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Non-equivalence of Methylenedioxy Protons in Cyclolignans*

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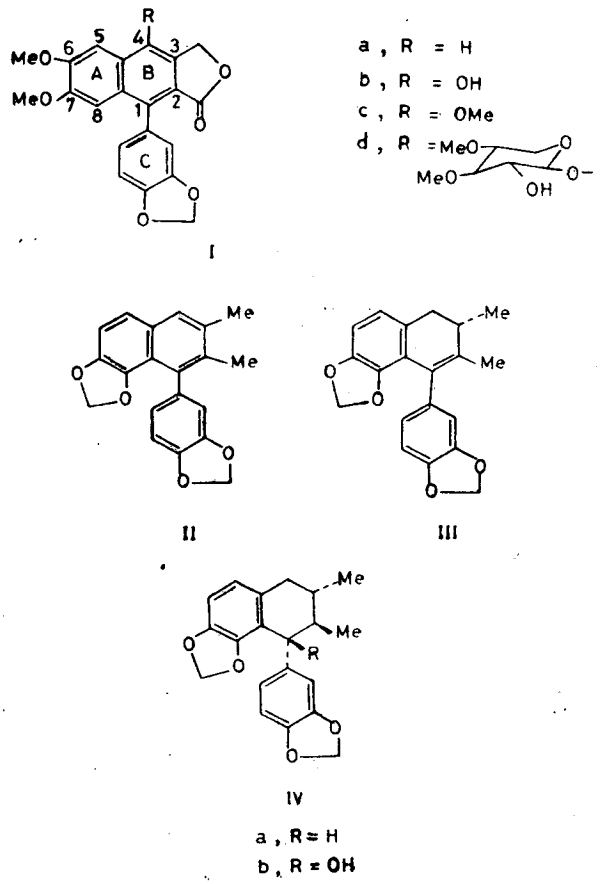
The conditions for observation of non-equivalence of CH_2O_2 protons in rings A and C of cyclolignans are discussed. The protons of the CH_2O_2 group when present in ring A at 7,8-position are equivalent when ring B is aromatic and non-equivalent when it is hydroaromatic. When the CH_2O_2 group is present in ring C at 3′,4′-positions non-equivalence is observed if there is a second CH_2O_2 function at 7,8-positions or if there is a C=O group attached to C-2 of ring B.

DURING the course of our work on the cyclolignanolides from *Cleistanthus collinus*[1], we had observed that the methylenedioxy protons in ring C in dehydrocollinusin (justicidin B) (Ia), diphyllin (Ib), its acetate, methyl ether (justicidin A) (Ic), ethyl ether, tosylate, 3,4-di-O-methyl-D-xyloside (cleistanthin) (Id), acetylcleistanthin, O-methylcleistanthin and cleistanthin tosylate appeared as an AB quartet in their NMR spectra†. A literature survey indicated that in a few other cases non-equivalence of the CH_2O_2 protons in rings A and C of cyclolignans had been noted. We wish to summarize here our present findings and observations of earlier authors and delineate structural features necessary for causing such non-equivalence in cyclolignans.

CH_2O_2 protons in ring A — Dehydrootobain (II) has two CH_2O_2 groups both of which appear as singlets, the one on ring A at higher field, at δ 5·78 compared to the one on ring C at δ 6·05 (ref. 2 and 3). This is a consequence of the ring C aryl group taking up an orthogonal conformation. Being symmetrically disposed with respect to ring C, the CH_2O_2 protons on ring A are equivalent and appear as a singlet. In otobaene (III)[4], otobain (IVa)[2,3] and hydroxyotobain (IVb)[4], ring B is no more coplanar with A; the ring A CH_2O_2 protons are not equivalent with respect to ring C and appear as a quartet. In IVa[3], for instance, they have a chemical shift difference of 0·09 ppm and a coupling constant of 1·2 Hz.

