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THE STRUCTURE OF NIMBINIC ACID*

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Although hydrolysis of nimbin (I) with potassium bicarbonate gives nimbinic acid (1) - a monocarboxylic acid, hydrolysis of dihydro - (II), and hexahydronimbin (II- with the furan ring also saturated) under the same conditions gives only the corresponding dicarboxylic acids, since the C_4-quaternary carboxylic ester gets very great assistance for hydrolysis from the hydroxyl group at C_6, produced by the initial hydrolysis of the acetate there. Hence, it was difficult to decide which of the two carboxyl groups has got hydrolysed in nimbinic acid.

The assistance of the C_6-hydroxyl group was demonstrated thus. Nimbin hydrolyses stepwise with mild base at room temperature to desacetyl nimbin (III), nimbinic acid, and nimbic acid (IV). But when dihydrodesacetyl nimbin (V) is mesylated to its C_6 α-mesylate (VI), m.p. 174°, $(\alpha)_D$ +172°, the compound even on refluxing with 10% methanolic potassium hydroxide gives only a monocarboxylic acid 6α-mesylate, m.p. 183-85°, $(\alpha)_D$ +128°. This compound must therefore be the C_{11}-carboxylic acid (VII).

Nimbinic acid on hydrogenation gives dihydronimbinic acid, m.p. 220°, which on mesylation gives dihydronimbinic acid mesylate which has the same m.p., mixed m.p., $(\alpha)_D$ and identical IR and PMR spectra with those of (VII). Similarly Desacetyl nimbin mesylate (VIII), m.p. 174°,

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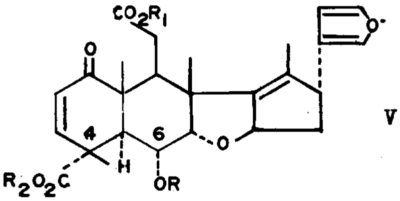


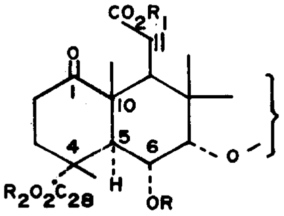
I, R=Ac, $R_1=R_2=CH_3$

III, R=H, $R_1=R_2=CH_3$

IV, $R=R_1=R_2=H$

VIII, R=Mes, $R_1=R_2=CH_3$

IX, $R=R_1=H$, $R_2=CH_3$



II, R=Ac, $R_1=R_2=CH_3$

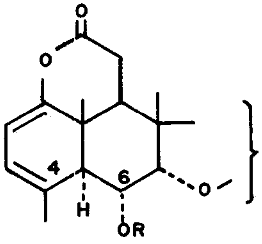
V, R=H, $R_1=R_2=CH_3$

VI, R=Mes, $R_1=R_2=CH_3$

VII, R=Mes, R_1=H, $R_2=CH_3$

X, $R=R_1=H$, $R_2=CH_3$

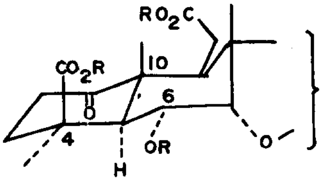
XI, $R=R_1=R_2=H$



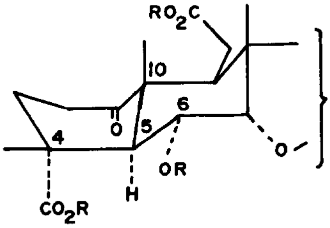
XII, R=H ('pyronimbic acid')

XIII, R=Ac (acetate of XII)

XIV, R=Mes (mesylate of XII)



XV



XVI

$(\alpha)_D$ +143°, on hydrolysis with 10% methanolic potassium hydroxide gives a monocarboxylic acid 6α-mesylate, m.p. 190°, $(\alpha)_D$ +158°, which is identical with the product obtained by mesylating nimbinic acid. Hence nimbinic acid is the 6α-hydroxyl, C_{11}-carboxyl derivative (IX) of nimbin, and dihydronimbinic acid, (X). This is further confirmed by the fact that while the PMR spectra in pyridine solution of nimbic acid (IV) shows a downfield shift of around 10 cps for its C_4-methyl signal, compared to the same signal in desacetyl nimbin (III), as expected(2), in nimbinic acid (IX), it is in the same place as in desacetyl nimbin. Similarly in the pyridine solution spectra, the C_4-methyl signal is at the same place in dihydrodesacetyl nimbin (V), and in dihydronimbinic acid (X), but moves downfield by around 10 cps, only in dihydronimbic acid (XI).

