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THE ALKALOIDS OF *STRYCHNOS NUX VOMICA*—IX

REDUCTION OF STRYCHNINE METHOSULPHATE WITH THE AID OF SODIUM AMALGAM IN THE PRESENCE OF CARBON DIOXIDE

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Abstract—The reaction between strychnine methosulphate and sodium amalgam afforded ten bases which were isolated, their structures determined, and a mechanism—confirmed experimentally—proposed for their formation.

ALTHOUGH the structure of strychnine has been confirmed by synthesis,[1] a number of questions relating to its chemistry still require clarification. In our laboratory many of these problems[2] including the Emde degradation of quaternary strychnine salts have been investigated. The action of sodium amalgam on strychnine methosulphate was studied[3] in 1932 before modern spectral methods of analysis and separation techniques had been developed and the authors merely found that the reduction affords a complicated mixture of free bases with concomitant fission of the ether linkage. The purpose of the present work was to investigate the reaction in greater detail.

Strychnine methosulphate (I) was treated with sodium amalgam using the experimental conditions described[3] earlier. The free bases were separated from the reaction mixture, and from the remaining aqueous solution a crystalline substance was isolated, which was identified as methylstrychnine (II).[4] The mixture of free bases was analysed by TLC which indicated ten compounds (Fig. 1). These were designated as bases A to K, in the order of diminishing R_f in TLC. All were isolated with the aid of column chromatography and crystallization as homogeneous (TLC), analytically pure, and crystalline substances. Their structures (with the exception of base A) were determined on the strength of spectroscopic data (IR, UV, and NMR), supplemented with the results of chemical reactions as need arose (cf. Experimental). The results are compiled in Table 1. Two of the bases (D and F) were identified as iso-Nb-methyldihydrochanostrychnine (VI),[2] and strychnine (III) respectively. Base A is identical with anhydrotetrahydromethylstrychnine-K,[5] for which Robinson[3, 5, 6] had proposed the formula XIV. This formula agrees with our data as well as with the mechanism proposed for the action of sodium amalgam on strychnine methosulphate.

The fact that treatment of strychnine methosulphate (I) with sodium amalgam leads

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[1] R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker and K. Schenker *Tetrahedron* **19**, 247 (1963).

[2] Part VIII, O. Achmatowicz and S. Achmatowicz, *Rocz. Chem.* **38**, 613 (1964).

[3] W. H. Perkin jun., R. Robinson and J. C. Smith, *J. Chem. Soc.* 1239 (1932).

[4] G. R. Clemo, W. H. Perkin jun. and R. Robinson, *J. Chem. Soc.* 1589 (1957).

[5] W. H. Perkin jun., R. Robinson and J. C. Smith, *J. Chem. Soc.* 574 (1934).

[6] T. M. Reynolds and R. Robinson, *J. Chem. Soc.* 592 (1934).

to the formation of the bases A to K may be explained in the following way. Under the conditions of the reaction, a diffusion layer characterized by high local concentration of sodium hydroxide derived from the sodium amalgam develops in the solution close to the surface of the amalgam. The transformations of the quaternary salt (I) may take place in this layer and on the surface of the amalgam. They involve two competitive reactions: hydrolysis and reduction. Hydrolysis concerns the lactam system and leads to the formation of betaine—methylstrychnine (II). Reduction, leading to the formation of tertiary bases, takes place on the surface of the amalgam and depends on addition of one or two electrons to the electropositive centres of the molecule.[7, 8] In non-acid medium strychnine methosulphate (I) has two electropositive centres: the quaternary nitrogen atom, and the C_{22} atom (the double bond is strongly polarized

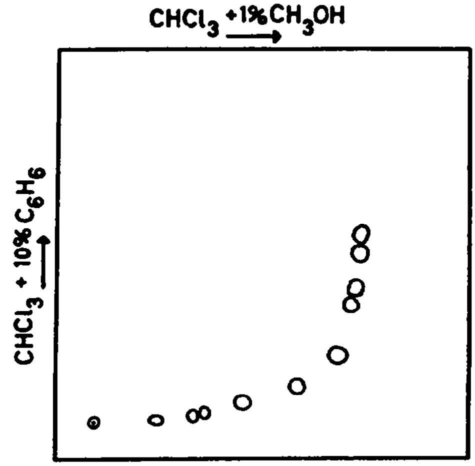

FIG. 1. Two-dimensional TLC of the mixture of tertiary bases.

TABLE 1

Base	m.p. (°)	Formula	Structure
A	201–2	$C_{22}H_{26}N_2O$	XIV
B	234–5	$C_{22}H_{28}N_2O$	XV
C	132–4	$C_{22}H_{26}N_2O_2$	V
D	194–5	$C_{22}H_{26}N_2O_2$	VI
E	133–5	$C_{22}H_{28}N_2O_2$	XIII
F	287–9	$C_{21}H_{22}N_2O_2$	III
G	163–4	$C_{22}H_{28}N_2O_2$	XII
H	168–9	$C_{22}H_{26}N_2O_2$	VII
I	190–2	$C_{22}H_{28}N_2O_2$	VIII
K	235–6	$C_{22}H_{28}N_2O_2$	X

