STUDY OF CONFORMATION OF α-NARCOTINE N-OXIDE AND RELATED COMPOUNDS

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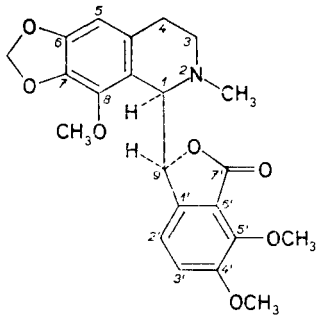
Conformation of quaternary derivatives of (−)-α-narcotine (*I*) in solution was investigated using α-narcotine N-oxide hydrochloride (*IV*) as the model compound. In solution, compound *IV* exists predominantly in the form with torsion angle H—C(1)—C(9)—H of about 270° and with half-chair conformation of the isoquinoline tetrahydropyridine ring.

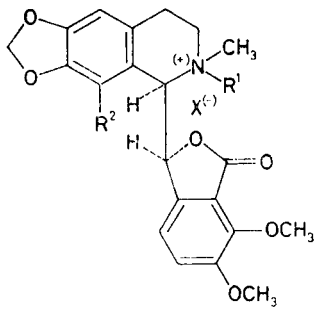
Phthalideisoquinoline alkaloids have found use[1,2] as antitussics ((−)-α-narcotine (*I*), (+)-α-narcotine N-oxide (*II*)) or as antagonists of γ-aminobutyric acid (GABA) ((+)-bicuculline (*III*)). Conformation of these alkaloids and their synthetic analogues was studied from the viewpoint of structure – GABA antagonist activity relationship. The highest activity was observed for compounds of the 1*S*,9*R*-series, particularly (+)-bicuculline[3,4] (*III*). In solution, phthalideisoquinoline alkaloids are conformationally flexible, the phthalide and the isoquinoline parts rotating about the C(1)—C(9) bond[5,6]. It has been found[5] that the mean value of the torsion angle ϑ about the bond H—C(1)—C(9)—H depends on the relative configuration at the C(1) and C(9) atoms, as well as on the substituent at N(2). In (+)-bicuculline (*III*) solution several energetically favourable conformers exist as was experimentally proved by Poolar and Stewards[7]; this agreed with results obtained by gas phase molecular mechanics calculation. In the solid phase, differences were found[8,9] between conformation of the isoquinoline tetrahydropyridine ring in (+)-bicuculline (*III*, absolute configuration 1*S*,9*R*) and (−)-α-narcotine (*I*, absolute configuration 1*R*,9*S*). Less attention was paid to N-oxides or quaternary derivatives of these alkaloids. Studies of physico-chemical properties of (−)-α-narcotine derivatives revealed that the optical rotation values of α-narcotine N-oxide hydrochloride (*IV*; $[\alpha]_D^{20}$ +118°) and α-narcotine N-oxide (*II*; $[\alpha]_D^{20}$ +135°) differ from that of (−)-α-narcotine (*I*; $[\alpha]_D^{20}$ −210°). Such a large difference might be due to different conformation of the compounds in question. We therefore investigated the solution conformation of narcotine N-oxide (*II*) and related compounds by NMR spectroscopy and present the results in this paper.

α-Narcotine N-oxide (*II*) was prepared by oxidation of (−)-α-narcotine (*I*) with *m*-chloroperoxybenzoic acid in chloroform. Treatment of chloroform solution of *II*

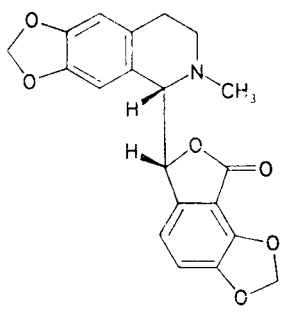
with aqueous hydrochloric acid, followed by concentration of the organic layer, afforded the crystalline hydrochloride *IV*. Whereas this hydrochloride was stable



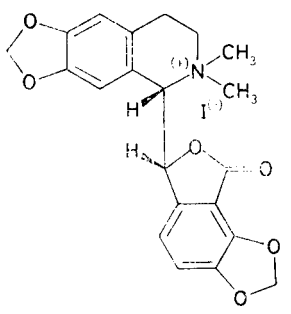
I



II, $R^1 = O^-$; $R^2 = OCH_3$
IV, $R^1 = OH$; $R^2 = OCH_3$; X = Cl
VII, $R^1 = CH_3$; $R^2 = H$; X = I
XI, $R^1 = CH_3$; $R^2 = OCH_3$; X = I

