

PREPARATION AND REACTIONS OF SOME SUBSTANCES
WITH PROTOBERBERINE SKELETON

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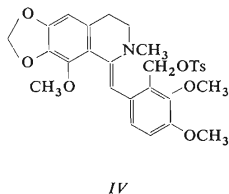
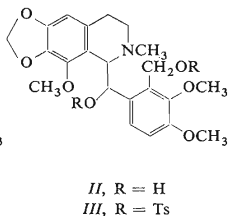
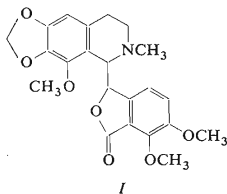
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α -Narcotinediol (*II*) has been converted into N-methyl-13,14-didehydro-1-methoxycanadinium *p*-toluenesulphonate (*VII*) which on refluxing with sodium iodide in acetic anhydride affords 5,8-dihydro-9,10-dimethoxy-13-methyl-6*H*-benzo[*g*]-1,3-dioxolo[7,8] benzopyrano [3,4,5-*ij*]-quinolizinium iodide (*X*). In acetic acid, in the presence of sodium iodide, the didehydro derivative (*VII*) gives rise to 1-methoxyberberinium iodide (*XIV*).

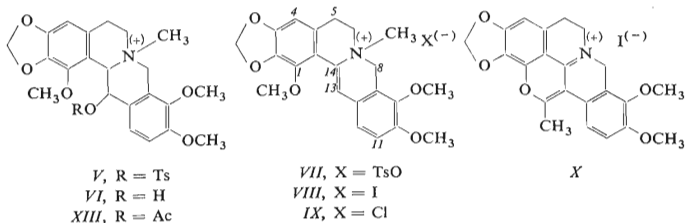
In a preliminary communication¹, the structure of the substance *X*, prepared *via* a three step synthesis from α -narcotine (*I*) has been reported. Reduction of α -narcotine (*I*) with sodium dihydro-bis(2-methoxyethoxy)aluminum² afforded α -narcotinediol (*II*). Tosylation of diol *II* with *p*-toluenesulphonyl chloride in pyridine and following basification with ammonia yielded³ the di-*p*-toluenesulphonyl ester *III*. Kame-tani and coworkers⁴ reported the product of tosylation of diol *II* in benzene in the presence of triethylamine to be substance *IV*.

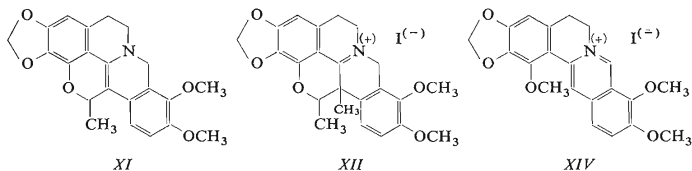
Reproduction of the procedure according to paper³ gave a substance whose elemental analysis was not in accord with structure *III*. The PMR spectrum of this substance shows the presence of 32 protons. The singlet at 2.27 p.p.m. (3 H) corresponds to the methyl at the aromatic nucleus and, together with the AA'BB' system of the aromatic protons (6.97 and 7.47 p.p.m., $J_{ortho} = 8.0$ Hz) (4 H), it is attributable to one *p*-toluenesulphonyl residue in the molecule. The singlet at 3.17 p.p.m. (3 H) is assignable to the $\text{CH}_3\text{—N}^+$ group (the quaternary character of this substance has also been confirmed by its reaction⁵ with silver oxide). The multiplets at 2.9–3.3