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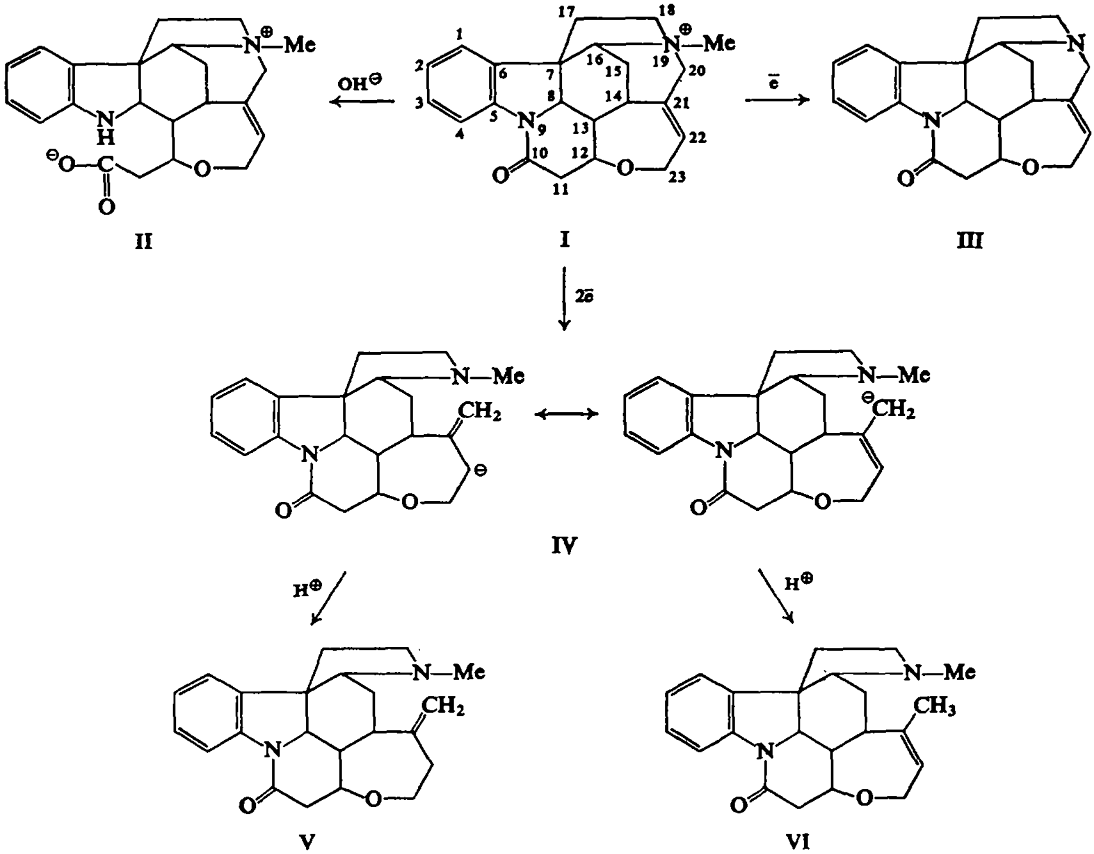
[7] J. H. Brewster, *J. Amer. Chem. Soc.* **76**, 6361 (1954).

[8] G. J. Hoijtink, *Rec. trav. chim.* **76**, 885 (1957).

by the presence of allylic $-\overset{|}{\underset{|}{N}}{}^{+}-$). Addition of an electron (or two) to the nitrogen atom leads to the formation of strychnine (III). This process is probably hindered by steric factors, as indicated by the low yield.

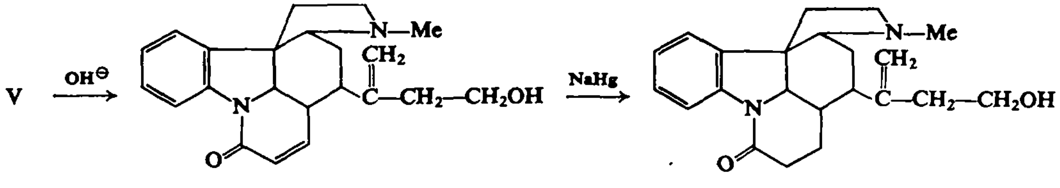


II I III

IV

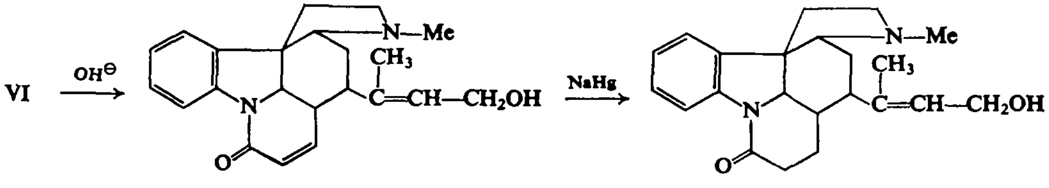
V VI

The main reaction involves addition of two electrons to the C_{22} atom with formation of the mesomeric carbanion (IV) which stabilized by the addition of a proton affords the bases C (V) and D (VI), both of which are subject to further reactions in the diffusion layer. In the former, alkaline β-elimination leads to fission of the ether linkage with formation of the base H (VII), which, as an α,β-unsaturated lactam, is reduced by the amalgam to the base I (VIII).



