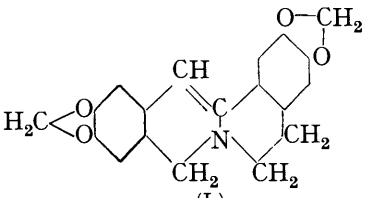
146. *Synthetical Experiments on Protopine and Allied Alkaloids. Part II. New Synthesis of the Berberine Ring-system, and of a Ring-homologue of the Aporphine Alkaloids.*

By THOMAS S. STEVENS.

THE work now described was commenced in 1925, in parallel with the researches of Haworth and Perkin which finally led to the synthesis of cryptopine and protopine (J., 1926, 1769). The first objective was the preparation of the dihydroberberine analogue (I), the readily obtainable substance (II) being used as the starting point, so that the methods elaborated might be available for application to actual alkaloid syntheses involving less accessible initial materials.



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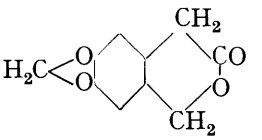

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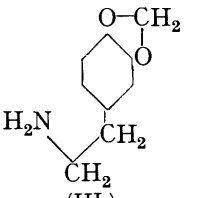

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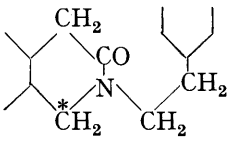

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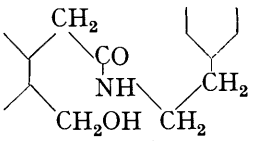

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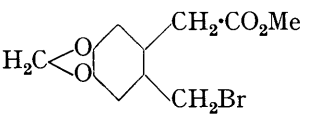

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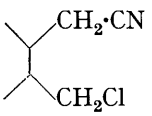

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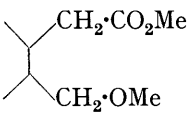
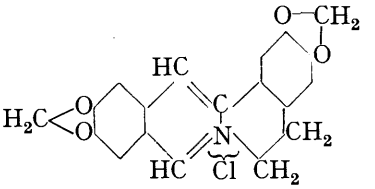


(VIII.)



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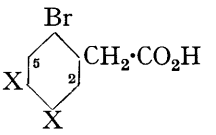
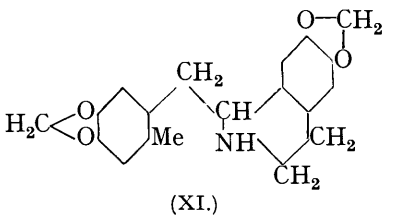


(X.)

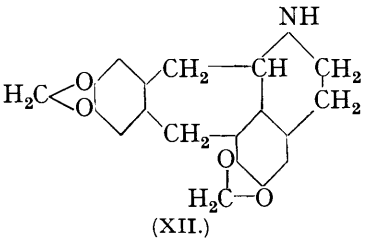
The series of reactions (II) + (III) ⟶ (IV) (compare the production of phthalide-anil from phthalide and aniline) ⟶ (I) was investigated, but the first step led only to the *hydroxy-amide* (V). The *lactam* (IV) was, however, obtained by the action of (VI) or (VII) upon (III), followed in each case by hydrolysis, but its dehydration to (I) could not be effected. Haworth, Perkin, and Pink (J., 1925, **127**, 1709) were similarly unable to dehydrate homophthalimides (as IV, with CO in place of $\overset{*}{C}H_2$).

The *methyl* ether of (V), prepared from (VIII) and (III), when treated with phosphorus pentachloride, underwent a double ring-closure, with elimination of water and methyl alcohol and simultaneous dehydrogenation, to give a 25% yield of the berberine analogue (IX), which has already been described by Buck, Perkin, and Stevens (J., 1925, **127**, 1462). A formal proof is thus supplied of the correctness of the orientations assigned to the berberine derivatives described in that paper. The same product (IX) was similarly obtained, in smaller quantity, from (V) itself. This synthesis of berberine derivatives is simpler, but less flexible, than that used by Haworth and Perkin (*loc. cit.*). Numerous unsuccessful attempts were made to condense formaldehyde with bromohomopiperonylic or bromohomoveratric acids (X: XX = CH_2O_2 or 2OMe) and their derivatives in order to obtain analogues of (II) suitably oriented for actual alkaloid syntheses. Here it was necessary that the entrant group should take up position 2; the alternative position 5 might have led to the synthesis of (XVII) (*vide infra*).