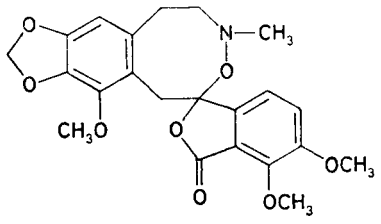


III



VI

both in the solid phase and solution, the N-oxide *II* rearranged readily into benzo-[1,2-*e*]-1,2-benzazocine *V* (ref.[10]). We have therefore paid our attention to the more stable compound *IV* rather than to the N-oxide *II*. In many instances, oxidation



V

of alkaloids at the asymmetric nitrogen atom gave a mixture of stereoisomeric N-oxides. On the basis of two sets of ^{13}C NMR signals it was possible to differentiate some stereoisomeric N-oxides of isoquinoline alkaloids[11,12] without isolating the individual isomers. The presence of only one set of signals in the ^{13}C NMR spectra of both the hydrochloride *IV* and the N-oxide *II* indicates thus the presence of only one stereoisomer. The chemical shifts of carbon signals in the spectra of compounds *II* and *IV*, given in Table I, are practically identical, except the signals of the carbon atoms in positions α and β to the quaternary nitrogen atom N(2). For the compound *II* these signals are shifted 0·6 to 1·0 ppm downfield relative to those for compound *IV*. This behaviour is undoubtedly caused by the difference in inductive effect of the N^+—OH (*IV*) and N^+—O^- (*II*) groupings.

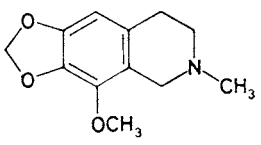
Of phthalideisoquinoline alkaloids, (+)-bicuculline (*III*) was subjected to conformational investigation. Three energy minima, corresponding to torsion angles $\vartheta = 45°$, 170° and 270°, were found[7] in this compound. The structural differences

TABLE I

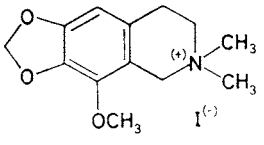
Chemical shifts (δ, ppm) in ^{13}C NMR spectra of compounds *I*, *II* and *IV*

Carbon	*I*	*II*	*IV*
1	60·9	73·9	72·9
3	50·1	59·7	58·8
4	28·1	25·8	25·2
4a	132·2	125·6	125·5
5	102·4	102·3	102·1
6	148·5	150·9	150·8
7	134·1	133·8	133·6
8	141·3	139·6	139·4
8a	120·3	109·1	108·3
9	81·9	75·0	74·6
1′	140·6	139·0	138·5
2·	117·8	119·4	120·0
3′	118·4	119·9	119·9
4′	152·3	152·9	152·7
5′	147·8	147·8	147·5
6′	117·2	117·5	117·1
7′	168·2	166·4	166·2
N(2)–CH_3	46·3	54·7	53·8
OCH_2O	100·8	101·4	101·2
C(8)–OCH_3	59·4	58·6	58·4
C(4′)–OCH_3	55·9	57·0	56·9
C(5′)–OCH_3	62·2	62·2	61·9

between (+)-bicuculline (*III*) and (−)-α-narcotine (*I*) are not so profound to affect principally the conformational behaviour. The temperature dependence of the coupling constant $J(1, 9)$ observed by us in the spectrum of compound *I* (4·10 Hz at 318 K, 3·75 Hz at 253 K), as well as shift of the H-2′ proton signal (6·17 → 6·02 ppm), are analogous to those observed for (+)-bicuculline (*III*) and confirm the presence of several energetically advantageous conformers of the alkaloid *I* in solution. On the other hand, quaternary salts such as bicuculline methiodide (*VI*) exist in solution only in a single conformer with torsion angle close to 270° (ref.[13,14]). As judged from chemical reactions, the same conformation is assumed[15] for β-hydrastinine methiodide (*VII*). The value of the coupling constant $J(1, 9)$ (0·6 Hz) in the spectrum of compound *IV* indicates the presence of a predominating conformer with a torsion angle close to 90° or 270°. Protons of compound *IV* which have substantially different chemical shifts in comparison with those of *I* may be classified into two groups. The first comprise the protons H-1, H-3, H-4 and H-9 the shift of which is influenced predominantly by the $N^+—OH$ grouping in compound *IV*. Analogous changes were also observed with the pair of tetrahydroisoquinoline alkaloids *VIII* and *IX* (Table II). The second group consists of the protons H-2′, C(8)—OCH_3, H-9