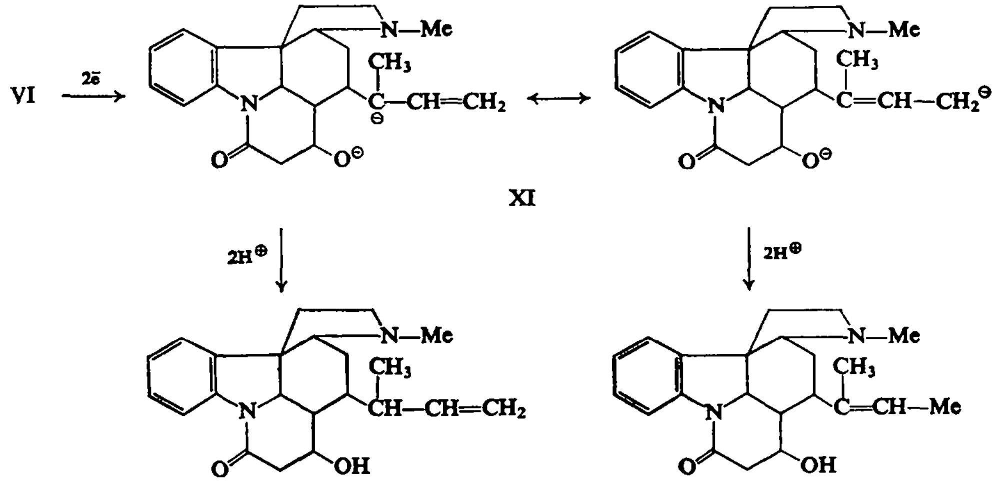
VII VIII

Base D (VI) undergoes similar changes and affords the base K (X) as a result of the reduction of compound IX, which was not isolated.



IX X

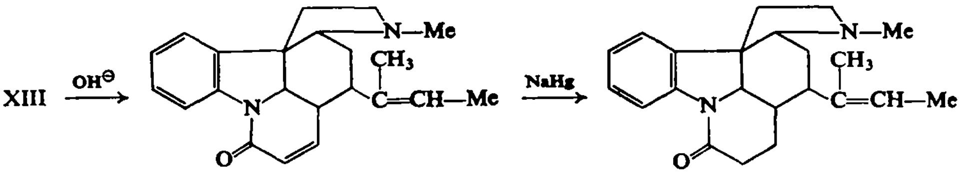
Unlike base C (V), base D (VI) incorporates an allylic ether linkage. It therefore undergoes reductive splitting[9] under the action of the amalgam. The mechanism of this reaction resembles that proposed for the reduction of the quaternary salt. Two electrons are added to the double bond polarized by the inductive effect of the ether oxygen, and mesomeric carbanion XI is formed. This carbanion (XI) is stabilized by addition of two protons and formation of bases E (XIII) and G (XII). Of the two possible epimers at the C_{21}, only one was detected—the base G (XII), which shows the addition of the proton to the C_{21} atom to be stereospecific.



XI

XII XIII

Under the influence of OH⁻ ions the base E (XIII) undergoes β-elimination and is converted to the base A (XIV), which is reduced by the amalgam to the base B (XV).



XIV XV

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[9] R. L. Burwel jun., *Chem. Rev.* 54, 615 (1957).

As the mechanism proposed for the decomposition of strychnine methosulphate by sodium amalgam explains the formation of all the products isolated, it should be possible to verify this experimentally. A reducing agent capable of eliminating the secondary reactions, should lead exclusively to a high yield of the bases C (V) and D (VI), which according to the mechanism are formed during the first stage of the reduction. As the mechanism assumes passage of electrons from the reducing agent to the substance; it should neither produce a strong base nor cause reductive decomposition of allyl ether, in order to avoid disintegration of the carbon–oxygen bond. A nickel-aluminium alloy[10] satisfies all these requirements and consequently was reacted with the salt (I) under conditions similar to those used in the reaction with sodium amalgam, and in 10 minutes afforded a 90% yield of a crystalline product composed exclusively of the bases C (V) and D (VI) in the proportion of 1:1. This highly satisfactory result encouraged research on the further stages of the proposed mechanism. The base C (V) was converted with sodium methoxide to the base H (VII) which on reduction with sodium amalgam gave the base I (VIII). Similarly, the base D (VI) was converted to the compound IX, which had not been isolated in the reaction between sodium amalgam and strychnine methosulphate, and this compound afforded on reduction the base K (X).*

The experiments prove the bases to be genetically related in keeping with the proposed mechanism and show the action of sodium amalgam on strychnine methosulphate to involve consecutive processes of reduction and alkaline fission of the carbon–oxygen bond. The results are also connected with the reduction of polyfunctional systems by sodium amalgam.

EXPERIMENTAL

The m.p. were determined on a Kofler block and are uncorrected. IR spectra: Hilger H800 spectrophotometer; UV spectra: Unicam SP500 spectrophotometer; NMR spectra: a Varian A-60 and Perkin-Elmer permanent magnet instruments in $CDCl_3$ with TMS as internal standard ($\delta = 0$). Aluminium oxide G for TLC acc. to Stahl (Merck). Strychnine methosulphate,[3] methylstrychne,[4] and iso-Nb-methyldihydrochanostrychnine[2] were prepared as recommended in the lit.