The C_4-methyl group has been found (1) to have a 1,3-<u>cis</u> diaxial like relation (3), with the C_6α-equatorial hydroxyl or mesylate group. Table 1 gives the deshielding of the C_4-methyl group when the C_6α-equatorial acetoxy group is substituted by a hydroxy or mesylate group.

TABLE 1

Chemical shifts of the C_4-Me (in τ values) in the PMR spectra of the following compounds.

Compound	C_4-Me at	Compd.	C_4-Me at	Compd.	C_4-Me at	
(XIII)	8.12	(II)	8.72	(I)	8.64	(OAc)
(XII)	7.9	(V)	8.50	(III)	8.42	(OH)
(XIV)	7.91	(VI)	8.52	(VIII)	8.43	(OMes)

The Table clearly shows that the C_4-methyl group in dihydronimbin is equatorial. The C_4-carboxylic acid ester is deduced to be axial (4) from the IR bands at 1148 (strongest), 1183 (medium) and 1230 cm^{-1} (weak) in dihydronimbinic acid (X) in carbon disulphide solution.

These conformations at C_4 in dihydronimbin can be accommodated in (a), α-methyl and β-carboxylic ester in a chair conformation of ring A as in (XV), as was originally considered (1), or (b), β-methyl and α-carboxylic ester groups in a boat-like form of ring A as in (XVI). If (XV) represents dihydronimbin, then the C_4-carboxyl group has a 1,3-*cis* diaxial relation with the C_{10}-methyl group. But the PMR spectra in pyridine solution of dihydronimbinic acid (X) and dihydronimbic acid (XI), or that of the C_1-hydroxy derivative of dihydronimbin, m.p. 190°, $(\alpha)_D$ +222° (obtained by reducing dihydronimbin with sodium borohydride) and the corresponding dicarboxylic acid obtained by hydrolysing it, m.p. 183-84°, $(\alpha)_D$ +120° (alc), do not show any downfield shift for the C_{10}-methyl signal in the acids compared to that in their respective esters, as would be expected (2) from the above relationship. Hence ring A of dihydronimbin is not as represented in (XV), and therefore, should be as represented in (XVI). This is strongly supported by the fact that in comparing the spectra in pyridine solution, the C_5-proton signal is found to move downfield by 24 cps in dihydronimbic acid (XI), compared to the same signal in dihydronimbinic acid (X), showing thereby that the C_4-carboxyl group is in a *cis* diaxial relationship (2) with the C_5-proton. Furthermore, the CD curve of nimbin shows a negative cotton effect ($\Delta\varepsilon = -2.18$) in the range of the R- band [and very strongly negative at about 232 mμ ($\Delta\varepsilon = -33$)] which is only consistent (5) with the ring A containing the enone system so twisted, that the C_4 β-substituent is more *quasi*-equatorial than *quasi*-axial. The absolute configuration assigned to nimbin before (1) is independently supported by the rotations (6) of dihydronimbic acid (XI), $(\alpha)_D$ +262° (py) and the C_{28}, C_6-γ-lactone-C_{11}-acid, m.p. 230°, $(\alpha)_D$ +206° (py), obtained by treating (XI) with acetic anhydride and pyridine at room temperature.

The present results are in agreement with the fact that in cedrelone and dihydrocedrelone, which have similar environments in their A/B rings as nimbin and dihydronimbin, ring A is found to exist in a half boat and boat form respectively (7). PMR spectra of cedrelone and its C_6-mesylate, m.p. 172°, $(\alpha)_D$ -30°, show that the C_4 β-*quasi*-equatorial methyl group is shifted downfield by 0.16 and 0.2 τ units respectively, compared to the same signal in cedrelone acetate. In the C_1-hydroxy derivative m.p. 195-96°, $(\alpha)_D$ +196° (8) (obtained by reducing dihydrodesacetyl nimbin (V) with sodium borohydride) also, the C_4 β-methyl group is found deshielded by the C_6 α-hydroxy group by 0.2 τ units compared to the corresponding C_6 α-acetate. It would thus appear that in a normal terpenoid, devoid of a C_3-equatorial hydroxyl group, if the gem dimethyl group or its equivalent at C_4, would have 1,3 *cis* diaxial interactions with the C_{10}-axial methyl group and with an equatorial or equatorial-like substituent at C_6, then the ring A of the compound is likely to exist in a flexible conformation, to get some relief from the non-bonded interactions involved.

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8 All rotations were taken in chloroform solution, and PMR spectra in $CDCl_3$ solution (on a Varian A-60 spectrometer) unless otherwise stated.