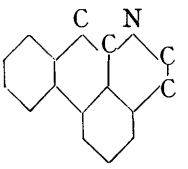
An attempt to prepare (I) from (V) by the action of phosphorus oxychloride yielded a product which could not be purified, but gave the colour reactions of a benzyldihydro-*iso*quinoline. Reduction produced a crystalline secondary base "A" whose analytical data were in better agreement with the formula $C_{19}H_{17}O_4N$ (XII) than with $C_{19}H_{19}O_4N$ (XI).



(XI.)

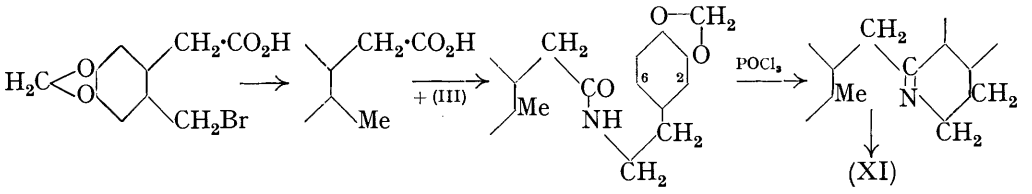


(XII.)



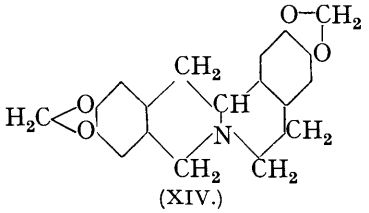
(XIII.)

These are the only formulæ which can be ascribed to "A" with any degree of probability, and (XI) has been excluded by the following synthesis:

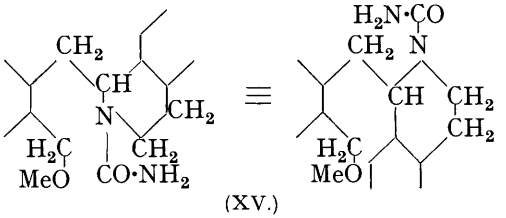


(The product was distinct from "A"; the assumption of ring closure at position 6 rather than at position 2 is supported by numerous analogies.) The remaining alternative (XII) contains the apomorphine skeleton (XIII), modified by the presence of an extra methylene group in the central ring.

Degradative and synthetic experiments designed to confirm the structure attributed to "A" met with very limited success. The base lost its nitrogen at the second stage of exhaustive methylation; the resulting unsaturated compounds yielded no homogeneous product on oxidation.



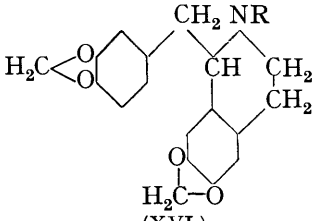
(XIV.)



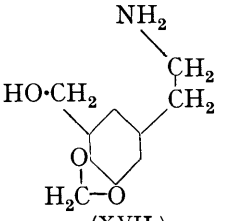
(XV.)

Conversion of (XIV) by successive action of cyanogen bromide, sodium methoxide, and sodium hydroxide into (XV), followed by treatment of the latter with phosphorus oxychloride, and hydrolysis, appeared to yield "A," but the small quantity obtained could

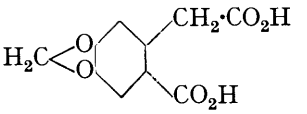
not be identified with certainty. The preparation of derivatives of "A" by condensation of (XVI; R = Me or SO_2Ph) with formaldehyde failed, as did attempts (see experimental part) to prepare (XVII) as initial material for a more elaborate synthesis.



(XVI.)



(XVII.)



(XVIII.)

It was incidentally observed that 6-carboxyhomopiperonylic acid (XVIII) yields 6-bromohomopiperonylic acid when treated with bromine water (compare Jones and Robinson, J., 1917, **111**, 909).

Experimental.

6-Hydroxymethylhomopiperonoyl-β-piperonylethylamine (V).—Equimolecular quantities of β-piperonylethylamine and the lactone (II) (Stevens, J., 1927, 178) were refluxed in benzene for 3 hours, and the solid, recrystallised from alcohol, formed white needles, m. p. 176°, sparingly soluble in alcohol or xylene (Found: C, 63·8; H, 5·4; N, 3·8. $C_{19}H_{19}O_6N$ requires C, 63·9; H, 5·3; N, 3·9%). The same product resulted when the base and the lactone were heated alone at 180—200°; higher temperatures led to decomposition.