The reaction of strychnine methosulphate (I) *with sodium amalgam.* A soln of strychnine methosulphate (92 g) in water (700 ml) was heated on a water bath to 70°. During vigorous stirring and the passage of CO_2, 4% NaHg was added portionwise (3 × 300 g at 15-min intervals). After 10 hr, the resulting bases were separated from the reaction mixture as they were formed. The crude product was dissolved in benzene (400 ml), filtered, and washed with water. The benzene soln was dried (K_2CO_3) and evaporated under red press. Tertiary bases (32 g) were obtained in 46% yield as an oil, which solidified on cooling to a brown-yellow resin.

Methylstrychnine (II). The brown-red aqueous soln obtained in the previous experiment after separation from Hg, was left for one month at room temp. The resulting crystals (17 g) were separated and a second crop collected (5 g) after concentration of the mother liquor. The compound (22 g in all), which was obtained in 30% yield, proved to be identical with authentic methylstrychnine in m.p., mixed m.p., and IR spectrum.

Separation of tertiary bases

The tertiary bases (16 g) were chromatographed on 480 g of aluminium oxide of activity III according to Brockman. Fractions of 500 ml were collected. The results are compiled in Table 2.

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* Reductive decomposition of the ether linkage in base D (VI) was a failure. This may have been due to the inferior solubility of the base in non-acid aqueous media.

[10] S. Sugasawa and H. Matsuo, *Chem. Abstr.* **51**, 6528b (1957); S. Sugasawa and S. Ushioda, *Tetrahedron* **5**, 48 (1959).

TABLE 2

No.	Eluent		Weight (mg)	Composition in TLC
1–4	ligroin		0	—
5	ligroin–benzene	9:1	5	A
6	ligroin–benzene	9:1	22	A+B
7	ligroin–benzene	9:1	30	A+B
8	ligroin–benzene	9:1	33	A+B
9	ligroin–benzene	4:1	60	A+B
10	ligroin–benzene	4:1	61	A+B
11	ligroin–benzene	4:1	58	A+B
12	ligroin–benzene	4:1	100	A+B+C
13	ligroin–benzene	1:1	321	B+C
14	ligroin–benzene	1:1	294	B+C
15	ligroin–benzene	1:1	270	B+C
16	ligroin–benzene	1:1	205	B+C
17	ligroin–benzene	1:1	214	B+C+D
18	ligroin–benzene	1:1	392	B+C+D
19	benzene		946	C+D
20	benzene		656	C+D
21	benzene		466	C+D
22	benaene		370	C+D
23	benzene		295	C+D
24	benzene		278	C+D
25	benzene		220	C+D
26	benzene		250	C+D+E
27	benzene–ether	9:1	783	D+E
28	benzene–ether	9:1	519	D+E
29	benzene–ether	9:1	428	E+F
30	benzene–ether	9:1	380	E+F+G
31	benzene–ether	4:1	690	E+F+G
32	benzene–ether	4:1	699	F+G
33	benzene–ether	4:1	656	F+G
34	benzene–ether	4:1	478	G
35	benzene–ether	4:1	382	G
36	benzene–ether	4:1	283	G
37	benzene–ether	1:1	481	G+H
38	benzene–ether	1:1	232	G+H
39	benzene–ether	1:1	359	H
40	benzene–ether	1:1	300	H+I
41	benzene–ether	1:1	316	H+I
42	benzene–ether	1:1	271	I
43	ether		268	I
44	ether		130	I
45	ether		22	I
46	ether		3	H+I+K
47	ether		1	H+I+K
48	ether–ethyl acetate	9:1	2	H+I+K
49	ether–ethyl acetate	4:1	3	H+I+K
50	ether–ethyl acetate	1:1	23	I+K
51	ethyl acetate		48	I+K
52	ethyl acetate		54	I+K
53	ethyl acetate–ethanol	9:1	1553	I+K
54	ethyl acetate–ethanol	4:1	152	I+K
55	ethyl acetate–ethanol	1:1	80	B+C+D+E+F+G+H+I+K
56	ethanol		525	A+B+C+D+E+F+G+H+I+K
57	ethanol–water	9:1	255	start spot

All were isolated with the aid of column rechromatography and crystallization as homogeneous, analytically pure, and crystalline substances:

Base A (XIV), m.p. 201–2° from MeOH. (Found: C, 79·35; H, 8·17; N, 8·49. $C_{22}H_{26}N_2O$ requires: C, 79·00; H, 7·84; N, 8·33%). IR: ν_{max} (chf) 2815 ($N—CH_3$), 1662 ($C=O$), 1613 ($HC=CHCO$) cm^{-1}. UV: λ_{min}^{EtOH} 255 mμ (1800), λ_{max} 310 mμ (7000) (Fig. 2).

