Structure of Dibromoticonine, a Bromination Product of Nicotine

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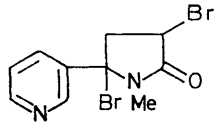
The fate of the pyrrolidine ring of nicotine on its oxidative bromination to dibromoticonine has been re-examined. From chemical and spectral (including ^{13}C n.m.r.) properties dibromoticonine is now established as 3,4-dibromo-5-hydroxy-1-methyl-5-(3-pyridyl)-Δ^3-pyrrolin-2-one. The bromine atoms can be selectively replaced by hydrogen under proper reductive conditions to give the isomeric monobromoticonines.

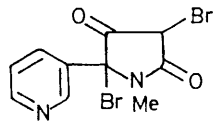
PINNER [1] showed that two different crystalline products could be obtained on oxidative bromination of nicotine. The compound which he called dibromocotinine and to which he assigned structure (I) has found use as an intermediate in the chemical synthesis of the nicotine metabolite continine.[2] The other product was called dibromoticonine and given structure (II). It likewise has synthetic utility; on catalytic hydrogenation [3] it forms 5-hydroxycotinine [the cyclic form of γ-(3-pyridyl)-γ-oxo-*N*-methylbutyramide], an important intermediate in the biological degradation of nicotine.[4] The structures assigned by Pinner remained unchallenged until recently, even though the evidence leading Pinner to his assignments was rather fragmentary. Both an n.m.r.[5] and a mass spectral study [6] of dibromocotinine have recently shown its correct structure to be (III). The present paper reports a more drastic revision of the structure of dibromoticonine.

Bromination of nicotine in hydrobromic acid at 100° gave crystalline dibromoticonine hydrobromide; [1] dissolution in sodium hydroxide followed by neutralization with acetic acid provided the free base, having the expected analytical figures and m.p. Pinner degraded dibromoticonine with strong base to nicotinic acid, methylamine, and malonic acid; we have obtained similar results, although, as will be seen, little structural information is provided by the degradation.

The solubility of dibromoticonine in base suggests that one oxygen atom may be present in a hydroxy-group. The pK_a of the compound in 70% ethanol is 10·4. The i.r. spectrum showed extensive absorption in the 3000—2500 cm^{-1} region, as expected for a hydroxy-group involved in strong hydrogen bonding, and this



(I)



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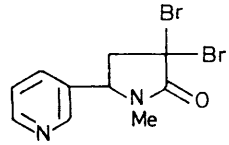

(III)

was confirmed by the formation of *O*-methyl (IV) and *O*-acetyl (V) derivatives. Intense carbonyl absorption at 1710 cm^{-1} confirmed the presence of a lactam function.

Pinner removed one bromine atom from the dibromoticonine molecule by reduction with zinc in potassium hydroxide, to give a compound (isolated as the hydrochloride) which he named monobromoticonine (VI). We repeated this reaction satisfactorily, obtaining the free base. However, reduction with zinc in an acidic

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[1] A. Pinner, *Ber.*, 1892, **25**, 2807; 1893, **26**, 292; *Arch. Pharm*, 1893, **28**, 378.
[2] H. McKennis, jun., L. B. Turnbull, and E. R. Bowman, *J. Amer. Chem. Soc.*, 1958, **80**, 6597; E. R. Bowman and H. McKennis, jun., *Biochem. Prep.*, 1963, **10**, 36.
[3] H. McKennis, jun., E. R. Bowman, L. D. Quin, and R. C. Denney, in preparation.
[4] R. H. Meacham, jun., E. R. Bowman, and H. McKennis, jun., *J. Biol. Chem.*, 1972, **247**, 902.
[5] L. D. Quin and P. M. Quan, unpublished results.
[6] A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1965, **87**, 2926.

medium led to the isolation of an isomeric monobromo-compound (VII). The existence of these two isomers suggested that the bromine atoms in dibromoticonine were on different carbon atoms. The i.r. spectra of the isomers retained the features for the oxygen functions found in dibromoticonine.

