Alkaloids of Australian Strychnos *Species. Part II.* The Constitution of Strychnospermine and Spermostrychnine.*

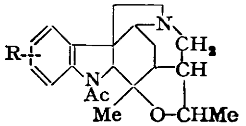
By F. A. L. Anet and Sir Robert Robinson.

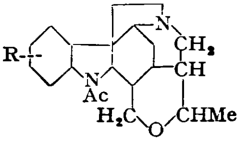
[Reprint Order No. 6190.]

The structures of the two alkaloids of *Strychnos psilosperma*, strychnospermine and spermostrychnine, have been determined. The former alkaloid is a methoxy-derivative of the latter, which has been related to strychnine by way of deoxydihydrospermostrychnine. The position of the methoxyl group of strychnospermine has been determined by ultraviolet spectroscopy and by colour reactions, including the formation of a rhodamine by demethylation and condensation with phthalic anhydride.

Strychnospermine, the main alkaloid of the Australian plant, *Strychnos psilosperma*, was assigned the formula $C_{21}H_{28}O_3N_2$ by Anet, Hughes, and Ritchie (*Nature*, 1950, **166**, 476), later changed to $C_{22}H_{28}O_3N_2$ (*idem, Austral. J. Chem.*, 1953, **6**, 58). It was found (*loc. cit.*, 1953) to contain one methoxyl and at least two *C*-methyl, but no *N*-methyl groups in the molecule. The alkaloid was a tertiary base, forming a hydrochloride and a methiodide, and contained a *N*-acetyl group as shown by hydrolysis with acid or alkali to deacetylstrychnospermine, $C_{20}H_{26}O_2N_2$, which gave a basic *N*-nitroso-derivative. The colour reactions of the alkaloid were similar to those of strychnine (positive Otto reaction) whilst those of the deacetyl base resembled those of strychnidine or strychnic acid. The remaining oxygen atom appeared to be unreactive and was assumed to occur in a cyclic ether group. On the basis of these reactions, the ascertained molecular structure of strychnine, and Woodward's theory of the biogenesis of that alkaloid (*Nature*, 1948, **162**, 155), the most probable formula for the base was considered to be (I; R = OMe). Another alkaloid, spermostrychnine, $C_{21}H_{26}O_2N_2$, was found in smaller amount in the same plant (*loc. cit.*, 1950). It resembled strychnospermine, but it did not contain a methoxyl group and was therefore considered to be (I; R = H) (*loc. cit.*). Several other structures, including (II), were considered for these bases, but were thought to be less likely.

(I)





(II)

In the present work strychnospermine was first investigated because of its greater accessibility. The question of the number of *C*-methyl groups in strychnospermine has been re-examined, as it was of importance in connexion with the substituents in the oxide ring and because the figures previously obtained by Anet *et al.* (*loc. cit.*) were not entirely conclusive. It became evident from new determinations that deacetylstrychnospermine contained only one *C*-methyl group and strychnospermine two such groups. A macro-determination with the former base gave only 85% of the amount of acetic acid corresponding to one *C*-methyl group. The microanalytical values tended to be higher for some unknown reason. Similar high values have been found by Elderfield and Gray for certain alstonine derivatives (*J. Org. Chem.*, 1951, **16**, 521), and by Karrer, Eugster, and Rüttner for emetine (*Helv. Chim. Acta*, 1948, **31**, 1219), as well as by the present authors in the case of ajmaline and some of its derivatives [Anet, (Mrs. D. Chakravarti), Robinson, and Schlittler, *J.*, 1954, 1242]. Of the two formulæ (I and II) already mentioned, (II) should be preferred to (I) on these, and also on biogenetic grounds.

The ultraviolet absorptions of strychnospermine and of deacetylstrychnospermine are shown in Fig. 1. These are consistent with a *N*-acetyldihydroindole and a dihydroindole structure respectively, containing a methoxyl group in the benzene ring (Raymond Hamet,

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* Part I, *Austral. J. Chem.*, 1953, **6**, 58.

Ann. pharm. franç., 1950, **8**, 482). The infrared spectrum of strychnospermine showed an intense band at 6·06 μ and no absorption indicative of a NH or OH group. The deacetyl base, on the other hand, showed no carbonyl absorption, but had a band at 3·00 μ, which could be due to a NH group. The absence of a strong band in both these compounds at about 13·4 μ indicated the absence of a 1 : 2-disubstituted benzene ring, thus proving that the methoxyl group was attached to the benzene ring, but it was not possible to assign the exact position of this substituent from the infrared spectra alone.

With boiling hydrobromic acid strychnospermine smoothly gave deacetyldemethylstrychnospermine dihydrobromide by hydrolysis of both the acetyl and the methoxyl group. This salt was very soluble in water, but was readily hydrolysed to the sparingly soluble monohydrobromide in water, a reaction which took place immediately on addition of sodium acetate to the solution of the dihydrobromide in dilute acid. The second basic function is therefore a weak one, and is in fact analogous to N(*a*) in strychnidine (Clemo, Perkin, and Robinson, *J.*, 1927, 1589). Although the free base was not obtained crystalline it was observed to be easily soluble in dilute aqueous sodium hydroxide to give a solution which was oxidised rapidly in the air. Reaction of the dihydrobromide with acetic anhydride in the presence of anhydrous sodium acetate at 100° readily gave demethylstrychnospermine, which was soluble in alkali and was converted into strychnospermine methiodide by methyl iodide in alcoholic alkali. Fusion of deacetyldemethylstrychnospermine dihydrobromide with phthalic anhydride gave an intense rhodamine-like dye (similar to Rhodamine 6G in colour and fluorescence), showing that the phenolic hydroxyl group was *meta* to the nitrogen atom.

FIG. 1.