3-Keto-6 : 7-methylenedioxy-2-β-piperonylethyl-1 : 2 : 3 : 4-tetrahydroisoquinoline (IV).—The nitrile (VII) (Stevens, *loc. cit.*) (1 mol.) and β-piperonylethylamine (2 mols.) were boiled for 2 hours in benzene, water added to dissolve the solid, and the product precipitated as hydrochloride by hydrochloric acid. *6-β-Piperonylethylaminomethylhomopiperonylonitrile*, liberated by ammonia and extracted with chloroform, crystallised from ligroin in needles, m. p. 77—79° (Found: C, 67·3; H, 5·5. $C_{19}H_{18}O_4N_2$ requires C, 67·5; H, 5·3%). When treated with hydrogen peroxide and alkali in aqueous-alcoholic solution, it yielded the lactam (IV), which was more advantageously prepared as follows: The ester (VI) (Stevens, *loc. cit.*) (1 mol.) was heated for a short time with β-piperonylethylamine (2 mols.) in benzene, excess of alcoholic potash added, and the whole boiled for 2 hours and poured into excess of boiling 10% acetic acid. The substance (IV) was extracted from the resulting solid by hot alcohol or aqueous acetic acid, and crystallised from benzene–ligroin in pale yellow needles, m. p. 144—146° (Found: C, 67·0; H, 5·5. $C_{19}H_{17}O_5N$ requires C, 67·2; H, 5·1%). It resisted the known methods of cyclisation and was mostly recovered unchanged even after fusion with phosphoric oxide at 150°. The residue from the extraction of (IV) was acidic, crystallised from acetic acid in microscopic laminæ, m. p. 225—232° (decomp.), and was evidently *bis-(6-carboxymethyl-homopiperonyl)-β-piperonylethylamine* (Found in material dried at 100°: C, 63·3; H, 5·1. $C_{29}H_{27}O_{10}N$ requires C, 63·4; H, 5·0%).

Synthesis of 2 : 3 : 10 : 11-Bismethylenedioxyprotoberberinium Chloride* (IX).—*6-Methoxymethylhomopiperonyl-β-piperonylethylamine*, prepared by heating equimolecular quantities of β-piperonylethylamine and methyl methoxymethylhomopiperonylate (VIII) (Stevens, *loc. cit.*) for 3 hours at 170°, and crystallised first from methyl alcohol and then from benzene–ligroin, formed a microcrystalline powder, m. p. 103—105° (Found: C, 64·4; H, 6·0; OMe, 8·2. $C_{20}H_{21}O_6N$ requires C, 64·7; H, 5·7; OMe, 8·4%). It was dissolved, with excess of phosphorus pentachloride, in chloroform, and kept in a warm place for several days. The basified mixture was extracted with chloroform, from which a crude picrate was precipitated; the portion of this which dissolved only sparingly in acetic acid was treated with benzene and hot hydrochloric acid, and the berberinium chloride was collected after cooling (Found: Cl, 8·7. Calc. for $C_{19}H_{14}O_4NCl,2H_2O$: Cl, 9·0%). The substance was identified with that prepared by Buck, Perkin, and Stevens, by direct comparison of the chlorides, bromides, and picrates, and by reduction (zinc and sulphuric acid) to the corresponding tetrahydroberberine, m. p. and mixed m. p. 214°.

Substance "A."—Phosphorus oxychloride (6 c.c.) was added to the amide (V) (3 g.) sus-

* See Buck, Perkin, and Stevens (*loc. cit.*) for numbering of protoberberine, and protopapaverine. The name protolaudanosine is used analogously.

pended in boiling toluene (30 c.c.). The solid quickly dissolved, and after 1 hour's boiling, ligroin was added to the cooled solution and the solvents were decanted from the gummy phosphate. When the latter was dissolved in aqueous alcohol and treated with alkali, a yellow solid was obtained, which rapidly turned brown in the air, and then formed yellow salts and gave a green coloration on boiling with acetic anhydride (compare Buck, Haworth, and Perkin, J., 1924, **125**, 2180). The phosphate was dissolved in hot dilute sulphuric acid and reduced with zinc dust; the resulting, sparingly soluble sulphate yielded the base " A " (6 : 7 : 3′ : 4′-*bismethylenedioxy*-8 : 6′-*methylene*-1 : 2 : 3 : 4-*tetrahydroprotopapaverine*), which, repeatedly crystallised from alcohol, formed needles, m. p. 188° (Found : C, 70·8; H, 5·3; N, 4·4; *M*, Rast, 335. $C_{19}H_{17}O_4N$ requires C, 70·6; H, 5·3; N, 4·3%; *M*, 323). The nearly colourless solution in concentrated sulphuric acid gave with a crystal of potassium nitrate an intense brownish-purple coloration, which slowly faded to yellow. The p-*nitrobenzoyl* derivative, prepared in warm pyridine, crystallised from much acetic acid in clusters of minute, pale yellow, prismatic needles, decomp. 285° (Found : C, 65·8; H, 4·5. $C_{26}H_{22}O_7N_2$ requires C, 66·1; H, 4·3%). The benzenesulphonyl derivative, similarly obtained, crystallised from benzene–alcohol in irregular prisms, m. p. 215—218°.