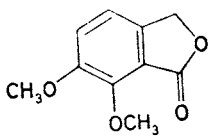


VIII



IX

and H-3′ whose chemical shift is affected mostly by the molecular conformation (torsion angle ϑ and conformation of the tetrahydropyridine ring of the isoquinoline part of the molecule). These protons are subject to different shielding by the benzene rings of the phthalide and isoquinoline parts. The anomalously low shift of the C(8)—OCH_3 signal (3·27) in *IV* relative to that (δ = 4·04 ppm) for compound *I* is caused by shielding by the phthalide benzene ring which can manifest itself only when the torsion angle is about 270° but not about 90°. A more marked difference was observed for the H-2′ proton signal. For the ϑ value of +40 to +50°, assumed[6] for the predominating conformer of compound *I*, the H-2′ signal occurs at δ = = 6·07 ppm and is shielded by the benzene ring of the isoquinoline part. The un-



X

shielded equivalent proton of the phthalide *X* resonates at $\delta = 7{\cdot}24$ ppm. The shift to $\delta = 8{\cdot}05$ ppm in the spectrum of compound *IV* is explained by the absence of the shielding by the benzene ring, and the presence of steric interaction with the nitrogen atom in the N^+—OH grouping or with the C(1) carbon atom at $\vartheta = 270°$. A further proof in favour of this conformation has come from the NOE experiment[16] (Table III). Irradiation of the C(8)—OCH_3 protons resulted in NOE on the H-3′ and H-2′ protons which is possible only when the torsion angle ϑ is close to 270°; analogously, the increased intensity of the H-2′ signal (9·9%) after irradiation of H-1 supports the assumption of this conformation. The relatively rigid structure of compound *IV* is also manifested by the distinctly resolved signals of the tetrahydropyridine ring. In the spectra of compounds *VIII* and *IX* the signals of the axial and equatorial protons H-3 and H-4 are averaged. A partial flexibility of this part of the molecule

TABLE II

Chemical shifts (δ, ppm) in ^{1}H NMR spectra of compounds *I*, *II*, *IV*, *VIII*, *IX* and *XI*

Proton	*I*[a]	*II*[a]	*IV*[a]	*VIII*[a]	*IX*[a]	*XI*[a]
1	4·40	5·75	6·32	3·44	4·57	6·13
3*ax*	2·60	4·25	4·25	2·60	4·09	4·05
3*eq*	2·30	3·90	3·90	2·60	4·09	3·90
4*ax*	1·92	3·13	3·19	2·79	3·15	3·13
4*eq*	2·40	3·45	3·44	2·79	3·15	3·40
5	6·31	6·36	6·36	6·30	6·40	6·35
9	5·57	6·56	6·55	—	—	6·27
2′	6·07	7·71	8·05	—	—	8·11
3′	6·95	7·35	7·36	—	—	7·32
C(8)–OCH_3	4·04	3·31	3·27	3·97	4·05	3·50
C(4′)–OCH_3	3·86	3·92	3·92	—	—	3·90
C(5′)–OCH_3	4·09	3·98	3·98	—	—	3·92
N(2)–CH_3	2·55	3·60	3·71	2·46	3·58	3·45 (*ax*) 4·20 (*eq*)
OCH_2O	6·06	5·86 5·83	5·82 5·85	5·84	5·94	5·84 5·78
N^+(2)–OH	14·20	—	—	—	—	—

[a] Coupling constants *J*(H, H) in Hz. *I*: (1, 9) = 4·1; (9, 2′) = 0·7; (2′, 3′) = 8·4; OCH_2O = 1·3. *II*: (1, 9) < 1; (3*ax*, 3*eq*) = 13; (3*ax*, 4*eq*) = 8; (3*eq*, 4*eq*) = 1; (3*ax*, 4*ax*) = 11; (3*eq*, 4*ax*) = 8·5; (4*eq*, 4*ax*) = 18; (2′, 3′) = 8·4; OCH_2O = 1·4. *IV*: (first order approximation) (1, 9) = 0·6; (1, 3*eq*) = 2·1; (3*eq*, 3*ax*) = 12·8; (3*ax*, 4*ax*) = 11·1; (3*ax*, 4*eq*) = 7·8; (3*ax*, N–CH_3) = 0·7; (3*eq*, 4*ax*) = 8·7; (3*eq*, 4*eq*) = 1·0; (4*ax*, 4*eq*) = 18·2; (4*ax*, 5) = 1·0; (4*eq*, 5) < 1; (2′, 3′) = 8·1; (9, 2′) = 0·9; OCH_2O = 1·4. *VIII*: (3, 4) = 5·7. *IX*: (3, 4) = 6·6. *XI*: (1, 9) < 1; (2′, 3′) = 8·2; OCH_2O = 1·3.