(2 H) and 3.7–4.1 p.p.m. (2 H) are attributable to the $\text{Ar}-\text{CH}_2-\text{CH}_2-\text{N}^{(+)}$ fragment and the signals at 3.70, 3.82, and 3.95 p.p.m. to three methoxyl groups. The two doublets of the AB system at 4.57 and 5.30 p.p.m. with $J = 7.5$ Hz correspond to the $-\text{CH}(\text{N}^{(+)})-\text{CH}(\text{O})$ -grouping, the broad singlet at 4.90 p.p.m. (2 H) to the $\text{Ar}-\text{CH}_2-\text{N}^{(+)}$ protons, and the quartet at 5.90 p.p.m. (2 H) with $J_{\text{gem}} = 1.1$ Hz to the methylenedioxy group. The other signals in the spectrum (6.25 s, 1 H, 6.83 d, and 7.20 d with $J_{\text{ortho}} = 8.0$ Hz, 2 H) are attributable to aromatic protons. From that follows that the obtained product should be ascribed structure *V*. On refluxing with 1M-HCl (2 h), the substance *V* did not change. Alkaline hydrolysis of this substance gave, however, a quaternary chloride which was identical with N-methyl-1-methoxy-13-hydroxycanadinium chloride⁶ (*VI*). Tosylation of the compound *VI* afforded again the quaternary monotosyl derivative *V*.

Heating of the substance *V* with acetic anhydride results in elimination of the *p*-toluenesulfonyl group and formation of N-methyl-13,14-didehydro-1-methoxycanadinium *p*-toluenesulphonate (*VII*). The latter has been converted into the quaternary iodide *VIII*. This compound is identical with the iodide prepared from the chloride⁷ *IX*. Heating of substance *VII* with acetic anhydride in the presence of sodium iodide affords a quaternary iodide $\text{C}_{22}\text{H}_{20}\text{INO}_5$. The UV spectrum of this substance (Fig. 1) does not resemble the spectra⁸ of the so far known protoberberine derivatives. In the PMR spectrum, the two triplets at 3.27 (2 H) and 4.05 p.p.m. (2 H) ($J = 7.0$ Hz) are attributable to the $\text{Ar}-\text{CH}_2-\text{CH}_2-\text{N}^{(+)}$ grouping and the singlet at 5.00 p.p.m. (2 H) to the $\text{Ar}-\text{CH}_2-\text{N}^{(+)}$ fragment; the signal of the methylenedioxy group appears at 6.25 p.p.m. The singlet at 6.95 p.p.m. and the two doublets of the AB system with $J_{\text{ortho}} = 9.0$ Hz at 7.05 and 7.32 p.p.m. are ascribed to the aromatic protons. In comparison with the substance *VII*, the spectrum of the quaternary iodide $\text{C}_{22}\text{H}_{20}\text{INO}_5$ exhibits only two signals of methoxyl groups (3.93 and 3.96 p.p.m.) but not a signal corresponding to the $\text{CH}_3-\text{N}^{(+)}$ group. Moreover, this spectrum exhibits a singlet of the olefinic methyl at 2.88 p.p.m. which is deshielded by the electronegative atom attached to the same carbon. On the basis of the above mentioned facts, structure *X* has been assigned to the obtained quaternary iodide.





Reduction of the iodide *X* with sodium borohydride in methanol afforded the tertiary amine $C_{22}H_{21}NO_5$. The proposed structure *XI* is consistent with its UV (Fig. 1) and PMR spectra: the doublet at 1.47 p.p.m. (3 H) and the quartet at 5.43 p.p.m. (1 H) with $J = 7.0$ Hz correspond to the $CH_3-CH(O)$ grouping. The unresolved multiplet in the region from 2.4 to 3.3 p.p.m. is attributable to the $Ar-CH_2-CH_2-N$ protons and two singlets at 3.82 and 3.85 p.p.m. relate to the methoxyl groups. The protons of the $Ar-CH_2-N$ group appear in the spectrum as two doublets of the AB system at 4.02 and 4.48 p.p.m. with $J_{gem} = 15.0$ Hz. The singlet at 6.23 p.p.m. (1 H) and the two doublets at 6.52 and 6.73 p.p.m. (2 H) with $J_{ortho} = 9.0$ Hz are assignable to the aromatic protons. The protons of the methylenedioxy group appear as two doublets at 5.87 and 5.93 p.p.m. with $J_{gem} = 1.0$ Hz. We did not succeed to reduce the stilbene double bond in the substance *XI* neither with excess of sodium borohydride nor with formic acid.