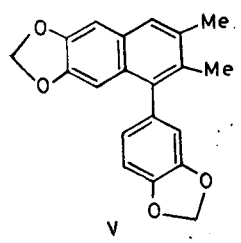
CH_2O_2 protons in ring C — In dehydroepigalbacin (V), the CH_2O_2 groups in both rings A and C appear as sharp singlets while in dehydrootobain (II) and the related diacetate (VIa)[5] the one on ring C appears as a broadened singlet. In the diol (VIb)[5] the CH_2O_2 protons in ring C are even more non-equivalent and are seen as a clear quartet.



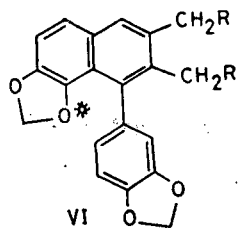
This is most likely due to the differential long-range shielding effect of the oxygen (marked with an asterisk in VI) atom of ring A on the CH_2O_2 protons in ring C which is orthogonal to ring B due to hindered rotation.

The signals of CH_2O_2 protons of ring C in helioxanthin[5] (VII) appear as an AB quartet in DMSO at probe temperature (35°), become a broad

*Contribution No. 220 from CIBA Research Centre.
†All the NMR spectra reported here except those indicated to be otherwise were run on a Varian spectrometer at 100 Hz.

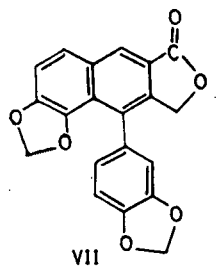


V

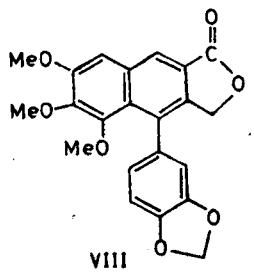


VI

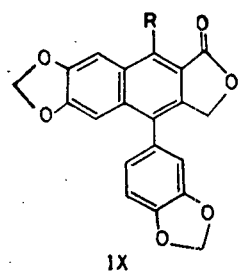
a, R = OAc
b, R = OH



VII



VIII



IX

a, R = H
b, R = OMe

singlet at 60° and collapse to a sharp singlet at 100°, as a consequence of rapid rotation of ring C. There is a report[6] that in compound (VIII), the CH_2O_2 protons in ring C appear as a singlet. It is possible that in this case the free rotation of the C—OMe at C_8 does not allow differential shielding of the CH_2O_2 protons.

Justicidin E[7] (IXa), an isomer of helioxanthin, in which the CH_2O_2 occupies the 6,7 positions in ring A, shows both CH_2O_2 groups as singlets. This is the case with justicidin D[8] (≡ neojusticin[9]) (IXb) also.

It was interesting to find that justicidin B (Ia), diphyllin (Ib) and its derivatives which differ from IX in having the lactone C=O at C-2 instead of C-3 in the naphthalene moiety showed non-equivalent CH_2O_2 in ring C. This is best explained by assuming hindered rotation of the ring C-aryl and differential long-range anisotropic effect of the C=O. We have studied in detail the effects of solvents and temperature on the NMR spectrum of justicidin A (Ic) (Table 1). At normal probe temperature (35°), in $CDCl_3$, the CH_2O_2 protons had an apparent separation of 0·045 ppm (J = 1·5 Hz) which was increased by the addition of benzene. In Py-d_5, maximum separation was observed, while in DMSO-d_6, even at probe temperature, the CH_2O_2 protons were practically equivalent. Modification of the long-range effects of a carbonyl group by formation of

TABLE 1 — CHEMICAL SHIFT DIFFERENCE OF CH_2O_2 PROTONS OF JUSTICIDIN A (Ic)

Solvent	Temperature	Δδ (ppm)
DMSO-d_6*	40°	0
$CDCl_3$-C_6H_6 (1 : 2)*	40°	0·077
$CDCl_3$-C_6H_6 (1 : 1)*	40°	0·06
$CDCl_3$	35°	0·045
$CDCl_3$	0°	0·055
$CDCl_3$	−10°	0·062
$CDCl_3$	−20°	0·065
$CDCl_3$	−30°	0·070
$CDCl_3$	−40°	0·073
$CDCl_3$	−50°	0·075
$CDCl_3$	−60°	0·077
$CDCl_3$	−70°	0·08
Py-d_5	40°	0·08
Py-d_5	>90°	0

*These were run at 60 MHz in a Varian A-60 spectrometer.