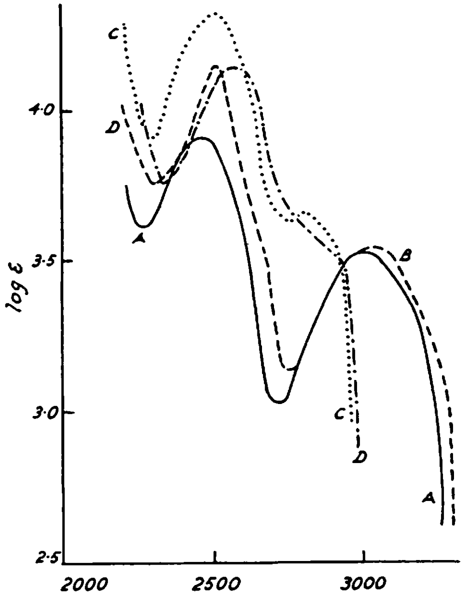


FIG. 2.

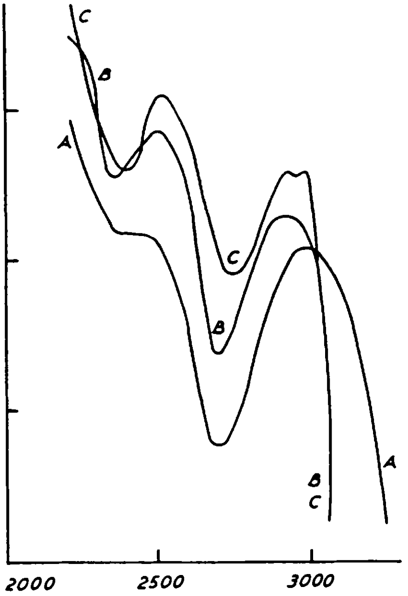


FIG. 1. *Absorption spectra of (A) deacetylspermostrychnine, (B) strychnic acid* N*-oxide, (C) spermostrychnine, and (D) strychnine.*

FIG. 2. *Absorption spectra of (A) deacetylstrychnospermine, (B) strychnospermine, and (C) α-colubrine.*

Reduction of strychnospermine with lithium aluminium hydride gave deacetyl-*N*-ethylstrychnospermine, which on demethylation with hydrobromic acid, followed by fusion with phthalic anhydride, afforded a rhodamine dye, the colour of which was bluer (similar to Rhodamine B) than that of the dye obtained from deacetyldemethylstrychnospermine. The colour of the former dye was identical with that of the rhodamine dye obtained from demethylated hexahydro-7-methoxy-11 : *N*-dimethylcarbazole (prepared by Dr. M. F. Millson), but very different from that obtained from demethylated hexahydro-5-methoxy-11 : *N*-dimethylcarbazole, which gave a much bluer red, almost red-purple, dye with a bright red instead of yellow-green fluorescence.

The position of the methoxyl group in strychnospermine was confirmed by a comparison of the ultraviolet spectra of the alkaloid and of its deacetyl derivative with those of model compounds prepared by Dr. H. T. Openshaw. We are greatly indebted to Dr. Openshaw for communicating these results to us before their publication.

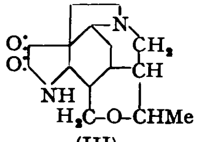
	Base		Acetyl deriv.	
	$\lambda_{max.}$	ε	$\lambda_{max.}$	ε
Hexahydro-5-methoxycarbazole	(231)	8200	254	14,000
	287·5	1200	297	6,300
Hexahydro-6-methoxycarbazole	243	7500	262	15,500
	308·5	3400	296	4,200
Hexahydro-7-methoxycarbazole	(236)	4800	253·5	9,700
	296	4300	295·5	6,200
Hexahydro-8-methoxycarbazole	243	6900	256	11,900
	288	2100	288	2,900
Deacetylstrychnospermine	(242)	3900	251	9,100
	300	3600	293	4,600

The methoxyl group of strychnospermine is in the same relative position as that of β-colubrine, and indeed the spectra of the two alkaloids are very similar (Raymond Hamet, *loc. cit.*) (see Fig. 2).

Reduction of bromostrychnospermine with lithium aluminium hydride afforded bromodeacetyl-*N*-ethylstrychnospermine, which gave intense colour reactions with traces of oxidising agents.

Strychnospermine *N*-oxide was obtained in a hydrated form by the action of aqueous hydrogen peroxide on the base, but it could not be converted into an analogue of *pseudo*-strychnine with potassium chromate (Bailey and Robinson, *J.*, 1948, 703). Strychnospermine methiodide, like dihydrostrychnine methiodide, was unaffected by sodium amalgam; it gave deacetylstrychnospermine methiodide on hydrolysis with dilute acid.

Oxidation of demethylstrychnospermine with chromic acid in dilute sulphuric acid gave a water-soluble compound, $C_{15}H_{20}O_3N_2$ (III), analogous to dioxonucidine (Leuchs and Kröhnke, *Ber.*, 1930, **63**, 1045). Like the latter, the above compound reacted with hydrogen peroxide in barium hydroxide solution with the liberation of one mol. of carbon dioxide and the formation of an amino-acid, which, however, was not obtained crystalline. The infrared spectrum of this *apo*spermostrychine (III) showed bands at 5·55, 5·68, 5·78, and 6·00 μ in the carbonyl region, consistent with a five-membered ring keto-amide.



(III)

Zinc dust distillation of deacetylstrychnospermine afforded 3-ethylpyridine, isolated as the picrate, and a neutral fraction which gave a strong Ehrlich reaction.

