LXXXII.—*A New Synthesis of Oxyberberine and a Synthesis of Palmatine.**

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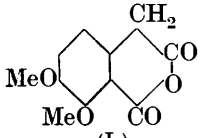
THE general method devised for the synthesis of the berberine type of alkaloid (Haworth, Perkin, and Pink, J., 1925, **127**, 1709) has been applied to the synthesis of *epi*berberine and of 2 : 3 : 9 : 10-bismethylenedioxyprotoberberine † by utilising 3 : 4-methylenedioxyhomophthalic acid (Haworth and Perkin, J., 1926, 1769) as the starting point.

The present communication describes the preparation of 3 : 4-*dimethoxyhomophthalic anhydride* (I) and the use of this substance in the synthesis of oxyberberine and palmatine. 3 : 4-Dimethoxyhomophthalic anhydride (I) was prepared by a slight modification of the method used in the preparation of 3 : 4-methylenedioxyhomophthalic acid (Haworth, Perkin, and Stevens, J., 1926, 1764). β-Veratrylpropionic acid was brominated and the β-6-*bromoveratrylpropionic acid* converted into 4-*bromo*-6 : 7-*dimethoxy*-1-*hydrindone* (II) by treatment with concentrated sulphuric acid. The iso*nitroso*-derivative was prepared in the usual manner and treated with

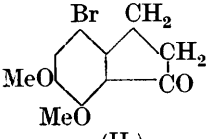
* Compare Späth and Quietensky (*Ber.*, 1925, **58**, 2267).

† Kitasato (*Proc. Imp. Acad. Tokyo*, 1926, **2**, 124) has recently isolated an alkaloid from *Coptis japonica*, which he has named coptisine. This alkaloid appears to be identical with 2 : 3 : 9 : 10-bismethylenedioxyprotoberberine, obtained as an intermediate stage in the synthesis of protopine (Haworth and Perkin, *loc. cit.*, p. 1783).

toluene-*p*-sulphonyl chloride in alkaline solution, and the resulting 6-*bromo*-2-*carboxy*-3 : 4-*dimethoxyphenylacetonitrile* was hydrolysed to 6-*bromo*-3 : 4-*dimethoxyhomophthalic acid* (III). This acid was debrominated in alkaline solution with sodium amalgam, and the crude 3 : 4-dimethoxyhomophthalic acid converted into its *anhydride* (I) by the action of acetyl chloride.



(I.)



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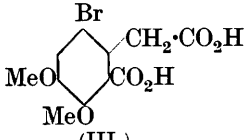
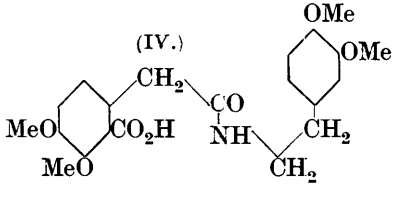
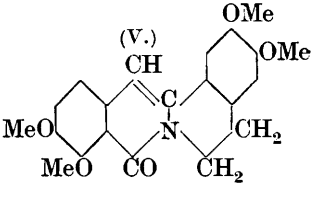


(III.)

In order to establish the constitution of the anhydride (I), and the possibility of its application to the syntheses of substances of the berberine type, it was first condensed with β-piperonylethylamine, the resulting unpurified amic acid esterified, the crude methyl ester boiled with phosphorus oxychloride, and the resulting oxyberberine identified by comparison with a specimen obtained by the action of sodium hydroxide on berberinium chloride.

For the synthesis of palmatine, 3 : 4-dimethoxyhomophthalic anhydride (I) was condensed with β-veratrylethylamine, and N-β-*veratrylethyl*-3 : 4-*dimethoxyhomophthalamic acid* (IV) was obtained as a gum which so far has not been crystallised. The *methyl* ester, prepared from the silver salt of the acid (IV), was converted by treatment with phosphorus oxychloride into a substance, $C_{21}H_{21}O_5N$, m. p. 183°, which exhibited the properties characteristic of a substance of the oxyberberine type. There can be no doubt that this substance is *oxypalmatine* (V), which does not appear to have been previously described. The oxypalmatine was reduced electrolytically and thus converted into a base, m. p.