Exhaustive Methylation.—Methyl sulphate and sodium carbonate were added in moderate excess to a suspension of the base " A " in boiling methyl alcohol. The base quickly dissolved, and after 1 hour's heating the acidified and concentrated solution was treated with solid potassium bromide. 6 : 7 : 3′ : 4′-*Bismethylenedioxy*-8 : 6′-*methyleneprotolaudanosine methobromide* was precipitated, and formed cream-coloured rectangular laminæ from water, m. p. 210—220° (decomp.) (Found : Br, 17·5; loss at 130°, 3·8. $C_{21}H_{22}O_4NBr,H_2O$ requires Br, 17·7; loss, 4·0%). Heated for 2 hours on the water-bath with excess of methyl-alcoholic potash, it yielded 6 : 7 : 3′ : 4′-*bismethylenedioxy*-8 : 6′-*methyleneprotolaudanosine methine*, which was purified through the sparingly soluble *hydrochloride*, minute leaflets, m. p. 170—174° with previous softening (Found : HCl, 9·0. $C_{21}H_{21}O_4N,HCl$ requires HCl, 9·4%). The free base formed needles from ligroin, m. p. 101° (Found : C, 71·5; H, 5·9; equiv., 351. $C_{21}H_{21}O_4N$ requires C, 71·8; H, 6·0%; equiv., 351). The *methobromide*, prepared *via* the methosulphate, crystallised from water in small needles, which softened from 210° and decomposed at 265° (Found : Br, 16·9; loss at 130°, 7·0. $C_{22}H_{24}O_4NBr,2H_2O$ requires Br, 16·6; loss, 7·5%). The nitrogen-free compound formed on treatment with alkali was amorphous and presumably polymerised.

Synthesis of 6 : 7 : 3′ : 4′-*Bismethylenedioxy*-6′-*methyl*-1 : 2 : 3 : 4-*tetrahydroprotopapaverine* (XI).—A solution of the lactone (II) in acetic acid–hydrobromic acid was kept for some hours and reduced with zinc dust at 80°. A chloroform extract of the filtered, diluted, and acidified (hydrochloric) mixture yielded to sodium bicarbonate solution 6-*methylhomopiperonylic acid*. This formed small prisms from benzene, m. p. 148—151°, which were sparingly soluble in water (Found : C, 62·0; H, 5·3. $C_{10}H_{10}O_4$ requires C, 61·8; H, 5·2%). Heated at 190° for 2 hours with a slight excess of β-piperonylethylamine, it gave 6-*methylhomopiperonoyl*-β-*piperonylethylamine*, needles from alcohol, m. p. 158—160° (Found : N, 4·2. $C_{19}H_{19}O_5N$ requires N, 4·1%). This amide was cyclised and reduced as described for the preparation of " A " above; after liberation with ammonia and extraction with chloroform, the base (XI) crystallised from benzene–ligroin in minute needles, m. p. 92—94° (Found : equiv., 328. $C_{19}H_{19}O_4N$ requires equiv., 325). The *picrate* formed deep orange prisms from much acetic acid, m. p. 240° (decomp.) (Found : C, 54·5; H, 3·8. $C_{19}H_{19}O_4N,C_6H_3O_7N_3$ requires C, 54·2; H, 4·0%).