Attempts were made to open the postulated ether ring in strychnospermine or in one of its derivatives, but it is known that, although simple derivatives of basic cyclic ethers are easily split by hydrobromic acid (cf. Cerkovnikov and Prelog, *Annalen*, 1938, **535**, 37), more complex compounds, such as the various dihydrostrychnidines, are extremely stable (Wieland and Jennen, *Annalen*, 1940, **545**, 99; Perkin and Robinson, *J.*, 1929, 964). It was therefore expected that vigorous conditions would be required in the present case, and indeed deacetyldemethylstrychnospermine was recovered unchanged after being heated with 65% hydrobromic acid, in a sealed tube, at temperatures up to 150°. At higher temperatures the product contained some non-ionic bromine, showing that the reaction had taken place to some extent, but the resulting aminophenol readily suffered oxidation and no pure substance could be isolated. This reaction was not further investigated as it was realised that spermostrychnine, which does not contain a methoxyl group, would be more amenable to the above line ot attack.

The ultraviolet spectra of spermostrychnine and of its deacetyl derivative are shown in Fig. 2 and are almost identical with those of strychnine and of strychnic acid *N*-oxide respectively (Prelog and Szpilfogel, *Helv. Chim. Acta*, 1945, **28**, 1671). The infrared spectra of the first two compounds showed features analogous to those of the corresponding strychnospermine series, except that in the first two a strong band was present at about 13·3 μ, characteristic of an *o*-disubstituted benzene ring.

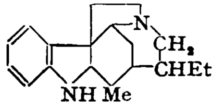
It was realised by Anet *et al.* (*loc. cit.*) that spermostrychnine would most likely prove to be demethoxystrychnospermine, and this has now been proved to be the case by oxidising spermostrychnine with chromic acid. The compound obtained, $C_{15}H_{20}O_3N_2$, was identical, as shown by m. p. and mixed m. p., as well as by comparison of rotations and infrared spectra, with the compound (III) obtained by the oxidation of demethylstrychnospermine.

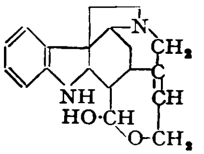
Zinc dust distillation of deacetylspermostrychnine hydrobromide gave a mixture of alkylindoles and, in the basic fraction, 3-ethylpyridine. Traces of carbazole or of an alkylcarbazole were probably also present, but the amount obtained was too small for purification. The formation of the above degradation products is obviously consistent with the structure proposed for the alkaloid.

The *N*-oxide of spermostrychnine reacted only slowly with aqueous potassium chromate solution, but it ultimately gave a base, which behaved like *pseudo*strychnine in giving a neutral nitroso-compound. This could not be crystallised and was not further investigated.

By the action of hydrogen bromide in acetic acid (50% w/v) on deacetylspermostrychnine at 180—200°, a product was obtained which contained much non-ionic bromine. It was not isolated in a pure condition but its solution in acetic–hydrobromic acid was directly reduced with zinc dust. The resultant base was acetylated and isolated as a crystalline perchlorate. The pure salt, $C_{21}H_{28}ON_2,HClO_4,1{\cdot}5H_2O$, lost a part of its water of crystallisation at 117° and all of it at 130°. The regenerated base, although not crystalline, gave satisfactory analyses for $C_{21}H_{28}ON_2$ after sublimation. This deoxydihydrospermostrychnine must have arisen by reductive removal of the cyclic ether oxygen atom of spermostrychnine and therefore should have the structure (IV). It can be seen that such a compound should be obtainable from strychnine by suitable degradation. The Wieland–Gumlich aldehyde (V) (Wieland and Gumlich, *Annalen*, 1932, **494**, 191; Wieland and Kazine, *ibid.*, 1933, **506**, 60) appeared to be the most promising starting material, but it should be noted that several stereoisomers of the structure (IV) can exist and this might well have confused the issue.

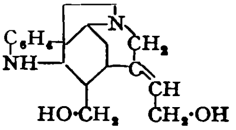
(IV)



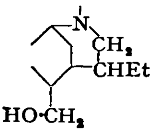


(V)

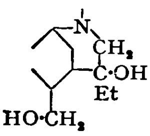
Reduction of the Wieland–Gumlich aldehyde, which from its infrared spectrum was shown to exist in the cyclic form (V), with lithium aluminium hydride in tetrahydrofuran solution, or better with potassium borohydride in aqueous alcohol, gave the corresponding alcohol (VI). The reduction of this with hydrogen in the presence of palladium–charcoal in acetic acid proceeded readily, but it was found that if the hydrogenation was stopped after the absorption of one mol. of hydrogen much unchanged starting material could be recovered, and that it was not until nearly two mols. of hydrogen had been taken up that a seemingly homogeneous compound was obtained. The beautifully crystalline dihydrochloride of the reduced base was purified by several recrystallisations from aqueous acetone. This salt analysed for $C_{19}H_{26}O_2N_2,2HCl$, even when dried at 100° *in vacuo*, and it contained one *C*-methyl group. The infrared spectrum showed that it contained no acetone of crystallisation. The regenerated base, after several recrystallisations from aqueous methanol, followed by drying at room temperature, or at 100°, or by sublimation *in vacuo*, did not give reproducible analytical figures. The results were always intermediate between those required for $C_{19}H_{26}O_2N_2$ and for $C_{19}H_{26}ON_2$ (see Experimental section), and they also showed the presence of a *C*-methyl group. Although the analytical results were so unsatisfactory the compound appeared to be pure and showed a sharp and constant m. p. The reason for these peculiar results could not be ascertained. Since the substance contains a *C*-methyl group it may be (VII), which has the latter formula and could be produced by the hydrogenolysis of the allylic hydroxyl group, or (VIII), which has the alternative formula and could arise by a preliminaty allylic rearrangement followed by hydrogenation of the vinyl group.