Methylation of the amine *XI* with methyl iodide gave a quaternary iodide of the empirical formula $C_{23}H_{24}INO_5$; the chemical shift of the singlet of the methyl group (1.72 p.p.m.) in its PMR spectrum excludes the presence of the methyl on the quaternary nitrogen atom and indicates that methylation takes place in the β -position of the enamine system thus giving rise to the compound *XII*.

Reaction of the quaternary tosylate *V* with acetic anhydride and sodium iodide yielded the quaternary iodide *XIII* and the compound *X*. Since the substance *X* also arises from the compound *VII*, enamine *VIII* is an intermediate product which arises

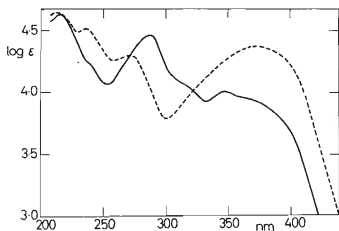


FIG. 1
Ultraviolet Spectra of the Substance *X* (—) and the Substance *XI* (----) in Ethanol

during formation of the substance *X* from the quaternary chloride *V*. Consequently, in acetic anhydride, in the presence of sodium iodide, selective cleavage of the methoxyl group at $C_{(1)}$ and acetylation in the β -position of the enamine grouping take place. Closure of the pyrane ring occurs after enolization of the acetyl group at $C_{(13)}$ which causes a shift of the double bond from the positions 13, 14 to 14, 7 under simultaneous cleavage of the $N^{(+)}-CH_3$ group.

Selective cleavage of the methoxyl group at $C_{(1)}$ does not take place when the reaction of the quaternary tosylate *VII* with sodium iodide is carried out in glacial acetic acid. This reaction gives only rise to demethylation of the original substance at the nitrogen atom under formation of 1-methoxyberberinium iodide (*XIV*). We assume that the primary product of the reaction is a tertiary amine which oxidizes very easily during isolation. This phenomenon has already been observed⁷ earlier during demethylation of the substance *IX* with sodium *p*-methylphenylthiolate. 1-Methoxyberberinium iodide (*XIV*) was also obtained by heating *N*-methyl-1-methoxy-13-hydroxycanadinium chloride (*VI*) with sodium iodide in glacial acetic acid.

EXPERIMENTAL

The melting points have been determined on a Kofler-block and are uncorrected. The PMR spectra were measured on a Varian T-60 in 5% w/v concentration with tetramethylsilane as internal standard, the chemical shifts are given in δ -values (p.p.m.). The UV spectra were measured on a spectrophotometer Unicam SP-700 in 95% ethanol, the IR spectra on an Infracan H-900 in KBr tablets, the mass spectrum on a G.E./A.E.I. MS-9. The solutions of the substances in organic solvents were dried over anhydrous sodium sulphate.

α -Narcotinediol (*II*)

The substance was prepared by reduction of α -narcotine (*I*) with sodium dihydro-bis(2-methoxyethoxy)aluminat in 91% yield, m.p. 133–134°C (ethyl acetate-ether) (ref.⁹ m.p. 135°C). $[\alpha]_D^{25} +64^\circ \pm 3^\circ$ (c 0.80 in chloroform).

α -13-*p*-Toluenesulphonyloxy-2,3-methylenedioxy-1,9,10-trimethoxy-5,6,13,14-tetrahydro-8*H*-dibenzo[*a,g*]-*N*-methylquinolizidinium Chloride (*V*)

To a solution of α -narcotinediol (*II*) (4.17 g, 0.01 mol) in pyridine (25 ml) was added in portions *p*-toluenesulphonyl chloride (3.8 g, 0.02 mol) at 0°C. The mixture was left standing overnight at room temperature, made alkaline with concentrated ammonia, and the solvent evaporated *in vacuo*. The residue was dissolved in water and extracted with chloroform. After concentration of the extract, the product was precipitated with ether. Repeatedly carried out precipitation gave 3.6 g (61%) of the substance *V*, m.p. 142–143°C, $[\alpha]_D^{25} -101^\circ \pm 2^\circ$ (c 0.89 in chloroform). For $C_{29}H_{32}ClNO_8S$ (590.0) calculated: 59.03% C, 5.47% H, 2.37% N; found: 59.27% C, 5.73% H, 2.22% N.