causes probably the diffuse character of the corresponding proton signals in the spectrum of (−)-α-narcotine (*I*) in chloroform. Conformation of the tetrahydropyridine ring in the isoquinoline part of *IV* could be determined on the basis of NOE effects: irradiation of H-9 resulted in NOE at 4·25 ppm (H-3*ax*) and irradiation of N(2)—CH_3 increased the signal at 3·19 ppm (H-4*ax*). Combination of these facts with the values of corresponding coupling constants of the H-3 and H-4 protons proves the existence of a half-chair conformation of the tetrahydropyridine ring in which both the N-methyl group and the phthalide moiety are in the axial position. The fine splitting of the H-3*ax* and H-3*eq* proton signal reflects four-bond coupling with the N(2)—CH_3 protons and the H-1 proton, respectively. The first coupling (0·7 Hz) is due to the diaxial arrangement of the N(2)—CH_3 group and the H-3*ax* proton, the second one (2·1 Hz) due to the W-arrangement of the H-3*eq* and H-1 atoms. The conformation of compound *IV*, based on all results discussed so far, is depicted in Fig. 1. Since the coupling constants $J(1, 9) < 1$ Hz have also been found for compounds *II* and *XI*, and chemical shifts of the H-2′ and C(8)—OCH_3 protons, as well as other ^{1}H NMR parameters are analogous to the above-discussed

TABLE III

^{1}H–^{1}H NOE (%) in the spectrum of compound *IV*

Proton irradiated	Proton observed									
	2′	3′	1	9	3*ax*	3*eq*	4*ax*	4*eq*	C(8)–OCH_3	N(2)–CH_3
H-1	9·9	[a]	—	5·8	—	—	—	—	[b]	1·3
H-1′	3·5	[a]	4·0	—	4·6	[a]	—	—	—	—
N(2)–CH_3	[a]	—	10·7	[a]	—	1·5	4·3	[a]	—	—
C(8)–OCH_3	2·2	2·3	[b]	—	—	—	—	—	—	—

[a] Negative NOE < 1%; [b] NOE < 1%.

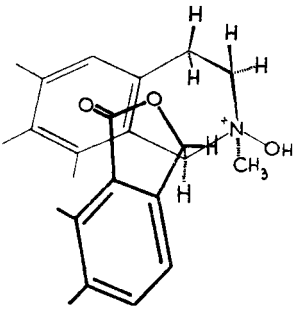


FIG. 1

Conformation of α-narcotine N-oxide hydrochloride (*IV*)

data for compound *IV*, we justifiably assume that also compounds *II* and *XI* have the same conformation as the compound *IV*.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Optical rotation was measured in chloroform on a Perkin–Elmer 141 instrument, IR spectra were recorded with a Perkin–Elmer 983 spectrometer, mass spectra were obtained with a Jeol JMS 100D instrument. NMR spectra were measured on a Bruker AM-300 spectrometer (FT, 300·13 MHz for ^{1}H). The spectra were taken in deuteriochloroform with tetramethylsilane as internal standard. Measurement parameters: spectral width 4 500 Hz, pulse width 45°, repetition time 3·5 s, digital resolution 0·15 Hz/point. Prior to the differential ^{1}H–^{1}H NOE experiment[16], the sample of *IV* was degassed by several freeze-thaw cycles and in the last cycle the space above the sample was filled with argon. Concentration of the solution was 0·05 mol l^{-1}, total volume 0·45 ml. The amplitude $\gamma B_2/2\pi$ of the decoupler radiofrequency field for presaturation was 2·4 Hz, presaturation time 8 s. Acquisition time 7 s, digital resolution 0·05 Hz, total number of scans in one experiment 160.

Oxidation of (−)-α-Narcotine (*I*)

A solution of (−)-α-narcotine (*I*; 3 g) in chloroform (50 ml) was mixed with *m*-chloroperoxybenzoic acid (1·6 g). The reaction was monitored by TLC on Silufol in chloroform–ethanol (19 : 1). After stirring for 1 h, the reaction mixture was washed with aqueous solution of sodium carbonate, water and 1% aqueous hydrochloric acid. The chloroform phase was dried, concentrated and the residue crystallized from benzene–acetone (1 : 1) to give 2·6 g of crystalline product *IV*, m.p. 195°C (decomp.). IR spectrum (KBr): 3 400, 1 767, 1 615, 1 600, 1 499 cm^{-1}. Mass spectrum, *m/z* (%): 430 (5), 413 (7), 380 (6), 370 (17), 221 (15), 220 (100), 208 (10), 206 (9), 192 (8), 190 (18). For $C_{22}H_{23}NO_8$.HCl (465·9) calculated: 56·72% C, 5·19% H, 3·01% N, 7·61% Cl; found: 56·69% C, 5·20% H, 3·01% N, 7·61% Cl.

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