The n.m.r. spectrum of dibromoticonine in [$^2H_6$]dimethyl sulphoxide was simple, consisting of a singlet for the *N*-methyl group, pyridine ring signals at δ 7·7—9·4, and a hydroxylic proton signal (removed by deuterium oxide) at δ 8·15. The n.m.r. spectra of the isomeric monobromoticonines were similar (Table 1),

TABLE 1

^{1}H N.m.r. data [a]

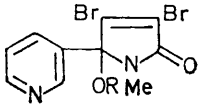
Compound	Pyridine protons	NMe [b] protons	OH [c]	Other
(VIII)	7·7—9·4	3·1	8·15	
(VI)	7·8—9·3	3·0	8·4	7·13 [b] (C=CH–C=O)
(VII)	7·5—9·2	3·0	8·0	7·64 [b] (CH=C–C=O)
(IV)	7·7—9·4	3·1		3·65 [b] (OMe)
(V)	7·3—9·1	2·8		2·25 [b] (OMe)

[a] δ Values (solvent anhydrous [$^2H_6$]dimethyl sulphoxide) determined on a Varian A-60 spectrometer with tetramethylsilane as external reference. Peak areas corresponded to the assigned features. [b] Singlet. [c] Singlet, sensitive in position to traces of water in the solvent.

but each possessed an additional signal, a singlet in the olefinic region. This implies that the bromine atoms in dibromoticonine are attached to the carbon atoms of a double bond.

U.v. spectra for the three bromo-compounds showed the expected absorption at 262 nm characteristic of the pyridine ring. A second, stronger peak appeared at 225 for dibromoticonine and 218 nm for the monobromoticonines. This absorption supports the placement of the double bond in conjugation with the carbonyl group.[7]

All these observations agree with the hypothesis that dibromoticonine is 3,4-dibromo-5-hydroxy-1-methyl-5-(3-pyridyl)-Δ^3-pyrrolin-2-one (VIII).

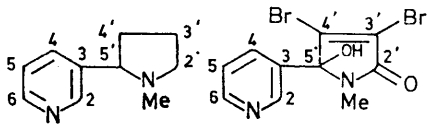


(VIII) R = H
(IV) R = Me
(V) R = Ac

The ^{13}C n.m.r. spectrum (Table 2) confirmed this structure. Assignment of the unsubstituted pyridine ring carbon signals was straightforward, since the chemical shifts were nearly the same as in nicotine.[8] The *N*-methyl and amide carbonyl signals were also easily recognized from their very high [9a] and low [9b] field positions, respectively. The olefinic carbon atoms of the five-membered ring are assigned to signals at 70·9 and 59·2 p.p.m. These signals are clearly in the sp^2-carbon region, but are subject to two additional

TABLE 2

^{13}C N.m.r. data [a] for nicotine [b] and dibromoticonine [c]

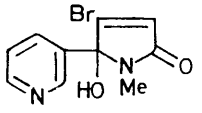


Carbon		
2	43·7	42·2
3	54·2	47·0
4	58·5	56·8
5	69·9	67·8
6	44·7	44·3
2′	136·7	28·0
3′	170·8	70·9
4′	158·1	59·2
5′	124·8	99·7
N·CH_3	153·3	167·0

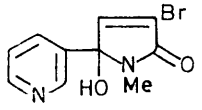
[a] P.p.m. upfield from CS_2. [b] Ref. 8. [c] In methanol–chloroform (*ca.* 3:2 v/v). The position of the carbonyl signal is particularly dependent on the solvent; in pure methanol, it appears at 21·4 p.p.m.

influences. The 'heavy-atom' effect of bromine [9c] causes an upfield shift relative to unsubstituted carbon, but that carbon atom β to the carbonyl is also deshielded as a result of the conjugation.[9d] It is therefore assigned to the signal at 59·2 p.p.m. The saturated carbon atom of the five-membered ring resonates at 99·7 p.p.m.; the shift in position from that in nicotine (124·8 p.p.m.) is a consequence of the presence of hydroxy- and olefinic substituents. The signal due to the pyridine ring carbon atom to which it is attached is also downfield (7·2 p.p.m.) relative to that in nicotine. Peak intensities were consistent with the assignments; signals attributed to carbon atoms lacking a proton are of lower intensity since they are not enhanced by the nuclear Overhauser effect.

The ^{1}H n.m.r. spectra of the monobromoticonines provided a basis for their structure assignment. The isomers differ in that one has a proton on the α-carbon atom of the αβ-unsaturated system, while the other has



(VI)

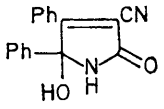


(VII)

the proton on the β-carbon. The olefinic proton of the latter structure should be more deshielded.[10] The monobromoticonine from zinc reduction in acid medium (δ 7·64) can therefore be assigned structure (VII), with the isomer from the basic reduction (δ 7·13) given structure (VI).