Alkaline hydrolysis: A solution of the substance *V* (200 mg) in 1M methanolic potassium hydroxide (10 ml) was refluxed for 30 min, evaporated *in vacuo*, the residue diluted with water, acidified with 5% HCl to c. pH 6, and extracted with chloroform. After evaporation, the residue was purified by chromatography on Al_2O_3 (6 g) with chloroform-ethanol (95 : 5). Yield 115 mg

of a substance, m.p. 235–238°C (ethyl acetate), which on the basis of the infrared spectrum is identical with 13-hydroxy-1-methoxycanadinium methochloride⁶ (VI).

N-Methyl-13,14-didehydro-2,3-methylenedioxy-1,9,10-trimethoxy-5,6-dihydro-8*H*-dibenzo-
[a,g]quinolizidinium Iodide (VIII)

A solution of the substance V (7 g) in acetic anhydride (100 ml) was refluxed for 2 h. After distillation *in vacuo*, the residue was dissolved in hot water. After cooling, a yellow substance VII was obtained which was recrystallized from water. Yield 5.9 g (89%), m.p. 123–125°C, λ_{\max} 220, 244sh and 343 nm ($\log \epsilon$ 4.56, 4.18, and 4.36). For C₂₉H₃₁NO₇S (553.6) calculated: 62.91% C, 5.64% H, 2.53% N; found: 62.55% C, 5.78% H, 2.59% N.

The aqueous solution of *p*-toluenesulphonate VII was treated with a solution of sodium iodide to give the iodide VIII, m.p. 168–169°C (methanol). For C₂₂H₂₄INO₅ (509.3) calculated: 51.87% C, 4.75% H, 2.75% N; found: 51.69% C, 4.88% H, 2.70% N. PMR (deuteriochloroform-trifluoroacetic acid, 9 : 1): 3.15 s (CH₃—N⁽⁺⁾); 3.95 s, 3.98 s, 4.10 s (3 CH₃O—); 4.75 d and 5.12 d, J_{AB} = 14.0 Hz (Ar—CH₂—N⁽⁺⁾); 6.00 s (O—CH₂—O); 6.50 s (Ar—H); 6.98 and 7.15 d, J_{ortho} = 9.0 Hz (2 Ar—H); 7.68 s (olef. H); 3.25 t and 4.05 t, J 7.0 Hz (Ar—CH₂—CH₂—N⁽⁺⁾).

5,8-Dihydro-9,10-dimethoxy-13-methyl-6*H*-benzo[*g*]-1,3-dioxolo-[7,8]-benzopyrano[3,4,5-*ija*]quinolizinium Iodide (X)

A. A mixture of *p*-toluenesulphonate VII (250 mg), sodium iodide (180 mg), and acetic anhydride (7 ml) was refluxed for 2 h. After cooling, the precipitate was filtered, washed with water, and crystallized from methanol; yield 88 mg (38%) of yellow crystals, m.p. 266–268°C, λ_{\max} 290 and 348 nm ($\log \epsilon$ 4.46 and 4.00). For C₂₂H₂₀INO₅ (505.3) calculated: 52.29% C, 3.99% H, 2.77% N; found: 52.75% C, 4.17% H, 2.43% N.

B. A mixture of the substance V (10 g), acetic anhydride (100 ml), and sodium iodide (6 g) was refluxed for 2 h. On application of the same procedure as sub A, a substance (3.03 g, 35%) was obtained whose melting point and infrared spectrum were identical with those of the substance prepared sub A. The mother liquors were heated with charcoal, filtered, and concentrated *in vacuo*. The residue was dissolved in chloroform and chromatographed on Al₂O₃ to give 3.8 g of quaternary iodide XIII, m.p. 235–237°C (ethanol). For C₂₄H₂₈INO₇ (569.4) calculated: 50.62% C, 4.91% H, 2.46% N; found: 50.47% C, 5.11% H, 2.35% N. PMR (deuteriochloroform): 2.10 s (CH₃CO—); 2.9–3.3 m and 3.6–4.0 m (Ar—CH₂CH₂—N⁽⁺⁾); 3.77 s (CH₃—⁽⁺⁾) 3.87 s, 4.02 s, and 4.08 s (3 CH₃O—); 5.08 d and 5.47 d, J_{gem} = 15.0 Hz (Ar—CH₂—N⁽⁺⁾); 5.95 s (O—CH₂—O); 5.12 d and 5.98 d, J_{vic} = 3.0 Hz (—CH(N⁽⁺⁾)—CH(O)—); 6.37 s (Ar—H); 6.90 d and 7.03 d, J_{ortho} = 9.0 Hz (2 Ar—H).