Synthesis of " A " from Bismethylenedioxytetrahydroprotoberberine.—Excess of cyanogen bromide was added to a suspension of the base (XIV) in hot benzene, and the mixture kept at 70° for 3 hours. The solvent was distilled, and the residue heated for ½ hour with excess of methyl-alcoholic sodium methoxide and for 1½ hours more after addition of water. The acid-soluble material, a weak base, formed leaflets from methyl alcohol, m. p. 75—80° (unchanged by repeated crystallisation), and was probably 6 : 7 : 3′ : 4′-*bismethylenedioxy*-2-*carbamyl*-6′-*methoxymethyl*-1 : 2 : 3 : 4-*tetrahydroprotopapaverine* (XV) (Found : N, 6·9, 7·0. $C_{21}H_{22}O_6N_2$ requires N, 7·0%). It was boiled for 1½ hours with phosphorus oxychloride in toluene, treated with alcohol and sodium hydroxide solution, and the product extracted with chloroform and boiled for 4 hours with butyl-alcoholic potash. A small quantity of basic material resulted, which, after recrystallisation, melted at 175° alone or mixed with " A," and gave the colour reaction of that substance. Alteration in conditions did not improve the yield, and lack of material prevented repetition on a large scale.

6 : 7 : 3′ : 4′-*Bismethylenedioxy*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydroprotopapaverine* (XVI; R = Me) was prepared by refluxing the crude product of cyclisation of homopiperonoyl-β-piperonylethylamine (Buck, Perkin, and Stevens, *loc. cit.*) in benzene with excess of methyl sulphate,

and reducing the gummy methosulphate with zinc dust and dilute sulphuric acid; the resulting sparingly soluble sulphate was recrystallised from alcohol–ether. The *picrate*, orange-yellow prisms from much acetic acid, decomposed at 210° (Found : N, 9·9. $C_{19}H_{19}O_4N,C_6H_3O_7N_3$ requires N, 10·1%). 6 : 7 : 3′ : 4′-*Bismethylenedioxy*-2-*benzenesulphonyl*-1 : 2 : 3 : 4-*tetrahydroprotopapaverine* (XVI; R = SO_2Ph), prepared from the secondary base (Buck, Perkin, and Stevens, *loc. cit.*) in warm pyridine–benzene, formed long rectangular laminæ from benzene, m. p. 110—113° (Found : N, 3·4. $C_{24}H_{21}O_6NS$ requires N, 3·1%).

Attempts to prepare (XVII).—*Aceto*-6-*bromo*-β-*piperonylethylamide*, from the amine (Stevens, *loc. cit.*), formed needles, m. p. 125°, from aqueous methyl alcohol (Found : N, 4·9. $C_{11}H_{12}O_3NBr$ requires N, 4·9%). This amide, and 6-bromohomopiperonylic acid (X) and its nitrile and methyl ester, were separately treated with formaldehyde under a variety of conditions in the hope that the group $-CH_2{\cdot}OH$ might enter in position 5, but this could not be effected. 6-Bromohomopiperonylic acid, obtained by bromination of homopiperonylic acid in warm acetic acid, was identical with material prepared from 6-bromopiperonal according to Girardet (*Helv. Chim. Acta*, 1931, **14**, 514). The *methyl* ester crystallised from methyl alcohol in needles, m. p. 84° (Found : Br, 29·1. $C_{10}H_9O_4Br$ requires Br, 29·3%), and with methyl-alcoholic ammonia at 130° yielded the *amide*, needles from much benzene, m. p. 181° (Found : Br, 31·2. $C_9H_8O_3NBr$ requires Br, 31·0%). The amide (1 g.), phosphorus oxychloride (2 c.c.), and toluene (5 c.c.) were boiled for 2½ hours, poured into sodium carbonate solution, and the *nitrile* extracted with chloroform; it formed long prisms from aqueous methyl alcohol, m. p. 65—67° (Found : Br, 32·7. $C_9H_6O_2NBr$ requires Br, 33·2%). The same substance was prepared from 6-bromopiperonylpyruvic acid (Girardet, *loc. cit.*) *via* the *oxime* [minute prisms from aqueous alcohol, m. p. 166—167° (decomp.) (Found : N, 5·0. $C_{10}H_8O_5NBr$ requires N, 4·6%)], as described by Edwards for the bromine-free analogue (J., 1926, 744).

Action of Bromine Water on 6-*Carboxyhomopiperonylic Acid* (XVIII).—The acid, dissolved in the least possible quantity of sodium carbonate solution, was treated with excess of bromine water. The first additions caused a deep blue coloration, which gave place to a yellowish precipitate; further gradual addition of carbonate restored the coloration and finally gave a clear dark solution, from which 6-bromohomopiperonylic acid (mixed m. p.) was obtained.

The author wishes to thank the Ramsay Memorial Trustees for a Fellowship, and the Carnegie Trustees for a Teaching Fellowship.

THE UNIVERSITIES OF OXFORD AND GLASGOW. [*Received, March 21st*, 1935.]