[7] D. H. Williams and I. Fleming, 'Spectroscopic Methods in Organic Chemistry,' McGraw-Hill, London, 1966, p. 26.
[8] W. O. Crain, jun., W. C. Wildman, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1971, **93**, 990.
[9] G. C. Levy and G. L. Nelson, 'Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley, New York, 1972, (*a*) p. 52; (*b*) p. 120; (*c*) p. 62; (*d*) p. 66.
[10] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969, 2nd edn., p. 184.

The 5-hydroxy-Δ^3-pyrrolin-2-one ring system established for dibromoticonine and the two monobromoticonines is unusual but not without precedent. It is known, for example, in the products from base-catalysed condensation of derivatives of acetamides and α-diketones [11,12] [*e.g.* (IX) from cyanoacetamide and benzil [12]]. Compound (IX), as well as some other



(IX)

hydroxy-lactams [13] (pseudoamides), possesses an acidic hydroxy-group.[11] A specimen of (IX) prepared in the present study had broad complex i.r. absorption (3200—2500 cm^{-1}) for the hydroxy-group similar to that observed for compounds (VI)—(VIII).

EXPERIMENTAL

3,4-Dibromo-5-hydroxy-1-methyl-5-(3-pyridyl)-Δ^3-pyrrolin-2-one (*Dibromoticonine*) (VIII).—A solution of nicotine (20 g, 0·12 mol) and aqueous 20% hydrobromic acid (50 ml) was prepared at 0° in a flask fitted with a cold-finger reflux condenser containing ice. Bromine (50 g, 0·31 mol) pre-chilled to 0° was cautiously added. A preheated oil-bath (130°) was then placed around the flask; with rapid stirring a homogeneous red solution resulted within 5 min. After 25 min, the solution was allowed to cool and poured into water (20 ml). The dibromoticonine hydrobromide (10·8 g, 24%) that crystallized was dissolved in 10% sodium hydroxide solution; crude dibromoticonine precipitated on neutralization with 10% acetic acid. Crystallization from 70% ethanol gave white needles, m.p. 200—201° (lit.,[1] 196°); $\nu_{max.}$ (KBr) 3000—2500 (OH) and 1710 cm^{-1} (C=O); $\lambda_{max.}$ (95% EtOH) 225 (ε 13,200) and 262 nm (4520) (Found: C, 34·7; H, 2·25; Br, 45·9; N, 8·0. Calc. for $C_{10}H_8Br_2N_2O_2$: C, 34·5; H, 2·3; Br, 45·95; N, 8·05%). The *methiodide*, prepared in refluxing methanol (20 h) and recrystallized from ethanol–ethyl acetate, had m.p. 245—247° (decomp.) (Found: C, 27·2; H, 2·5; N, 5·6. $C_{11}H_{11}Br_2IN_2O_2$ requires C, 27·0; H, 2·3; N, 5·7%). The *picrate* of the quaternary salt was prepared in ethanol and recrystallized from dimethylformamide; m.p. 259° (decomp.) (Found: C, 34·6; H, 2·4; N, 12·1. $C_{17}H_{13}Br_2N_5O_9$ requires C, 34·5; H, 2·2; N, 11·9%).

Reduction of Dibromoticonine with Zinc and Acid.—Dibromoticonine (5·0 g) was dissolved in acetic acid (50% v/v; 62 ml) and concentrated hydrochloric acid (3 ml) was added. The mixture was stirred in an ice-bath while zinc dust (5 g) was added in portions during 2 h. Unchanged zinc was filtered off. The pale-yellow filtrate was adjusted to pH 9 with concentrated ammonium hydroxide and extracted four times with chloroform (100 ml total). The combined extracts were dried ($MgSO_4$) and concentrated; the oily residue was dissolved in acetone (10 ml). The solution was cooled in ice–water to obtain crystalline *3-bromo-5-hydroxy-1-methyl-5-(3-pyridyl)-Δ^3-pyrrolin-2-one*, (VII), m.p. 173·5—174·5° (decomp.) (from acetone); $\nu_{max.}$ (KBr) 3000—2500 (OH) and 1695 cm^{-1} (C=O); $\lambda_{max.}$ (95% EtOH) 218 (ε 12,750) and 262 nm (3760) (Found: C, 44·7; H, 3·5; Br, 29·7; N, 10·4. $C_{10}H_9BrN_2O_2$ requires C, 44·6; H, 3·4; Br, 29·7; N, 10·4%). The *picrate*, prepared in and recrystallized from ethanol, had m.p. 181—182° (decomp.) (Found: C, 38·7; H, 2·7; N, 14·0. $C_{16}H_{12}BrN_5O_9$ requires C, 38·6; H, 2·4; N, 14·1%).

