General Synthetic Route to Modified Dianin's Compounds. Synthesis of a New Clathrate-forming 2-nor-Analogue

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Summary A new clathrate host (**6b**) related to Dianin's compound (**1**) has been prepared; a synthetic method allowing easy access to 2- and 4-modified analogues of (**1**) is described.

DIANIN'S compound (**1**) readily forms clathrates in which guest molecules are included into cavities formed from 6 molecules of the host.[1] Removal of one of the *geminal* methyl groups [see (**5b**)] was recently shown not to impede the ability of the chroman to form an inclusion compound with carbon tetrachloride.[2] In connection with a detailed study of structural and other factors that permit clathrate formation,[3] we report here the preparation of the isomer (**6b**) which lacks the 2-methyl group *trans* to the *p*-hydroxyphenyl substituent of (**1**), and forms an inclusion compound with cyclohexane.

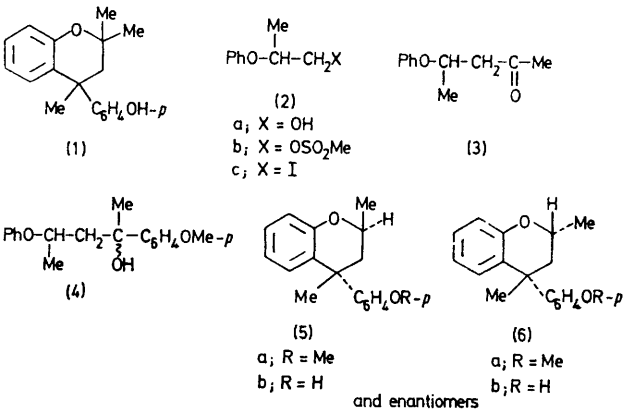
The compound (**6b**) was prepared *via* a general method which allows easy access to 2- and/or 4-modified analogues of (**1**). Thus, reduction of 2-phenoxypropionic acid with $LiAlH_4$ followed by esterification of the resulting alcohol (**2a**) with methanesulphonyl chloride led to the crystalline mesylate (**2b**), m.p. 38 °C, which was converted into the iodide (**2c**) by treatment with MgI_2–Et_2O[4] in *ca.* 70%

overall yield. The iodide (**2c**) was acylated *via* the protected cyanohydrin method[5] to give the previously unknown compound 4-phenoxypentan-2-one (**3**), liquid, 59%, δ ($CDCl_3$, rel. to Me_4Si) 1·31 (3H, d, ^3J 6 Hz), 2·16 (3H, s)

TABLE. 100 MHz ^1H n.m.r. data for (**5**) and (**6**) in $CDCl_3$ relative to Me_4Si.

	2-Me δ (^3J/Hz)	2-H δ	3-CH_2 δ	4'-OMe δ	ArH δ
(**5a**)	1·27d (6·2	3·81m	*ca.* 2m	3·75s	6·8—7·2
(**5b**)	1·26d (6)	3·87m	*ca.* 1·9m	—	6·5—7·2
(**6a**)	1·39d (6·1)	4·31m	*ca.* 1·9m	3·77s	6·7—7·2
(**6b**)	1·36d (6)	4·33m	*ca.* 1·9m	—	6·5—7·2

ca. 2·75 (m, diastereotopic CH_2), 4·85 (1H, m), and 6·8—7·5 (5H, m, ArH). Addition of (**3**) to *p*-anisylmagnesium bromide (ether–tetrahydrofuran, 1 : 1) followed by cyclisation of the diastereoisomeric mixture (**4**) in the presence of formic acid (30 min, 80 °C) afforded a mixture of the two chromans (**5a**) and (**6a**) in 93% yield (molar ratio 3 : 7, respectively), from which the major isomer (**6a**), m.p. 86 °C, was isolated by crystallisation [pentane, 50% yield from (**4**)]. Chromatography of the mother liquors (silica gel, hexane containing 1% acetone) furnished the minor product (**5a**). The structures of (**5a**) and (**6a**) were unambiguously assigned by detailed analysis of their 100 MHz ^1H n.m.r. spectra. The main features of the spectra are given in the Table. Structural assignments are based principally upon the fact that the 2-H lies in a pseudoaxial position in the two compounds; this situation allows long range W-coupling between the pseudoaxial 3-H and the 4-Me substituents in (**6a**) but not in (**5a**), as is actually observed. The demethylation of (**5a**) and (**6a**) was achieved cleanly with pyridine hydrochloride (20 min at 210 °C) affording the phenols (**5b**) and (**6b**), respectively, in quantitative yields. Compound (**5b**) so obtained was found to be identical (n.m.r.) with previously described 2-nor-analogue of Dianin's compound,[2] thus supporting our n.m.r. deductions.



Crystallisation of (**6b**) from cyclohexane gave a clathrate [m.p. *ca.* 85 °C (decomp.)] for which a host/guest ratio of 7 : 1 was found (n.m.r. integration).

It is thus demonstrated that removal of either *geminal* methyl group of (**1**) leads to analogues which retain the ability to form inclusion compound.

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