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# STEREOCHEMISTRY OF CYANOMACLURIN[a]

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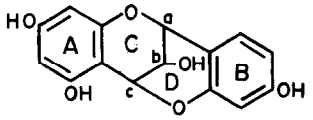
We assigned structure (I) to cyanomaclurin (1) on the basis of NMR data and the inertness of the non-phenolic hydroxyl function towards chromic acid oxidation and catalytic hydrogenation. The relative stereochemistry was also deduced from the following considerations. The three protons of the heterocyclic rings showed separate absorptions at




I

4.61, 4.88 and 5.67 in the spectrum[b] of its trimethyl ether (2). It was suggested that the signals at 4.61 and 4.88 might be assigned to protons $H_a$ and $H_c$ respectively, since $H_c$ is adjacent to the phloroglucinol ring. The former signal is broad, and the latter quite narrow.

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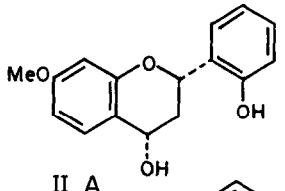
[a] Communication No.970 from the National Chem. Lab.,Poona.

[b] NMR spectra in $CCl_4$ or $CDCl_3$, unless otherwise mentioned; chemical shifts are on the $\tau$ scale.

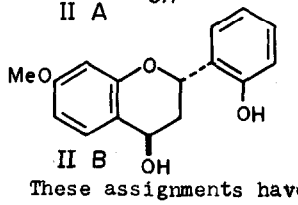
Clark-Lewis and Jackman (3) have shown that for flavan-3,4-diols $J_{3,4}$(ax-eq) is about 6.6 cps, while $J_{3,4}$(eq-eq) is nearly zero. On the basis of the assignments for $H_a$ and $H_c$ it was concluded that $H_b$ is <u>trans</u> to $H_a$ and $H_c$ in ring C. In ring D, which is also part of a flavan-3,4-diol system, protons $H_b$ and $H_a$, which are at the 3- and 4-positions, would therefore be in axial-equatorial relationship and the coupling between them would be large. Although the actual coupling constant could not be determined from the published spectrum of cyanomaclurin or its trimethyl ether, the fact that the signal for $H_a$ was broader than that for $H_c$ appeared to be consistent with this stereochemical assignment. Since in cyanomaclurin we have a fusion of two flavan-3,4-diol systems, the molecule is somewhat strained and the dihedral angles between the proton pairs cannot be quite the same as in ordinary flavan-3,4-diols. However, the inequality, $J_{3,4}$(ax-eq) > $J_{3,4}$(eq-eq), should still hold.

We wish now to point out that, in making these assignments for $H_a$ and $H_c$, the paramagnetic shift often shown by benzylic protons on the introduction of <u>ortho</u> oxygen substituents was overlooked and that these assignments have to be reversed, necessitating in turn an inversion of the configuration suggested for position 3. In agreement with the assumption made earlier, that protons benzylic to a phloroglucinol ring absorb at higher field than those benzylic to a resorcinol ring as in (I), it is seen that the methyl signal of <u>C</u>-methylphloroglucinol trimethyl ether is at 8.04, 0.14 ppm upfield from that of 2,4-dimethoxytoluene.

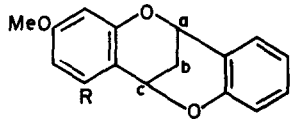
similar shift is seen for the corresponding hydroxy compounds in formic acid solution. However, the $C_4$ proton of 4-hydroxy-5,7-dimethoxy-2,2-dimethylchroman absorbs at 5.20, 0.25 ppm downfield from the corresponding absorption of 4-hydroxy-7-methoxy-2,2-dimethylchroman. The CH absorptions of the isopropyl groups of p-cymene (4), thymol (4), and its methyl ether occur at 7.17, 6.85 and 6.74 and form another set illustrating the reverse order which is clearly the effect of the ortho oxygen substituent. The paramagnetic shift is apparently dependent on conformation. The chromans examined are conformationally mobile and the observed absorption positions for their benzylic protons are presumably averages of those characteristic of the quasi-axial and quasi-equatorial environments. Since these compounds are closer than the methyl substituted compounds to cyanomaclurin as model systems for comparison, it is clear that the assignments previously made for $H_a$ and $H_c$ have to be reversed. The signals at 4.61 and 4.88 in the spectrum of the methyl ether thus represent $H_c$ and $H_a$ respectively.




II A




II B




III a; R=H

III b; R=OMe

These assignments have been confirmed by the synthesis

of two cyanomaclurin analogues (IIIa and IIIb) containing methoxyl groups in the 7- and 5,7-positions respectively of one chroman ring. 2'-Hydroxy-7-methoxyflavanone (m.p. 200°), prepared by the cyclization of 2,2'-dihydroxy-4'-methoxychalcone (5), gave on reduction with sodium borohydride a mixture of epimeric flavan-4-ols (IIA as the major product and IIB), which were separated into the components (m.p. 164° and 151° respectively) by fractional crystallisation. By treatment with acid both epimers were cyclised to the same neutral non-hydroxylic compound (IIIa; m.p. 105-106°), whose NMR spectrum showed it to be an analogue of (I). The benzylic protons of (IIIa) appear together as a triplet at 4.81 and the methylene protons ($H_b$) at 7.87. The second analogue (IIIb; m.p. 118°) with an additional methoxyl at the 5-position was prepared from 2'-hydroxy-5,7-dimethoxyflavanone (5) by a similar procedure, and its spectrum showed absorptions at 4.45 and 4.80 for the benzylic protons, illustrating the deshielding effect of the 5-OMe group on the $H_c$-proton.

The revised assignments for $H_a$ and $H_c$ make $J_{bc}$ larger than $J_{ab}$ and require $H_b$ to be <u>cis</u> to $H_a$ and $H_c$ in ring C. From spin decoupling experiments on cyanomaclurin $J_{ab}$ and $J_{bc}$ have been estimated to be 2.5 and 3.5 cps respectively. The relative magnitudes assumed for $J_{ab}$ and $J_{bc}$ are thus confirmed. A Dreiding model of cyanomaclurin shows that the dihedral angles made by $H_a$ and $H_c$ with $H_b$ are about 75° and 45° respectively.

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