Reduction of Dibromoticonine with Zinc and Base.—Dibromoticonine (5·0 g) was added to 15% potassium hydroxide (45 ml) at 0°, and the solution was treated with zinc dust (5 g) during 3 h. After an additional 2 h stirring, unchanged zinc was filtered off. The filtrate was treated with carbon dioxide, and the precipitate was filtered off. The filtrate was placed on a Dowex 21K (OH^-) column (3 × 20 cm), which was then washed with water until the eluate was neutral. A Koenig-positive [2] eluate was obtained by treating the column with M-acetic acid. The residue from evaporation of the eluate was dissolved in propan-2-ol (20 ml); addition of n-hexane (200 ml) precipitated some flocculent material which was removed. The filtrate was concentrated to an oil, which was dissolved in chloroform (15 ml). The solution was placed on a column (2 × 17 cm) of acid-washed alumina (packed with the aid of ether). The column was treated with ether (*ca.* 300 ml) and then methanol–ethanol (5 : 95 v/v; 200 ml). The latter eluate was concentrated to a residual mass which became partially crystalline. This was dissolved in hot acetone (10 ml) and then cooled in ice–water. The resultant crystals of *4-bromo-5-hydroxy-1-methyl-5-(3-pyridyl)-Δ^3-pyrrolin-2-one* (VI) were recrystallized from acetone; m.p. 150—153° (decomp.); $\lambda_{max.}$ (95% EtOH) 217 (ε 14,500) and 262 nm (4030) (Found: C, 44·8; H, 3·5; Br, 29·2; N, 10·5. $C_{10}H_9BrN_2O_2$ requires C, 44·6; H, 3·4; Br, 29·7; N, 10·4%). The *picrate* had m.p. 215—216° (decomp.) (from ethanol) (Found: C, 38·4; H, 2·5; N, 14·2. $C_{16}H_{12}BrN_5O_9$ requires C, 38·6; H, 2·4; N, 14·1%).

Methylation of Dibromoticonine.—Dibromoticonine (3·48 g, 0·01 mol) was dissolved in water (15 ml) containing sodium hydroxide (1 g), and the solution was cooled to 5°. Dimethyl sulphate (1·3 g, 0·01 mol) was added, and the mixture was stirred for 30 min at 5°, then left to attain room temperature during 2 h. The precipitate was filtered off and dried (0·52 g, 15%). Recrystallization from methanol gave *3,4-dibromo-5-methoxy-1-methyl-5-(3-pyridyl)-Δ^3-pyrrolin-2-one* (IV), m.p. 156—157° (Found: C, 36·6; H, 2·8; N, 7·6. $C_{11}H_{10}Br_2N_2O_2$ requires C, 36·5; H, 2·8; N, 7·7%). The same product was formed in nearly quantitative yield from dibromoticonine (1 g in 20 ml of absolute ethanol) and ethereal diazomethane.

Acetylation of Dibromoticonine.—A solution of dibromoticonine (1·0 g) in pyridine (10 ml) was treated with acetic anhydride (10 ml). After 24 h at room temperature, the solution was cooled in an ice-bath and then treated with methanol (*ca.* 25 ml). The residue from evaporation was dissolved in boiling ethanol (*ca.* 10 ml); the solution was cooled, and the product (0·94 g, 84%) was recrystallized from ethanol, methanol, and finally acetone to give *5-acetoxy-3,4-dibromo-1-methyl-5-(3-pyridyl)-Δ^3-pyrrolin-2-one* (V), m.p. 182—185° (decomp.) (Found: C, 37·1; H, 2·8; N, 7·0. $C_{12}H_{10}Br_2N_2O_3$ requires C, 37·0; H, 2·6; N, 7·2%).

[11] P. C. Jocelyn and A. Queen, *J. Chem. Soc.*, 1957, 4437.
[12] E. G. Howard, R. V. Lindsey, jun., and C. W. Theobald, *J. Amer. Chem. Soc.*, 1959, **81**, 4355.
[13] R. E. Lutz and F. B. Hill, jun., *J. Org. Chem.*, 1941, **6**, 175.

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