(VI)



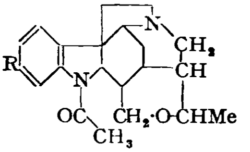
(VII)

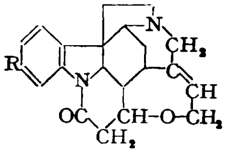


(VIII)

Nevertheless, treatment of the hydrogenated compound with hydrogen bromide in acetic acid (50% w/v) at 180—200°, followed by reduction with zinc dust and acetic acid and acetylation, gave a base, isolated as the perchlorate, $C_{21}H_{28}ON_2,HClO_4,1{\cdot}5H_2O$.

(IX)





(X)

This had the same crystalline form, m. p. and mixed m. p., solubility, rotation, and infrared spectrum as had deoxydihydrospermostrychnine perchlorate. Thus the carbon skeleton of the alkaloids of *S. psilosperma* can be regarded as established and (IX; R = H or OMe) represents the most probable position of the oxide ring. It is seen that there is a remarkable correspondence between the structures of, on the one hand, strychnine (X; R = H) and spermostrychnine (IX; R = H), and, on the other hand, between β-colubrine (X; R = OMe) and strychnospermine (IX; R = OMe).

EXPERIMENTAL

Strychnospermine.—The alkaloid was recrystallised from aqueous methanol and formed colourless needles, m. p. 208—209° (Found: C, 71·6; H, 7·7; *C*-Me, 8·7, 8·5, 8·4. Calc. for $C_{22}H_{28}O_3N_2$: C, 71·7; H, 7·7; 2*C*-Me, 8·2%).

Deacetylstrychnospermine.—The *base*, when crystallised from aqueous methanol and then sublimed *in vacuo*, formed colourless prisms, m. p. 221—222°, $[\alpha]_D^{20}$ −117° (*c*, 2·43 in $CHCl_3$) (Found: *C*-Me, 5·6, 5·6, 5·5. $C_{20}H_{26}O_2N_2$ requires 1*C*-Me, 4·6%). A macrodetermination of *C*-methyl, using 1·96 g. of the base, by Huebner and Troxell's method (*J. Org. Chem.*, 1953, **18**, 736) gave 3·9%; this value may be slightly low as the distillation was stopped after the collection of 800 c.c. of aqueous solution.

Deacetylstrychnospermine Methiodide.—Strychnospermine methiodide (0·5 g.) was boiled with concentrated hydrochloric acid (10 c.c.) and water (10 c.c.) for 2 hr. After dilution to 50 c.c. with water, potassium iodide was added to precipitate the *methiodide* which crystallised from water in colourless needles, m. p. 301—303° (Found: C, 54·4; H, 6·5; N, 5·5. $C_{21}H_{29}O_2N_2I$ requires C, 53·9; H, 6·3; N, 6·0%).

Strychnospermine N-*Oxide.*—A mixture of strychnospermine (2 g.), hydrogen peroxide (2·5 c.c. of 30%), and water (200 c.c.) was heated on a steam-bath for 1 hr., and then boiled for 5 min. after the addition of a little platinum black. On cooling, the filtered solution deposited colourless, glistening, flat needles (1·7 g.), m. p. 261—263° (decomp.). The N-*oxide* recrystallised from water, in which it was only sparingly soluble in the cold (Found: C, 60·4; H, 8·0. $C_{22}H_{26}O_4N_2,3H_2O$ requires C, 60·3; H, 7·8%). Strychnospermine *N*-oxide (1 g.) was dissolved in boiling water (100 c.c.) containing potassium chromate (0·1 g.). The mixture was refluxed for 8 hr., but even after this time only a small amount of a deep red precipitate had separated, and it did not give the reactions of a carbinol-amine. The solution smelled of formaldehyde, which was isolated in small amount as its dimedone derivative.

Deacetyldemethylstrychnospermine.—A mixture of strychnospermine (18 g.) and 40% hydrobromic acid (100 c.c.) was heated under reflux for 1½ hr. Water (300 c.c.) was added and the solution cooled to 0°, and, after several hours, filtered through sintered glass. The pink crystals (22 g.) of the *dihydrobromide* were washed with alcohol, then with ether, and crystallised from dilute hydrobromic acid in large prisms, m. p. 365° (decomp.) (Found: C, 45·2; H, 6·2; Br, 31·5. $C_{19}H_{24}O_2N_2,2HBr,2H_2O$ requires C, 44·7; H, 5·9; Br, 31·3%). Addition of sodium acetate to a solution of the salt in dilute acid caused the separation of the sparingly soluble crystalline *monohydrobromide*, m. p. 340° (Found: C, 58·5; H, 6·5; Br, 20·8. $C_{19}H_{24}O_2N_2,HBr$ requires C, 58·1; H, 6·4; Br, 20·3%). The free base was obtained by adding ammonia to a solution of one of the above salts and extracting with chloroform, but it did not crystallise. It was soluble in sodium hydroxide solution and gave a deep brownish-red colour with concentrated nitric acid. For the preparation of the related rhodamine dye, the dihydrobromide was heated strongly with an excess of phthalic anhydride and the cooled melt dissolved in alcohol.

Demethylstrychnospermine.—Deacetyldemethylstrychnospermine dihydrobromide (10 g.) was heated with acetic anhydride (60 c.c.) and anhydrous sodium acetate (3·3 g.) for an hour on a steam-bath. Water (140 c.c.) was added to destroy the excess of acetic anhydride, and the solution, after cooling in ice, was made alkaline with ammonia. The colourless precipitate was collected, a little more being obtained by chloroform extraction of the solution [total yield, 7·1 g.; m. p. 313—320° (decomp.)]. Crystallisation from aqueous methoxyethanol gave glistening needles of the *phenol*, m. p. 325—327° (decomp.), $[\alpha]_D^{23}$ +82° (*c*, 2·4 in 0·1N-HCl). The substance was soluble in sodium hydroxide solution and it gave a transient blue-violet colour on the addition of a drop of dilute potassium dichromate to its solution in 80% sulphuric acid (Found: C, 70·9, 71·1; H, 7·2, 7·5; N, 8·3; *C*-Me, 9·5. $C_{21}H_{28}O_3N_2$ requires C, 71·2; H, 7·4; N, 7·9; 2*C*-Me, 8·4%).