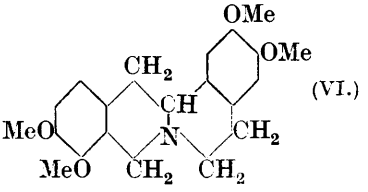




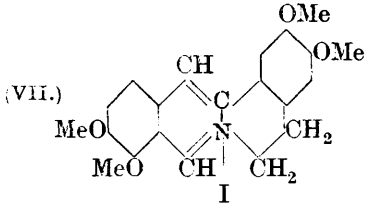
147°, which was identical with a specimen of tetrahydropalmatine (VI) obtained by reducing palmatine iodide. The synthetical tetrahydropalmatine was next oxidised by iodine to a bright yellow iodide and this was identical with a specimen of palmatine iodide (VII) obtained from the natural alkaloid.*

* Professor E. Späth was kind enough to furnish us with a sample of palmatine iodide of natural origin, which made direct comparison possible.

The authors are continuing these researches with a view to the synthesis of the ten-membered ring alkaloid (VIII).

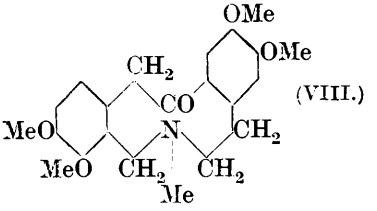


(VI.)



(VII.)

I



(VIII.)

EXPERIMENTAL.

β-6-*Bromoveratrylpropionic Acid.*—Bromine (1¼ mols.), dissolved in glacial acetic acid (1 part), was gradually added with shaking and cooling to β-veratrylpropionic acid (1 mol.) in glacial acetic acid (2 parts). The bromo-acid rapidly separated, and, after remaining for 12 hours, the mixture was diluted with water and the acid was collected and dried; it recrystallised from benzene in colourless prisms, m. p. 118—119° (yield, 90% of the theoretical) (Found : C, 46·0; H, 4·5. $C_{11}H_{13}O_4Br$ requires C, 45·7; H, 4·5%).

4-*Bromo*-6 : 7-*dimethoxy*-1-*hydrindone* (II).—β-6-Bromoveratrylpropionic acid (10 g.) was dissolved in concentrated sulphuric acid (50 c.c.) at 75°, and maintained at this temperature for 5 minutes. The deep red solution was poured into ice and extracted with chloroform; the extract was washed with aqueous sodium carbonate and dried, and the solvent removed.* The residual oil, which solidified on rubbing, crystallised from methyl alcohol in almost colourless needles (2·5 g.), m. p. 120—121° (Found : C, 48·5; H, 4·0. $C_{11}H_{11}O_3Br$ requires C, 48·7; H, 4·1%). The *oxime*, prepared by the action of hydroxylamine hydrochloride and potassium acetate on an alcoholic solution of the bromohydrindone (II), is sparingly soluble in ethyl alcohol, from which it crystallises in colourless prisms, m. p. 228—230° (Found : N, 4·7. $C_{11}H_{12}O_3NBr$ requires N, 4·8%).

4-*Bromo*-2-iso*nitroso*-6 : 7-*dimethoxy*-1-*hydrindone*. — The bromo-

* In attempts to prepare the hydrindone (II) on a larger scale, debromination occurred to a considerable extent, resulting in the formation of a mixture of the bromohydrindone (II) and 5 : 6-dimethoxy-1-hydrindone.

hydrindone (II) (2 g.), dissolved in the minimum of methyl alcohol containing concentrated hydrochloric acid (3 c.c.), was saturated with methyl nitrite; the precipitated iso*nitroso*-derivative crystallised from ethyl alcohol in slender, elongated, pale yellow prisms (2 g.), m. p. 236° (decomp.) (Found: C, 44·2; H, 3·4. $C_{11}H_{10}O_4NBr$ requires C, 44·0; H, 3·3%).

