Tetrahedron Letters No.27, pp. 3107-3110, 1968. Pergamon Press. Printed in Great Britain.

21,22-α-EPOXY-N-METHYL-SEC.-PSEUDOBRUCINE, AN ALKALOID FROM STRYCHNOS ICAJA BAILL. AN UNUSUAL CASE OF CIS-OPENING OF AN EPOXIDE RING

N.G. Bisset

Institut de Chimie des Substances Naturelles,
91, Gif-sur-Yvette, France*

(Received in UK 18 March 1968; accepted for publication 5 April 1968)

In a previous communication (1) the isolation of vomicine and icajine (N-methyl-sec.-pseudostrychnine) from the mixture of alkaloids present in the leaves of Strychnos icaja Baill. was described.

During chromatography of these leaf bases on an alumina column (activity III), material was eluted with ether/ethanol 97.5:2.5-90:10 which on further chromatography over silica-gel and elution with methylene dichloride/methanol 99:1 finally gave another alkaloid obtained as elongated hexagonal plates (methanol), m.p. 239-241° uncorr., $[\alpha]_D$ + 12° (c 1.09 in chloroform).

In 1953 Jaminet (2) reported the isolation, as the crystalline hydrochloride salt, of an alkaloid C from the leaves of the same plant. A sample of the free base, after purification by preparative thin-layer chromatography on neutral silica-gel plates in the system methylene dichloride/methanol 97:3, yielded a major crystalline fraction which proved to be identical (t.l.c., g.l.c., m.p. and mixed m.p., i.r. and mass spectra) with the base described above.

High-resolution mass measurement of the new alkaloid established its molecular formula as $C_{24}H_{28}N_2O_6$ (M^+ : found 440.1945; required 440.1947).

The u.v. spectrum [$\lambda_{max.}$ (in ethanol) 215.5 (log ε 4.32), 265 (4.05), and 301 (3.87) mμ], which is almost identical with that of brucine, and the i.r. spectrum [$\nu_{max.}$ (in Nujol) 1286, 1400, 1493, and 1655 $cm.^{-1}$] indicate a N_a-acyldihydroindole chromophore.

That the alkaloid belongs to the N-methyl-sec.-pseudobrucine (novacine) series (1) is shown indirectly by the following evidence:

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* Present address: Department of Pharmacy, Chelsea College of Science and Technology, Manresa Road, London, S.W.3.

The intensity of the carbonyl band at 1655 cm.$^{-1}$ relative to the phenyl C = C stretching band at 1493 cm.$^{-1}$ is much greater than that of the corresponding band in the brucine spectrum and suggests the presence of a second carbonyl group.

TABLE 1

N.m.r. signals (δ from TMS as internal standard)

	1-H	4-H	19-N-Me	2- and 3-OMe
Brucine	6.73	7.87	-	3.88, 3.93
Novacine	7.36	7.85	2.04	3.87, 3.90
Epoxynovacine	7.36	7.83	2.00	3.86, 3.88

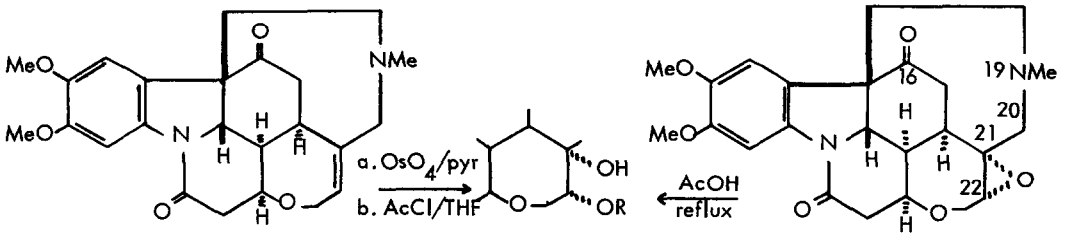
N.m.r. data (Table 1) indicate that this second carbonyl function can be located at C-16, as in novacine. A carbonyl in this position is able to contribute a shielding effect to the N-methyl group, whose signal is therefore found at relatively high field. At the same time, it has a deshielding effect on the C-1 proton, whose signal is found at low field (δ 7.36 as compared with δ 6.73 in the case of brucine which has no 16-carbonyl function); this effect of a 16-oxygen function has already been noted for the 16-alkoxy-strychnines (3) and in the strychnosplendine series (4).

The mass spectrum with "indole" peaks at m/e 190, 203, and 204, and with a M^+ - 59 peak at m/e 381, already noted in the spectra of icajine and vomicine (1), supports the formulation suggested.