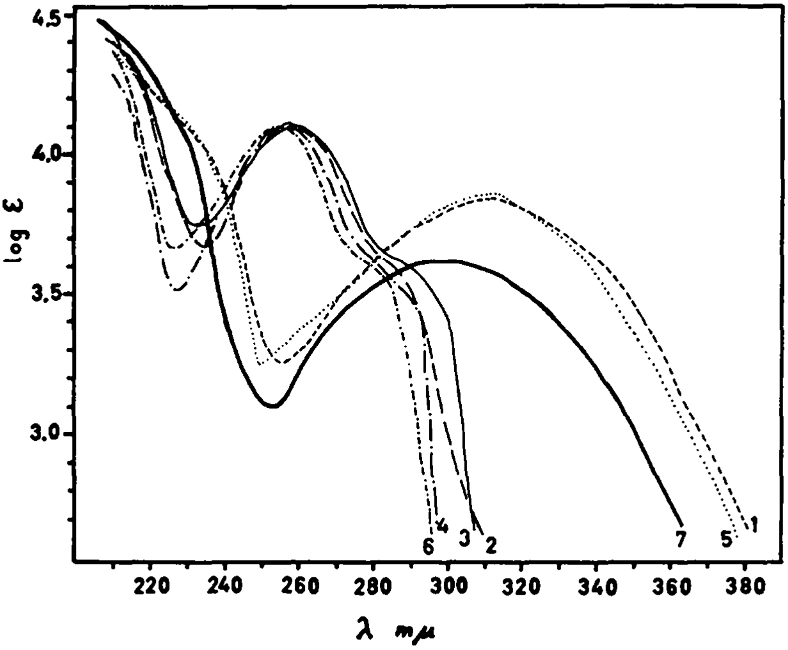

FIG. 2. UV spectra. 1—base A, 2—base B, 3—strychnine, 4—base G, 5—base H, 6—base I, 7—strychninolon a[12]

Base B (XV), m.p. 234–5° from MeOH. (Found: C, 78·85; H, 8·58; N, 8·24. $C_{22}H_{28}N_2O$ requires: C, 78·53; H, 8·39; N, 8·33%). IR: ν_{max} (chf) 2815 ($N—CH_3$), 1635 ($C=O$), 1400 (CH_2CO) cm^{-1}. UV: λ_{min}^{EtOH} 235 mμ (4800), λ_{max} 257 mμ (13200) (Fig. 2). NMR: δ 1·61 (doublet, J=9·5 c/s, 3H, $CH_3—CH=C$), 1·62 (singlet, 3H, $CH_3—\overset{|}{C}=C$), 2·35 (singlet, 3H, $N—CH_3$), 5·3 (multiplet, 1H, $—CH=C\langle$) ppm (Fig. 3). The presence of $CH_3—CH=C\langle$ was confirmed by ozonolysis (Fig. 7).

Base C (V), m.p. 132–4° from MeOH. (Found: C, 75·34; H, 7·73; N, 7·99. $C_{22}H_{26}H_2O_2$ requires: C, 75·40; H, 7·48; N, 7·99%). IR: ν_{max} (chf) 3107, 900 ($C=CH_2$), 2820 (NCH_3), 1660 ($C=O$), 1385 (CH_2CO), 1093 ($C—O—C$), cm^{-1}. UV: λ_{min}^{EtOH} 230 mμ (3900), λ_{max} 260 mμ (13100). NMR: δ 2·61 (singlet, 3H, $N—CH_3$), 4·82 (singlet, 2H, $\rangle C=CH_2$) ppm. The presence of $\rangle C=CH_2$ was confirmed by ozonolysis (Fig. 7).

Base D (VI), m.p. 194–5° from MeOH. (Found: C, 75·24; H, 7·48; N, 8·04. Calc. for $C_{22}H_{26}N_2O_2$: C, 75·40; H, 7·48; N, 7·99%). The compound was identical with authentic iso-Nb-methyldihydrochanostrychnine (VI) in m.p., IR spectrum, UV spectrum and R_f values in TLC.

Base E (XIII), m.p. 133–5° from MeOH. (Found: C, 74·98; H, 7·89; N, 8·02. $C_{22}H_{28}N_2O_2$ requires: C, 74·96; H, 8·01; N, 7·95%). IR: ν_{max} (chf) 3520 (OH), 2806 (NCH_3), 1660 ($C=O$), 1393 (CH_2CO) cm^{-1}. UV: λ_{min}^{EtOH} 228 mμ (3800), λ_{max} 255 mμ (13300). NMR: δ 1·66 (doublet, J=7 c/s, 3H, $CH_3—CH=C$), 1·81 (singlet, 3H, $CH_3—\overset{|}{C}=C$), 2·60 (singlet, 3H, $N—CH_3$), 5·6 (multiplet, 1H, $—CH=C\langle$) ppm. The presence of $CH_3=CH=C\langle$ was confirmed by ozonolysis (Fig. 7).

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[12] V. Prelog and S. Szpilfogel, *Helv. Chim. Acta* **28**, 1669 (1945).