Methylation of Demethylstrychnospermine.—Methylation with diazomethane in chloroform–methanol was not very satisfactory, owing to the low solubility of the compound, and no strychnospermine could be isolated. By heating demethylstrychnospermine with excess of methyl iodide in methanol containing one mol. of sodium methoxide, a good yield of strychnospermine was obtained, having m. p. and mixed m. p. 335—337° (decomp.).

*Deacetyl-*N*-ethylstrychnospermine.*—A solution of strychnospermine (0·2 g.) in chloroform (10 c.c.) was added to one of lithium aluminium hydride (0·1 g.) in ether (50 c.c.), and the mixture heated under reflux for 1½ hr. Excess of the reagent was decomposed with ethyl acetate, and then sodium hydroxide solution (20 c.c. of 5%) added. The ethereal layer was separated and on evaporation left a colourless oil which crystallised from light petroleum in rectangular and hexagonal prisms (0·15 g.), m. p. 130—131°. Recrystallisation afforded the *base* as clusters of prisms, m. p. 131—131·5° (Found: C, 74·6; H, 8·4, 8·6; N, 8·1, 8·1. $C_{22}H_{30}O_2N_2$ requires C, 74·6; H, 8·6; N, 7·9%). The new base was readily soluble in organic solvents and gave an intense crimson-red colour with ferric chloride in weak acid solution, and a crimson colour with concentrated nitric acid. It coupled readily with diazobenzenesulphonic acid to give an indicator-type dye. The compound was demethylated by boiling it for 1 hr. with 50% hydrobromic acid. The salt obtained from this reaction was fused with phthalic anhydride as described above. The colour of the resulting dye was identical with that of the dye obtained by demethylating hexahydro-7-methoxy-11 : *N*-dimethylcarbazole and fusing the product with phthalic anhydride. Both dyes closely resembled Rhodamine B in respect of colour, tinctorial intensity, and fluorescence.

*Deacetylbromo-*N*-ethylstrychnospermine.*—Bromostrychnospermine (0·5 g.), suspended in dry ether (40 c.c.), was added to a solution of lithium aluminium hydride (0·2 g.) in ether (40 c.c.). After boiling under reflux for 2 hr., the mixture was worked up as described above, to give a colourless oily base, which was converted into the *picrate* in alcohol. The salt, after several recrystallisations from aqueous alcohol, was obtained as yellow needles, m. p. *ca.* 210° with sintering at 195° (Found: C, 51·2; H, 4·8; N, 10·7; Br, 12·5. $C_{28}H_{32}O_9N_5Br$ requires C, 50·8; H, 4·9; N, 10·6; Br, 12·1%). Deacetylbromo-*N*-ethylstrychnospermine picrate gave the same colour reactions as did deacetyl-*N*-ethylstrychnospermine.

Oxidation of Demethylstrychnospermine by Means of Chromic Acid; Formation of apo*Spermostrychnine.*—Demethylstrychnospermine (7 g.), dissolved in water (150 c.c.) and concentrated sulphuric acid (50 c.c.), was slowly treated with a solution of chromic anhydride (18 g.) in water (20 c.c.) during ½ hr. The mixture was kept at room temperature for two days. The excess of chromic acid was then reduced with sulphur dioxide, which was in turn removed by boiling. The solution was made alkaline with barium hydroxide solution and filtered, and the precipitate washed with hot water. The combined filtrates (2 l.) were treated with just enough sulphuric acid to precipitate the barium as sulphate. After filtration the colourless solution was concentrated *in vacuo* to 10 c.c.; crystallisation then occurred. The solid (0·7 g.)

was collected, and more of the same substance (0·9 g.) was obtained on chloroform-extraction of the mother-liquor after neutralisation with sodium hydrogen carbonate. apo*Spermostrychnine* (III) crystallised from water in colourless prisms, m. p. 317—318° (decomp.), $[\alpha]_D^{18}$ $-18°$ (*c*, 2·2 in H_2O) (Found, in material dried at the room temperature: C, 61·1; H, 7·5; N, 9·8; NMe, 2·75; *C*-Me, 6·9; loss at 100°, 7·1. Found, in material dried at 100°: C, 65·0; H, 7·6. $C_{15}H_{20}O_3N_2,H_2O$ requires C, 61·3; H, 7·6; N, 9·5; 1NMe, 9·9; 1*C*-Me, 5·1; $1H_2O$, 6·1. $C_{15}H_{20}O_3N_2$ requires C, 65·2; H, 7·3%). It did not give a colour reactions with oxidising agents or diazonium salts.

Action of Hydrogen Peroxide on apo*Spermostrychnine*.—A solution of the base (0·260 g.) in 3% hydrogen peroxide (1 c.c.) was mixed with one of barium hydroxide (0·35 g.) in water (10 c.c.), kept for an hour and then heated on a steam-bath for 10 min. The precipitated barium carbonate was collected and dried at 100° (Found: 0·170 g. of $BaCO_3$. Required: 0·173 g.). The filtrate was acidified with sulphuric acid, and sulphur dioxide passed through the boiling solution for 15 min. The excess of sulphur dioxide was expelled and barium hydroxide solution added until the sulphate ions were removed. The filtered aqueous solution was evaporated to dryness *in vacuo*, leaving a solid (0·22 g.), $[\alpha]_D^{20}$ $-62°$ (*c*, 0·4 in H_2O), which was freely soluble in water giving an alkaline reaction, but was quite insoluble in ether or acetone. Neither this substance nor its perchlorate crystallised.