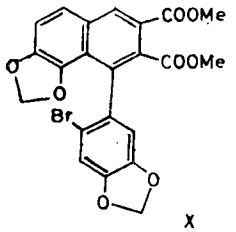
collision complexes with different solvents to different extents is known[10].

The low temperature spectra of justicidin A in $CDCl_3$ show an increase of the separation of the CH_2O_2 quartet (Table 1). It was 0·045 ppm at 35° and 0·08 ppm at −70°. This is to be expected, since at lower temperatures the rate of rotation of the ring C aryl would be much lower. Measurements at higher temperature in Py-d_5 showed that the CH_2O_2 quartet begins to coalesce at 60° and at 90° the AB spectrum degenerates to a broad singlet. This in turn becomes sharper if the temperature is raised to 95°, 100° and finally 105°. At 105° the former *AB* spectrum is almost a perfect singlet*. At 60°, it can be calculated[11] that the ring C aryl group must be making 23 rotations per second and that the approximate free energy of activation for rotation is about 17·5 kcal/mole. Detailed calculations were not attempted either for the low temperature $CDCl_3$ spectra or for the high temperature Py-d_5 spectra, because the chemical shift was not much larger than the coupling constants and the line widths.

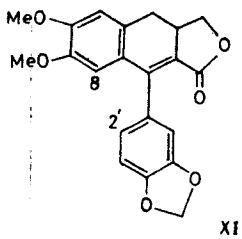
Thus, it appears that a CH_2O_2 group at the 3′,4′-positions in ring C becomes non-equivalent when there is a CH_2O_2 group at 7,8-positions or a carbonyl group attached to C-2. It is conceivable that when both the features are present in a molecule, their effects may mutually cancel out. We like to speculate that the reported singlet structure of the CH_2O_2 group in ring C of compound (X)[12] may be the result of such a cancellation.

While all the diphyllin derivatives having ring B aromatic showed non-equivalence of the CH_2O_2 protons in ring C, it was interesting to note that the dihydro compound, collinusin (XI)[1], showed the CH_2O_2 protons as a singlet in $CDCl_3$ and also in Py-d_5. Dreiding models indicate slightly lesser interference between C_2- and C_8-protons, thus allowing faster rotation of the C-ring compared to the compounds having an aromatic ring B. We expected

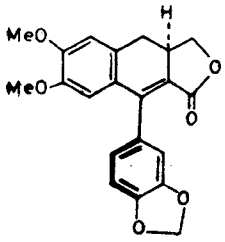
*The Py-d_5 NMR spectrum was not run at temperatures below 35°; it is assumed that the chemical shift between the CH_2O_2 protons will be about 0·1 ppm at slow exchange or in its absence.



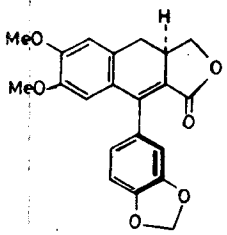
X



XI



XII



XIII

that lowering the temperature would make the rotation sufficiently slow on the NMR time scale to permit observation of non-equivalence. While going in $CDCl_3$ solution from $+40°$ to $-60°$, it was found that the CH_2O_2 protons remained a singlet up to 0°; below $-10°$, the CH_2O_2 proton signals began to show signs of multiplicity as also the aromatic region. At $-30°$ and below, it appeared as if the CH_2O_2 signals formed a composite of a singlet and a quartet. A plausible explanation would be that at $-30°$ and below, the rotation of the C-ring is sufficiently restricted to allow a freezing out of the two diastereoisomers (XII) and (XIII). In one of them, probably (XII), the CH_2O_2 protons may be differentially shielded by the C=O group while in the other it may not be so.

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