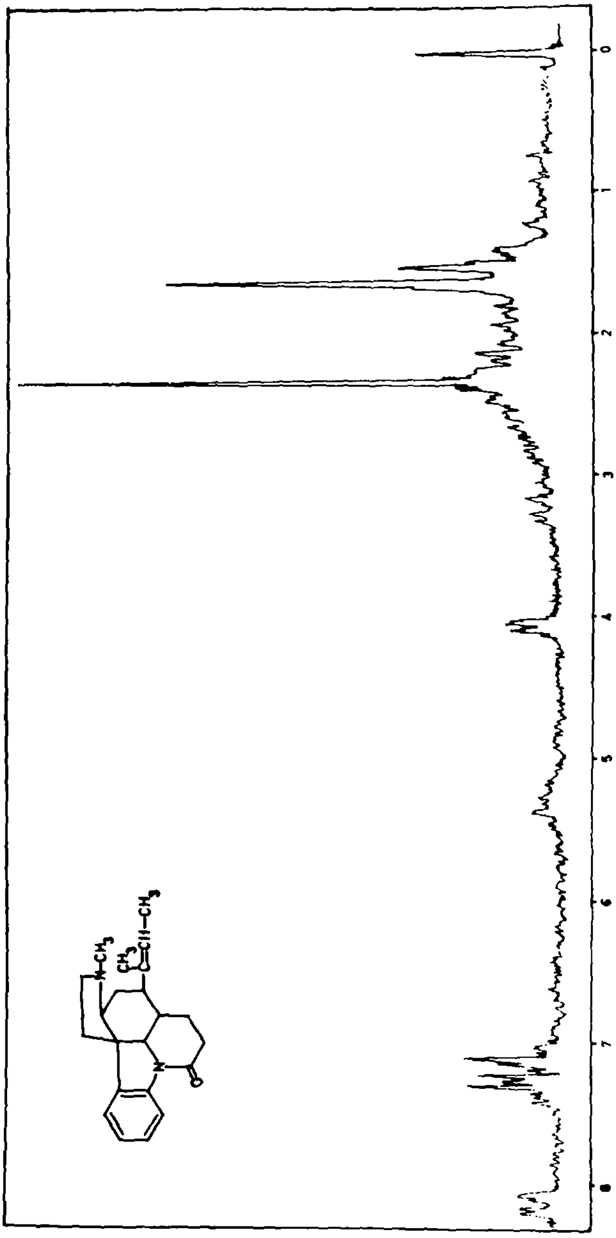

FIG. 3

Base F (III), m.p. 287–9° from EtOH. The compound was identical with strychnine in all respects: m.p. and mixed m.p.; superimposable IR spectra and UV spectra; same R_f values in TLC.

Base G (XII), m.p. 163–4° from benzene. (Found: C, 75·24; H, 8·01; N, 7·69. $C_{22}H_{28}N_2O_2$ requires: C, 74·96; H, 8·01; N, 7·95%). IR: ν_{max} (chf) 3520 (OH), 3077, 912 (—CH═CH_2), 2825 (NCH_3), 1642 (C═O), 1378 (CH_2CO) cm^{-1}. UV: λ_{min}^{EtOH} 228 mμ (3300), λ_{max} 256 mμ (13100) (Fig. 2). NMR: δ 1·18/doublet, J═6·5 c/s, 3H, CH_3—CH), 2·48 (singlet, 3H, N—CH_3), 5·23 (multiplet, 2H, —CH═CH_2), 6·03 (multiplet, 1H, —CH═CH_2) ppm (Fig. 4). The presence of CH═CH_2 was confirmed by ozonolysis (Fig. 7).

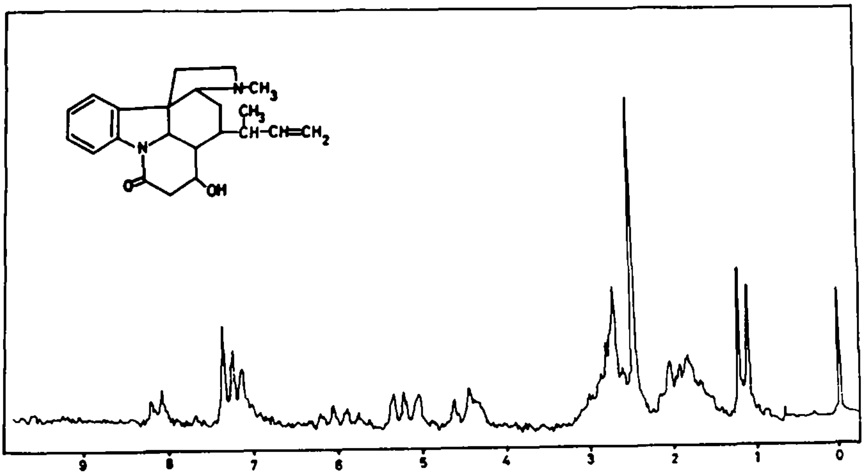

FIG. 4

Base H (VII), m.p. 168–9° from MeOH. (Found: C, 75·06; H, 7·42; N, 7·82. $C_{22}H_{26}N_2O_2$ requires: C, 75·40; H, 7·48; N, 7·99%). IR: ν_{max} (chf) 3640, 3460 (OH), 3080, 893 (C═CH_2), 2810 (N—CH_3), 1660 (C═O), 1614 (HC═CHCO) cm^{-1}. UV: λ_{min}^{EtOH} 250 mμ (1700), λ_{max} 310 mμ (7100) (Fig. 2). NMR: δ 2·33 (singlet, 3H, N—CH_3), 3·71 (triplet, J = 6·5 c/s, 2H, CH_2—CH_2—OH), 4·97 (singlet, 2H, >C═CH_2), 5·98 (doublet, J = 10 c/s, 1H, >CH—CH═CH—CO), 6·64 (doublet of doublets, J_1 = 10 c/s, J_2 = 6 c/s, 1H, >CH—CH═CH—CO) ppm (Fig. 5).

Base I (VIII), m.p. 190–2° from MeOH. (Found: C, 74·92; H, 8·23. $C_{22}H_{28}N_2O_2$ requires: C, 74·96; H, 8·01%). IR: ν_{max} (chf) 3610, 3430 (OH), 3070, 890 (C═CH_2), 2800 (NCH_3), 1637 (C═O), 1400 (CH_2CO) cm^{-1}. UV: λ_{min}^{EtOH} 227 mμ (4600), λ_{max} 255 mμ (12800) (Fig. 2). NMR: δ 2·31 (singlet, 3H, N—CH_3), 3·79 (triplet, J = 6·5 c/s, 2H, CH_2—CH_2—OH), 4·96 (singlet, 2H, >C═CH_2) ppm (Fig. 6). The presence of >C═CH_2 was confirmed by ozonolysis (Fig. 7).