5,13-Dihydro-9,10-dimethoxy-13-methyl-6*H*,8*H*-benzo[*g*]-1,3-dioxolo[7,8]-benzopyrano-
[3,4,5-*ija*]quinolizine (XI)

To a solution of the substance X (2 g) in 50% aqueous methanol (200 ml), sodium borohydride (2 g) was added in portions. The mixture was refluxed for 2 h. After cooling, the precipitate was filtered, dissolved in benzene, and chromatographed on Al₂O₃. The residue crystallized from ethyl acetate-ethanol; yield 1.2 g (82%) of amine XI, m.p. 164–166°C, λ_{\max} 238, 271, and 379 nm ($\log \epsilon$ 4.31, 4.09, and 4.15). The mass spectrum of this substance exhibited a molecular peak M⁺ 379. For C₂₂H₂₁NO₅ (379.4) calculated: 69.64% C, 5.57% H, 3.68% N; found: 69.99% C, 5.88% H, 3.41% N.

5,13-Dihydro-9,10-dimethoxy-12b,13-dimethyl-6*H*,8*H*-benzo[*g*]-1,3-dioxolo[7,8]-benzopyrano[3,4,5-*ija*]quinolizinium Iodide (*XII*)

A solution of the substance *XI* (264 mg) in methyl iodide (5 ml) and methanol (10 ml) was refluxed for 4 h and evaporated. The residue was crystallized from chloroform-methanol; yield 98 mg of the substance *XII*, m.p. 269–272°C, λ_{\max} 256, 336, and 394sh nm (log ϵ 4.11, 4.22, and 3.53). For $C_{23}H_{24}INO_5$ (521.3) calculated: 52.98% C, 4.64% H, 2.68% N; found: 52.63% C, 4.72% H, 2.53% N. PMR (deuteriochloroform-trifluoroacetic acid, 9:1): 1.17 d and 5.17 q, $J = 7.0$ Hz ($CH_3-CH(O)-$); 1.72 s (CH_3-C); 3.1–3.4 m and 4.1–4.4 m ($Ar-CH_2-CH_2-N^{(+)}$); 3.90 s, 3.98 s (2 CH_3-O); 5.20 broad s ($Ar-CH_2-N^{(+)}$); 6.15 s ($O-CH_2-O$); 6.57 s ($Ar-H$); 6.78 d and 6.92 d, $J_{ortho} = 9.0$ Hz (2 $Ar-H$).

1-Methoxyberberinium Iodide (*XIV*)

A. A mixture of *p*-toluenesulphonate *VII* (240 mg), sodium iodide (200 mg), and glacial acetic acid (10 ml) were refluxed for 5 h and evaporated *in vacuo*. The residue was crystallized from water, then from methanol yielding 70 mg of the iodide *XIV*, m.p. 218–224°C, which was converted with silver chloride in ethanol into the chloride of m.p. 185–190°C (ethyl acetate-methanol). On the basis of the infrared spectrum, it is identical with 1-methoxyberberinium chloride⁷.

B. A mixture of the compound *VI* (120 mg), sodium iodide (90 mg), and glacial acetic acid (5 ml) was refluxed for 5 h and evaporated *in vacuo*. The residue was dissolved in water, made alkaline with sodium bicarbonate, and extracted with chloroform. After evaporation, the residue was dissolved in ethyl acetate-ethanol (9:1) and chromatographed on Al_2O_3 . The evaporated eluate was crystallized from methanol to give 60 mg of a substance whose melting point and infrared spectrum were identical with those of the substance *XIV* prepared sub *A*.

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