Distillation of Deacetylstrychnospermine over Zinc Dust.—The experiment was carried out using the apparatus described by Schmid, Ebnöther, and Karrer (*Helv. Chim. Acta*. 1950, **33**, 1486). Deacetylstrychnospermine (0·5 g.) was mixed with zinc dust (20 g.) and pyrolysed in quantities of 1—2 g. in a stream of hydrogen, the temperature of the furnace being raised to 450° at the end of each operation. The tubes were washed with ether and the washings added to the condensate. The ether extract was shaken with three portions of dilute hydrochloric acid to remove the basic fraction. The ethereal solution, after evaporation, left a residue with an indolaceous odour and giving a strong Ehrlich reaction, but no crystalline picrate could be obtained from it. The hydrochloric acid extract was basified and steam-distilled, and the distillate treated with solid potassium hydroxide and extracted with ether. The addition of ethereal picric acid to the dried extract gave a crop of crystals, which was recrystallised from a little alcohol, forming yellow needles (*ca*. 5 mg.), m. p. 115—120°, mixed m. p. with 3-ethylpyridine picrate [m. p. 127—128° (Karrer *et al., loc. cit.*)] 115—122° (m. p. much depressed by admixture with picric acid) (Found: C, 46·7; H, 3·6. Calc. for $C_{13}H_{12}O_7N_4$: C, 46·5; H, 3·6%).

Attempted Cleavage of the Ether Ring of Strychnospermine.—The only product obtained from the reaction of 65% hydrobromic acid on strychnospermine at temperatures up to 150°, in a sealed tube, was deacetyldemethylstrychnospermine dihydrobromide. In other experiments, the above dihydrobromide (1 g.) was heated in a sealed tube with hydrobromic acid (20 c.c., saturated at $-5°$) at 150—160°. Evaporation of the mixture to dryness *in vacuo* gave a product containing some non-ionic bromine, but it was not obtained crystalline.

Spermostrychnine Methoperchlorate.—When perchloric acid was added to an aqueous solution of spermostrychnine methiodide colourless needles of the *perchlorate* were obtained, having m. p. 250° (decomp.) (Found: C, 59·0; H, 6·6; N, 6·7; Cl, 8·2. $C_{22}H_{29}O_6N_2Cl$ requires C, 58·6; H, 6·5; N, 6·2; Cl, 7·9%).

Deacetylspermostrychnine Hydriodide.—Sodium iodide was added to a solution of deacetylspermostrychnine in dilute hydrochloric acid. The *hydriodide* crystallised and was obtained as colourless, rectangular plates on recrystallisation from water. It did not melt, but blackened above 310° (Found: C, 52·6; H, 6·0; N, 6·5; I, 29·5. $C_{19}H_{25}ON_2I,\frac{1}{2}H_2O$ requires C, 52·7; H, 6·1; N, 6·5; I, 29·3%).

Deacetylformylspermostrychnine.—Deacetylspermostrychnine (0·1 g.) was heated with anhydrous formic acid (5 c.c.) for 1 hr. on the steam-bath. Dilution with water and addition of ammonia precipitated the *formylated base*, which crystallised from acetone in needles, m. p. 260° (decomp.), $[\alpha]_D^{18}$ ±0° (*c*, 2·0 in $CHCl_3$), $[\alpha]_D^{19}$ $-66°$ (*c*, 1·45 in 0·1N-HCl) (Found: C, 74·5; H, 7·7. $C_{20}H_{24}O_2N_2$ requires C, 74·1; H, 7·5%). The Otto reaction (80% sulphuric acid) gave an intense reddish-violet colour, fading through deep red.

Oxidation of Spermostrychnine by Means of Chromic Acid.—A solution of chromic anhydride (2·5 g.) in water (10 c.c.) was gradually added to one of spermostrychnine (0·8 g.) in water (70 c.c.) and 96% sulphuric acid (10 c.c.), the temperature being kept near 60°. After 6 hr. at 60° the solution was allowed to cool overnight. The mixture was worked up as described for the oxidation of demethylstrychnospermine except that the excess of bariun ions was removed with carbon dioxide. The product (0·15 g.) was recrystallised several times from water and then had m. p. 320° (decomp.), unchanged on admixture with *apo*spermostrychnine, $[\alpha]^{20}_{D}$ $-16°$ (*c*, 3·6 in H_2O) (Found : C, 60·9; H, 7·3. Calc. for $C_{15}H_{20}O_2N_2,H_2O$: C, 61·3; H, 7·6%). This base could also be termed *apo*strychnospermine since the benzene ring is removed in both cases and the methoxyl group of strychnospermine is the only feature of the molecule which is not reproduced in spermostrychnine.