Base K (X), m.p. 235–6° from MeOH. (Found: C, 75·04; H, 7·95. $C_{22}H_{28}N_2O_2$ requires: C, 74·96; H, 8·01%). IR: ν_{max} (chf) 3650, 3430 (OH), 2814 (NCH_3), 1637 (C═O), 1400 (CH_2CO) cm^{-1}. UV: λ_{min}^{EtOH} 228 mμ (4100), λ_{max} 255 mμ (12,000). NMR: δ 1·75 (singlet, 3H, CH_3—C═C), 2·31 (singlet, 3H, N—CH_3), 4·08 (multiplet, 2H, ═CH—CH_2—OH), 5·5 (multiplet, 1H, >C═CH—) ppm.

Ozonolysis. For ozonolysis the standard method was used.

A soln of the base (100 mg) in AcOEt (50 ml) was saturated with O_3 at −78° until a blue colour appeared. The excess of O_3 was removed in a stream of O_2. The AcOEt was removed under red. press., and the residue treated with water (20 ml) and Zn dust (0·2 g). Volatile compounds were steam-distilled (5 ml) from the mixture into an aq. solution of 2,4-dinitrophenylhydrazine hydrochloride. The pptd DNP was filtered and identified by TLC.[11] The results are given in Fig. 7.

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[11] A. Zamojski and F. Zamojska, *Chem. Analit.* 9, 589 (1964).