6-*Bromo*-2-*carboxy*-3 : 4-*dimethoxyphenylacetonitrile*. — The *iso*-nitrosohydrindone (2 g.) in aqueous sodium hydroxide (18 c.c. of 8%) was gradually treated with toluene-*p*-sulphonyl chloride (2 g.) with shaking, and solution completed by raising the temperature to 80°. When the mixture was cooled, filtered, and acidified with hydrochloric acid, the *nitrile* separated as an oil, which solidified on rubbing and crystallised from much boiling water in almost colourless needles, containing $1H_2O$, m. p. 98—100° (Found: loss at 100°, 5·1. Calc. for $1H_2O$, 5·6%. Found in material dried at 100°: C, 43·5; H, 3·6. $C_{11}H_{10}O_4NBr$ requires C, 44·0; H, 3·3%).

6-*Bromo*-3 : 4-*dimethoxyhomophthalic Acid* (III).—Crude 6-bromo-2-carboxy-3 : 4-dimethoxyphenylacetonitrile was boiled with sodium hydroxide solution (8%) until evolution of ammonia had ceased. The solution was acidified with dilute hydrochloric acid, extracted several times with ether and dried, the ether removed, and the residual light brown gum refluxed with a slight excess of acetyl chloride for ½ hour. After evaporation under reduced pressure, the *anhydride* separated, and crystallised from benzene in very pale yellow, glistening plates, m. p. 151° (Found: C, 44·0; H, 3·0. $C_{11}H_9O_5Br$ requires C, 43·9; H, 3·0%). 6-*Bromo*-3 : 4-*dimethoxyhomophthalic acid* (III) was obtained by hydrolysing the above anhydride with sodium hydroxide solution (8%), acidifying the mixture with hydrochloric acid, extracting it with ether, drying the extract and removing most of the solvent, adding benzene, and removing the remaining ether. The acid (III) slowly separated in colourless prisms, m. p. 166—167°, which were readily soluble in water and ether but sparingly soluble in benzene (Found: C, 41·4; H, 3·4. $C_{11}H_{11}O_6Br$ requires C, 41·6; H, 3·5%).

3 : 4-*Dimethoxyhomophthalic Anhydride* (I).—Pure bromodimethoxyhomophthalic anhydride (5 g.) was dissolved in sodium hydroxide solution (8%), diluted with water, and heated on the water-bath for 12 hours with sodium amalgam (150 g. of 4%). The solution was cooled, filtered, acidified, and extracted several times with ether, the extract dried, the ether removed, and the residual brown oil, consisting of 3 : 4-dimethoxyhomophthalic acid, converted into 3 : 4-*dimethoxyhomophthalic anhydride* (I) by boiling with acetyl chloride, which was then evaporated under reduced pressure. The

anhydride separated from dry benzene in almost colourless plates, m. p. 104—105°, which became sticky on long standing owing to absorption of water (Found: C, 59·6; H, 4·5. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%). A crystalline specimen of 3 : 4-dimethoxyhomophthalic acid has not yet been obtained.

Oxyberberine.—A benzene solution of 3 : 4-dimethoxyhomophthalic anhydride (I) (1·1 g.) and β-piperonylethylamine (from 2·0 g. of the hydrochloride) was refluxed for 1 hour, the solution extracted with aqueous sodium hydroxide (8%), the alkaline layer acidified, the precipitated oily amic acid extracted with chloroform and dried, and the solvent removed. The residual gum (1·5 g.) was dissolved in water containing sodium bicarbonate (0·35 g.), and the filtered solution was treated with silver nitrate (1·0 g.). After remaining over-night, the precipitated silver salt was collected, successively washed with water, methyl alcohol, and ether, dried, powdered, suspended in ether, and refluxed for 12 hours with excess of methyl iodide. After filtering from the silver salts, the ether was removed, and the residual gum boiled with phosphorus oxychloride for 5 minutes, forming a red solution. The excess of the oxychloride was removed under reduced pressure, and the residue was diluted with hot water, treated with charcoal, and filtered. The filtrate was made alkaline with sodium hydroxide, the amorphous precipitate extracted with chloroform, the solvent removed from the extract, and the residue digested for some time with dilute hydrochloric acid; the solid obtained crystallised from glacial acetic acid, containing a little water, in pale yellow needles, m. p. 197·5°. After three successive crystallisations from alcohol, xylene, and alcohol, pale yellow needles (0·15 g.), m. p. 198—200°, were obtained, which showed no depression in m. p. when mixed with a specimen of oxyberberine prepared by the action of sodium hydroxide on berberinium chloride. The colour reactions of the synthetical product corresponded with those exhibited by oxyberberine.