Zinc Dust Distillation of Deacetylspermostrychnine.—This was carried out as described for deacetylstrychnospermine, but the hydrobromide (1 g.) was used instead of the free base, as otherwise a considerable quantity escaped pyrolysis by volatilisation. The basic fraction was obtained as before and gave a crystalline picrate, which when crystallised from alcohol–ether and then four times from methanol–ether had m. p. 121—123°, and mixed m. p. with 3-ethylpyridine picrate (m. p. 127—128°) 124—126° (Found : C, 47·2; H, 3·7. Calc. for $C_{13}H_{12}O_7N_4$: C, 46·5; H, 3·6%). The non-basic fraction was distilled in a microsublimation apparatus, giving first fractions, b. p. 110°/0·1 mm. and 150—160°/0·02 mm. The first fraction, which gave a strong Ehrlich reaction, was dissolved in benzene and treated with a solution of picric acid in the same solvent. Careful addition of light petroleum gave dark red crystals (25 mg.), m. p. 120—135°. Recrystallisation from benzene–light petroleum gave reddish-brown needles, m. p. 120—148°, unchanged on admixture with the picrate, of the same m. p., obtained from a synthetic mixture of 3-ethylindole (70%) and skatole (30%) (Wieland and Witkop, *Annalen*, 1947, **558**, 144; Karrer *et al.*, *loc. cit.*). The second fraction was chromatographed in benzene solution over alumina. The benzene eluate was evaporated to dryness and the residue on crystallisation from light petroleum (b. p. 40—60°) gave a minute amount of crystals, m. p. *ca.* 200°, which showed colour reactions typical of carbazole. The amount obtained was insufficient for further purification.

Spermostrychnine N-*Oxide.*—A mixture of spermostrychnine (0·5 g.), hydrogen peroxide (0·5 c.c. of 30%), and water (15 c.c.) was heated for 2 hr. on a steam-bath. A little platinum black was then added and the filtered solution evaporated to dryness. The crystalline residue of the *N*-oxide was recrystallised from acetone and had m. p. 241—243° after sintering at 190—200°. A solution of the *N*-oxide (0·05 g.) in water (2 c.c.) was heated at 100° with potassium chromate (0·005 g.). After 6 hr. only a small amount of precipitate had separated. The solution was filtered, but the substance did not crystallise. It dissolved readily in acids and gave an amorphous neutral compound with nitrous acid.

Deoxydihydrospermostrychnine.—Deacetylspermostrychnine dihydrobromide, prepared from the free base (0·2 g.) and dilute hydrobromic acid, was heated in a sealed tube with hydrogen bromide in acetic acid (30 c.c.; 50% w/v) at 180—200° for 2 hr. The solution obtained was concentrated to a small volume *in vacuo*, diluted with acetic acid (20 c.c.), and treated with zinc dust (5 g.) on a steam-bath for 4 hr. The mixture was filtered and the filtrate made strongly alkaline and then extracted thrice with ether. Evaporation of the extract left an oil, which was warmed with acetic anhydride (2 c.c.) for 30 min. on a steam-bath. The acetylated base was obtained in the usual way and converted into the crystalline *perchlorate*, which after four recrystallisations from aqueous perchlorate acid formed colourless needles (0·08 g.). The perchlorate softened at 117—118° and gradually melted, but it did not clear until 155°. The softening point rose considerably when the perchlorate was dried above room temperature [Found, in material dried at the room temperature : C, 55·8; H, 7·5; *C*-Me, 8·7, 8·3%; $[\alpha]^{23}_{D}$ $+74°$ (*c*, 2·1 in 50% aqueous alcohol), $+70°$ (*c*, 1·0 in the same solvent). In material dried at 117° *in vacuo* : C, 57·0; H, 7·0%; $[\alpha]^{19}_{D}$ $+82°$ (*c*, 1·1 in 50% in aqueous alcohol). In material dried at 130° *in vacuo*: C, 59·7; H, 6·5. $C_{21}H_{28}ON_2,HClO_4,1\frac{1}{2}H_2O$ requires C, 55·8; H, 7·2; 3*C*-Me, 10·0. $C_{21}H_{28}ON_2,HClO_4,H_2O$ requires C, 51·0; H, 7·1. $C_{21}H_{28}ON_2,HClO_4$ requires C, 59·4; H, 6·9%]. The regenerated *base* did not crystallise. It was obtained as a colourless glass by distillation at 0·08 mm. (Found: C, 77·1; H, 8·9. $C_{21}H_{28}ON_2$ requires C, 76·8; H, 8·6%).

Preparation of the Wieland–Gumlich Aldehyde.—The following modification was found more convenient on a large scale, and to give better yields in the last step, than the original method (*loc. cit.*).

A suspension of finely-powdered strychnine (112 g.) in absolute alcohol (1 l.) and *iso*pentyl nitrite (200 c.c.) in a 5-l. flask fitted with a stirrer and an efficient condenser (jacket at −20°) was treated during several hours with a solution of sodium ethoxide prepared from absolute alcohol (1·5 l.) and sodium (31 g.). The temperature was kept at 70° during the addition, and for 4 hr. in all. The clear brown solution was concentrated to a small bulk *in vacuo* and mixed with water (1·5 l.). The mixture was acidified with acetic acid and the upper layer of *iso*pentyl alcohol separated. The alcohol was washed several times with dilute acetic acid and the combined aqueous solutions (*ca.* 2 l.) were treated with charcoal, filtered, and then made alkaline with ammonia. The crystalline precipitate was collected, and washed with water, then with methanol, and finally with ether. The light brown powdery product (84 g.) was completely soluble in dilute alkali and acid.

The above hydroxyiminostrychnine was added to concentrated hydrochloric acid (22 c.c.) in water (500 c.c.). The solution was heated to boiling (charcoal), filtered, and allowed to cool. The hydrochloride formed large yellow needles, which dried at 100° to a yellowish powder (70 g.). The dry hydrochloride (20 g.) was slowly added to thionyl chloride (60 c.c.) at room temperature. When all the product had dissolved it was poured on ice with vigorous stirring, and then kept for some time, the precipitate becoming crystalline. The hydrochloride (17 g,) was collected and washed with methanol and then with ether. It was dissolved in hot water (400 c.c.) containing sodium acetate (10 g.), and the mixture vigorously boiled for 1½ hr., a stream of nitrogen being passed meanwhile. The cold solution was made alkaline with ammonia and extracted with chloroform. The carefully dried extract was concentrated *in vacuo* at as low a temperature as possible, leaving a residue which was triturated with a little acetone and collected. The product (5·7 g.) crystallised from pure chloroform in colourless prisms containing solvent of crystallisation. It showed no carbonyl band in its infrared spectrum.