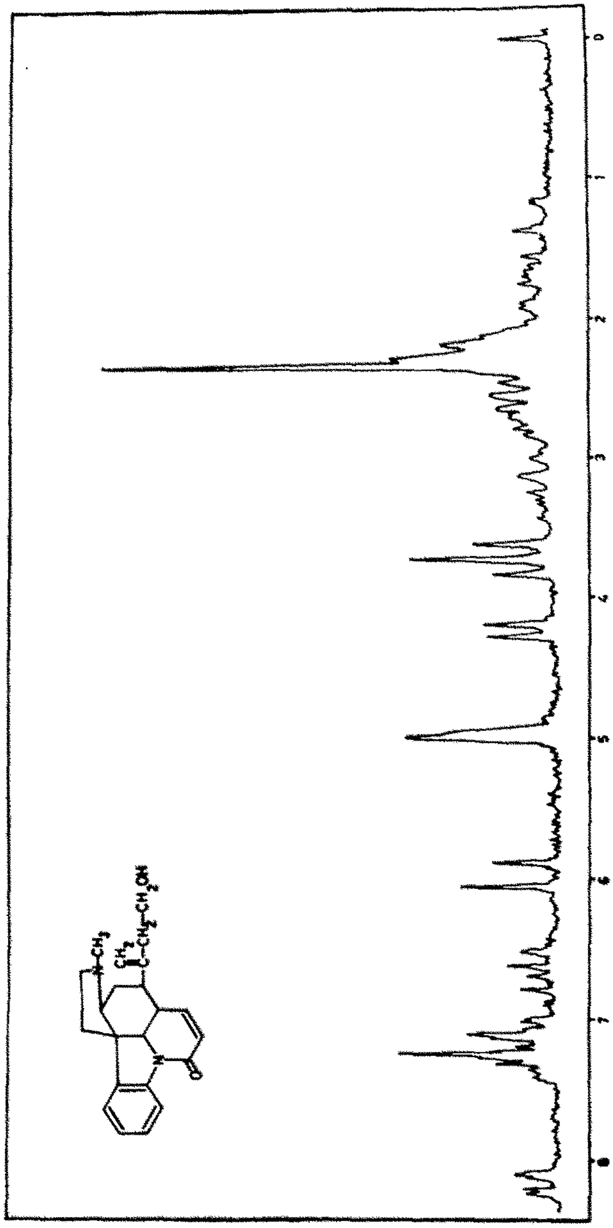

FIG. 5

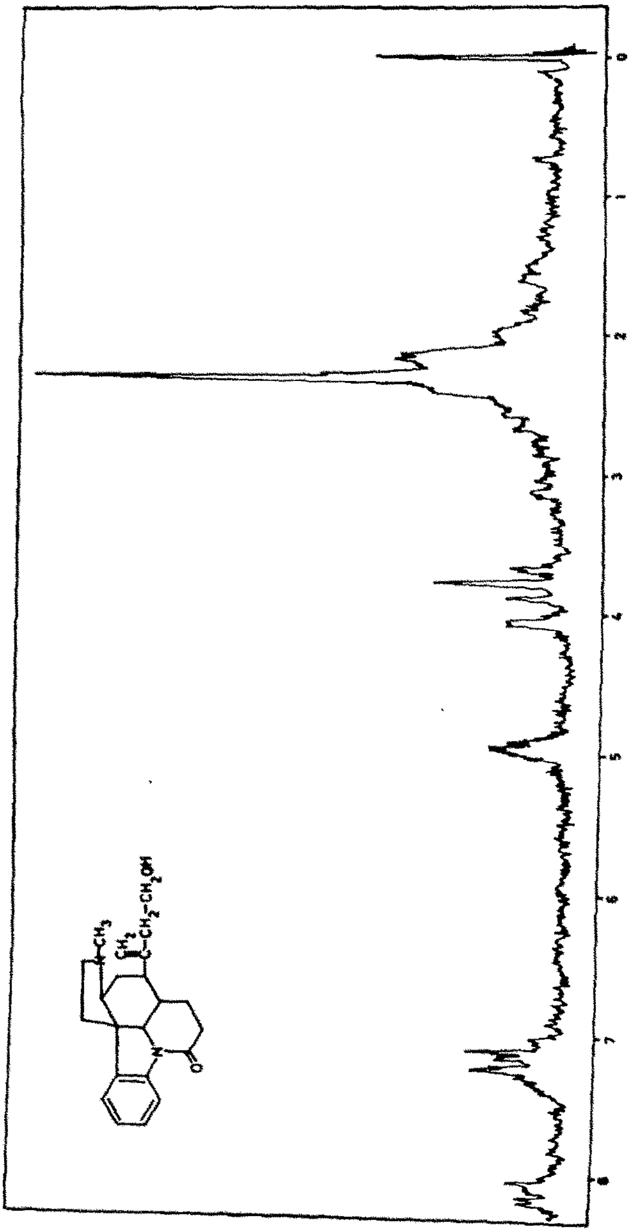

FIG. 6

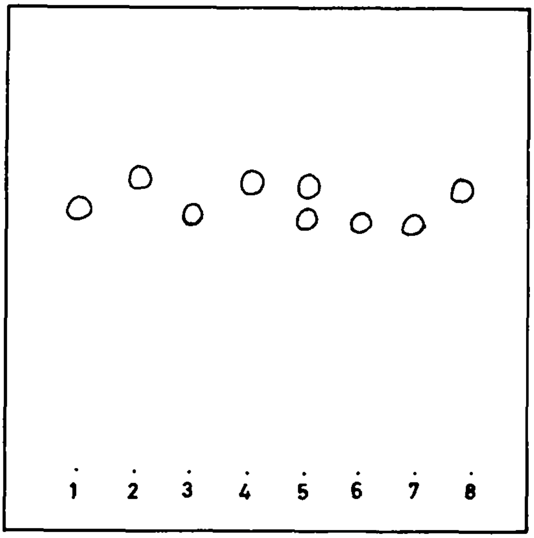

FIG. 7 TLC of 2,4-DNP of formaldehyde, acetaldehyde, and aldehydes obtained in ozonolysis of tertiary bases. 1—formaldehyde, 2—base B, 3—base C, 4—base E, 5—mixture of formaldehyde and acetaldehyde, 6—base G, 7—base I, 8—acetaldehyde.

The reaction of strychnine methosulphate (I) *with the Raney nickel alloy.* A hot soln of strychnine methosulphate (20 g) in water (100 ml) was mixed with a hot soln of Na_2CO_3 (20 g) in water (100 ml.) While the mixture was heated, powdered 50/50 Al-Ni alloy (15 g) was added portionwise during 5 min. The whole was heated on a water bath for a further 5 min and the warm reaction mixture then extracted repeatedly with benzene. After drying (K_2CO_3), the solvent was evaporated under red. press. and a crystalline product (13·5 g) obtained in 90% yield. TLC demonstrated the presence of two components, whose R_f matched those of the bases C (V) and D (VI) respectively. They were separated by crystallization from MeOH into base C (5·8 g) m.p. 132–4° and base D (5·4 g) m.p. 194–5°.

The action of sodium methoxide on base C (V). *Base H* (VII). Base C (3·0 g) was added to a soln of MeONa (0·6 g Na in 35 ml MeOH), and the MeOH was immediately evaporated on a water bath (about 10 min). The residue was treated with water (40 ml) and extracted with benzene (4 × 15 ml). The benzene soln crystallized after concentration and addition of ether. Recrystallization afforded in 60% yield a compound (1·8 g) identical with the base H in m.p., IR spectrum, and R_f in TLC.

Reduction of base H (VII) *with sodium amalgam. Base* I (VIII). Base H (1·0 g) was dissolved in 80% MeOH (12 ml) and 4% NaHg (10 g) was added portionwise at the temp of the water bath. The pH of the mixture was kept about 7 by addition of 2 N AcOH. MeOH was then evaporated and the residue diluted with water (40 ml), made alkaline with ammonia, and extracted repeatedly with benzene. After crystallization from MeOH the base I (0·95 g) was obtained in 95% yield.

The action of sodium methoxide on base D (VI)—*base* (IX). The procedure was the same as with base C (3·0 g of base D of 50 ml MeOH and 10 ml MeOH with 0·6 g Na). A compound (1·6 g) m.p. 199–201° (acetone) was obtained in 53% yield. (Found: N, 7·67. $C_{22}H_{26}H_2O_2$ requires: N, 7·99%). IR: ν_{max} (chf) 3610, 3420 (OH), 2806 (NCH_3), 1660 (C=O), 1615 (HC=CHCO) cm^{-1}. UV: λ_{min}^{EtOH} 252 mμ (1400), λ_{max} 305 mμ (5500).

Reduction of base (IX) *with sodium amalgam—base* K (X). The procedure was the same as for base H. A compound identical with the authentic base K in m.p., IR spectrum, and R_f in TLC was obtained in 70% yield.

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