives[5] may be fortuitous. The assignment of configurations, however, rests on the difference in chemical shift of the AB protons responsible for the high-field quartet, which is greater in the *cis*- than in the *trans*-hemiketals ($\Delta\delta_{AB}$ 0·18 and *ca.* 0·02 p.p.m.), and this greater magnetic nonequivalence in the *cis*-isomers agrees with predictions from examination of Dreiding models. Full experimental details of this investigation will shortly be submitted for publication.

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[1] R. Bryant, C. H. Hassall, and J. Weatherston, *J. Chem. Soc.*, 1964, 4941.

[2] C. H. Hassall and J. Weatherston, *J. Chem. Soc.*, 1965, 2844; for the absolute configuration see S. E. Drewes and D. G. Roux, *J. Chem. Soc.* (*C*), 1966, 1644.

[3] J. W. Clark-Lewis and D. C. Skingle, *Tetrahedron Letters*, 1966, 4199.

[4] R. Robinson and G. M. Robinson, *J. Chem. Soc.*, 1935, 744.

[5] J. W. Clark-Lewis, L. M. Jackman, and T. M. Spotswood, *Austral. J. Chem.*, 1964, **17**, 632.