Of the six oxygen atoms present in the new alkaloid, two are accounted for by the methoxyl groups, two by the carbonyl groups, and one presumably in a 7-membered ether ring. The remaining oxygen is not present as a hydroxyl or carbonyl function (i.r. and n.m.r. spectra), and the facts that there is one more oxygen present than in novacine and that there is no signal for an ethylenic proton in the n.m.r. spectrum - so that the 21,22-double bond is absent - suggest that an epoxide function could be present.

This was proved to be the case by treatment of the alkaloid with refluxing glacial acetic acid. Separation of the reaction mixture by preparative t.l.c. enabled two products to be isolated - one a hydroxy-acetoxy compound (11b), $C_{26}H_{32}N_2O_8$ [M^+ 500; needles (methanol); m.p. 215-219° uncorr. (decomp.);

$\lambda_{max.}$ (in ethanol) 216.5 (log ε 4.26), 264.5 (4.02), and 301 (3.90) mμ; $\nu_{max.}$ (in Nujol) 1494, 1650, 1708, 3465, and 3680 cm.$^{-1}$] and the other a dihydroxy compound (IIa), $C_{24}H_{30}N_2O_7$ [M^+ 458 ; long needles (methanol); m.p. 258-262° uncorr. (decomp.); $[\alpha]_D$ + 146° (c 1.07 in chloroform); $\lambda_{max.}$ (in ethanol) 217 (log ε 4.25), 263 (4.03), and 300 (3.88)mμ; $\nu_{max.}$ (in Nujol) 1490, 1620, 1663, and 3300 (broad) cm.$^{-1}$] (5). The acetyl group of the hydroxy-acetoxy compound is secondary, as is evident from a 1-proton quartet (J = 6.5 and 2.0 c./sec.) centred at δ 4.86 in the n.m.r. spectrum. Attempted acetylation of this compound led to recovery of the starting material and indicates that the hydroxyl group is probably tertiary. Evidently the grouping present is $-CH_2-CHOH-COH<$ rather than $-CHOH-CHOH-CH<$ and this can be accommodated only at C-21, C-22, and C-23 of the novacine skeleton. The new alkaloid is therefore a 21,22-epoxynovacine.



(I) (IIa) R = H (IIb) R = Ac (III)

This structure was confirmed in the following way: Hydroxylation of the double bond in novacine (I) with osmium tetroxide in pyridine (6) gave 21α,22α-dihydroxy-21,22-dihydronovacine (IIa), by attack from the less hindered rear side (7). Acetylation of the dihydroxy derivative with acetyl chloride in tetrahydrofuran in the presence of anhydrous potassium carbonate afforded the 21α-hydroxy-22α-acetoxy derivative (IIb). Somewhat surprisingly, these two partial-synthetic derivatives proved to be identical (m.p. and mixed m.p., i.r., n.m.r., and mass spectra) with the two compounds obtained from the epoxynovacine. It follows from this identity that the new base must be 21,22-α-epoxynovacine (21,22-α-epoxy-N-methyl-sec.-pseudobrucine) (III).

The treatment with refluxing glacial acetic acid has caused the epoxide ring in (III) to undergo cis-opening, with retention of configuration, rather than the more usual trans-(diaxial)-opening (8). Study of Dreiding models suggests that approach of the OAc^- ion will be difficult from the β-side of the molecule. There will be hindrance not only from the bulk of the cage-like ring system but more particularly from the C-8 hydrogen and from the protonated oxygen of the 7-membered ether ring. On the other hand,

approach from the α-side is less hindered and it would seem that these stereochemical circumstances are the main reason for the cis-opening of this epoxide. Presumably, there will also be anchimeric assistance from the oxygen of the 7-membered ether ring through formation of an intermediate carbonium ion with stabilization of a positive charge on one or other of the carbon atoms of the epoxide ring (the nitrogen atom in the 19-position is probably too far away to acquire even a weak positive charge).

A similar case in which cis-opening of an epoxide ring is brought about by steric factors has been reported by Langlois & Gastambide (9) for the diterpene compound methyl 13, 14-epoxy-anhydrido-maleopimarate.

The writer is indebted to Professor A. Denoël, Liège, for a sample of Jaminet's alkaloid C and to Dr. B.C. Das of this institute for the high-resolution mass measurement.

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It has been reported that hydroxylation with osmium tetroxide may also give rise to a little trans-diol, e.g. in the case of crataegalic acid [R. Tschesche, E. Henckel, & G. Snatzke, Liebigs Annln Chem. 676 : 175 (1964)]. The reaction with novacine, however, proceeds with ease and in excellent yield and there seems to be no reason to doubt that the compound formed is the cis-diol.

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