Reduction of the Wieland–Gumlich Aldehyde; Formation of the Glycol (VI).—(a) *With lithium aluminium hydride.* A solution of the aldehyde (4 g., containing 1 mol. of chloroform) in pure tetrahydrofuran (80 c.c.) was added to a boiling suspension of lithium aluminium hydride (1·4 g.) in the same solvent (100 c.c.). The mixture was refluxed for 2 hr. and then kept overnight. The excess of reagent was decomposed with ethyl acetate, and the mixture shaken with 5% sodium hydroxide solution (50 c.c.). The tetrahydrofuran layer was quickly decanted from the lower aqueous solution and evaporated to dryness. The residue crystallised from aqueous alcohol in colourless prisms (2 g.) of the *base*, m. p. 251—253° (Found: C, 72·9; H, 7·9; N, 8·7. $C_{19}H_{24}O_2N_2$ requires C, 73·0; H, 7·7; N, 9·0%).

(b) *With potassium borohydride.* The aldehyde (4 g.) in 80% methanol (50 c.c.) was added to a solution of potassium borohydride (0·5 g.) in water (15 c.c.). The mixture was kept for ½ hr. and then diluted with water (20 c.c.), and the methanol boiled off. The Wieland–Gumlich glycol (VI) crystallised during the concentration and was collected (2·7 g.) after cooling of the solution; it had m. p. 251—253°, undepressed by admixture with the product prepared by method (a). The *dihydrochloride*, prepared by adding acetone to a solution of the base in dilute hydrochloric acid, formed colourless needles, m. p. 245—250° (decomp.; sintering at 240°), $[\alpha]_D^{20}$ −4° (*c*, 1·8 in H_2O) (Found: C, 56·7; H, 7·2; Cl, 18·3. $C_{19}H_{24}O_2N_2,2HCl,H_2O$ requires C, 56·7; H, 7·0; Cl, 17·6%).

Catalytic Hydrogenation of the Wieland–Gumlich Glycol (VI).—The compound, $C_{19}H_{24}O_2N_2$ (VI) (0·5 g.), in 50% aqueous acetic acid (30 c.c.) was hydrogenated in the presence of palladium chloride (0·15 g. in 10 c.c. of water and 2 c.c. of concentrated hydrochloric acid) and charcoal (1·5 g.). The mixture took up 85 c.c. of hydrogen (22°/760 mm.) during 1 hr., after which absorption ceased. The catalyst was collected and washed with hot water, and the combined filtrate made strongly alkaline with aqueous sodium hydroxide. The crystals (0·4 g.) were collected, and, after drying, had m. p. 170°. They were dissolved in a little dilute hydrochloric acid and the *dihydrochloride* precipitated with acetone. The salt was recrystallised several times from water (3—4 c.c.) by the addition of acetone to incipient opalescence, and was then obtained as colourless glistening needles, m. p. 260—265° (decomp.), $[\alpha]_D^{21}$ −3·3° (*c*, 2·5 in H_2O) (Found: C, 58·6; H, 7·4; Cl, 18·5; *C*-Me, 5·6. Found, in material dried for 5 hr. at 100° *in vacuo*: C, 58·8; H, 7·3. $C_{19}H_{26}O_2N_2,2HCl$ requires C, 58·9; H, 7·5; Cl, 18·3; 1*C*-Me, 3·9%). The regenerated *base* crystallised from methanol in prisms, m. p. 172—174° [Found, in material dried at the room temperature: C, 73·4; H, 8·3. In material dried at 100° for 5 hr.: C, 73·0; H, 8·3. In material sublimed *in vacuo*: C, 74·6, 72·9, 74·7, 74·5; H, 8·2, 8·6, 8·4, 8·4; *C*-Me, 6·3%; *M* (micro-Rast), 244. $C_{19}H_{26}O_2N_2$ requires C, 72·6; H, 8·4; 1*C*-Me, 4·8%; *M*, 314. $C_{19}H_{26}ON_2$ requires C, 76·5; H, 8·8; 1*C*-Me, 5·0%; *M*, 298. $C_{19}H_{24}ON_2,0{\cdot}5H_2O$ requires C, 74·8; H, 8·2%].

Preparation of Dihydrodeoxyspermostrychnine (IV) *from Strychnine.*—The substance (0·15 g.) obtained by hydrogenation of the Wieland–Gumlich glycol (VI) as described above was heated in a sealed tube at 180—190° with hydrogen bromide in acetic acid (25 c.c.; 50% w/v) for 2 hr. The contents of the tube were worked up by reduction with zinc dust and reacetylation as described in the experiment on the cleavage of the ether ring of spermostrychnine. The perchlorate, after four crystallisations from water, formed colourless needles which softened at 117—118° and gradually melted, but did not form a clear liquid until 155°. This behaviour was unchanged on admixture with deoxydihydrospermostrychnine perchlorate. The salt had $[\alpha]_D^{20}$ +78° (*c*, 1·0 in 50% aqueous alcohol) (Found : C, 56·2; H, 7·4. Calc. for $C_{21}H_{28}ON_2,HClO_4,1\frac{1}{2}H_2O$: C, 55·8; H, 7·1%).

The authors thank Dr. F. B. Strauss and Mr. F. H. Hastings for the determinations of the spectra. They also thank the Royal Commissioners for the Exhibition of 1851 for an Overseas Scholarship awarded to one of them (F. A. L. A.).

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, March 2nd*, 1955.]