N-β-*Veratrylethyl*-3 : 4-*dimethoxyhomophthalamic Acid* (IV).—3 : 4-Dimethoxyhomophthalic anhydride (I) (1·2 g.) and β-veratrylethylamine (1·0 g.) were refluxed for 3 hours in benzene (10 c.c.), and the product was extracted with sodium hydroxide solution (5%), the alkaline layer acidified, the precipitated light brown oil extracted with chloroform, the extract dried, and the solvent removed. The residual oil (2·0 g.) was dissolved in water, containing sodium bicarbonate (0·5 g.), and treated with excess of silver nitrate. After 12 hours, the precipitated silver salt was collected, washed successively with water, methyl alcohol, and ether, dried in a desiccator, powdered, suspended in ether, and refluxed

with excess of methyl iodide for 12 hours. After filtering from silver salts, the ethereal solution was concentrated; the crystalline *methyl* ester, m. p. 90—94°, obtained recrystallised from ether in colourless plates, m. p. 93—94° (Found: C, 63·4; H, 6·5. $C_{22}H_{27}O_7N$ requires C, 63·3; H, 6·4%). It is soluble in most organic solvents with the exception of light petroleum.

Oxypalmatine (V).—The methyl ester was boiled with phosphorus oxychloride for 10 minutes, and the dark red solution concentrated under diminished pressure. A solution of the residue in boiling water was treated with charcoal, filtered, and made alkaline with sodium hydroxide, and the precipitate was extracted with chloroform. The extract was dried, the chloroform removed, and the residue digested with dilute hydrochloric acid; the crystalline solid obtained recrystallised from methyl alcohol in buff-coloured prisms, m. p. 183° (Found: C, 68·8; H, 5·6. $C_{21}H_{21}O_5N$ requires C, 68·6; H, 5·7%).

Oxypalmatine dissolves in glacial acetic acid and is precipitated by addition of water, and its solution in ethyl alcohol or benzene exhibits a bluish-violet fluorescence. When it is treated with sulphuric acid (50%), a sparingly soluble, bright yellow *sulphate* separates and the addition of a drop of concentrated nitric acid produces an intense violet coloration.

Tetrahydropalmatine (VI).—Oxypalmatine (1 g.), dissolved in methyl alcohol (60 c.c.) and concentrated sulphuric acid (40 c.c.), was reduced in an electrolytic cell with a current of $4\frac{1}{2}$ amps. for 18 hours with water-cooling and for a further 6 hours without cooling. The almost colourless solution was diluted with an equal volume of water, treated with charcoal, filtered, made alkaline with ammonia, and extracted with chloroform, and the extract was dried and the solvent removed. The residue, consisting of crude tetrahydropalmatine, was converted into the sparingly soluble hydrochloride by the action of a little dilute hydrochloric acid. The hydrochloride was collected, dissolved in hot water, and treated with sodium hydroxide; the amorphous base thus obtained crystallised from methyl alcohol in colourless, rhombic plates, m. p. 147° (Found: C, 71·2; H, 7·1. Calc. for $C_{21}H_{25}O_4N$: C, 71·0; H, 7·0%). A specimen of tetrahydropalmatine was prepared by reducing palmatine iodide with zinc dust and dilute sulphuric acid, and no alteration was observed in the melting point of a mixture of this and the synthetical base.

Palmatine Iodide (VII).—Synthetical tetrahydropalmatine (0·1 g.), dissolved in ethyl alcohol, was oxidised by boiling it with an excess of alcoholic iodine in the presence of potassium acetate. The red periodide which rapidly separated was collected, washed

with ethyl alcohol, suspended in much boiling water, and decomposed with sulphurous acid, and the solution obtained was filtered and cooled. The sparingly soluble palmatine iodide separated in long, orange-yellow needles, m. p. 241° (decomp.), and showed no depression in melting point when mixed with a specimen of palmatine iodide sent us by Professor E. Späth.

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