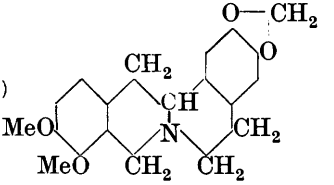
XXIX.—*Synthetical Experiments on Protopine and Allied Alkaloids. Part I.*

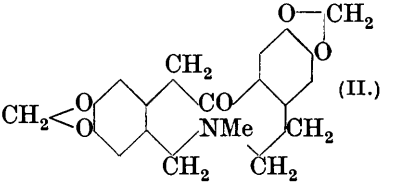
By THOMAS STEVENS STEVENS.

THE present investigation was undertaken with the object of elaborating methods for the production of the ten-membered ring of cryptopine, protopine, and related alkaloids by a direct ring-closure, without previous formation of a structure of the type of tetrahydroberberine (I) (compare Haworth and Perkin, J., 1926, 445, 1769). The synthesis of the isomeride (II) of protopine was first projected, on account of the accessibility of suitable initial materials, and this communication deals with attempts to bring about ring-closure between the carbonyl group and the adjacent benzene nucleus.

(I.)

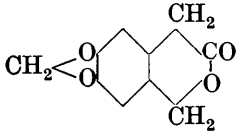
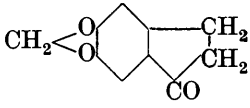


(II.)

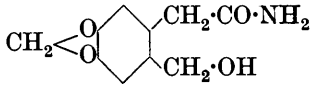
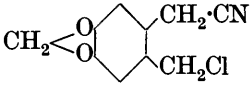


Homopiperonylic acid condenses readily with formaldehyde to give the *lactone* (III) of 6-hydroxymethylhomopiperonylic acid, which was employed as the initial material for the " left-hand half "

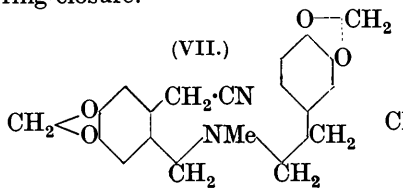
of the molecule (II). The constitution of this lactone was established by oxidation with permanganate, whereby it was converted into the methylenedioxyhomophthalic acid obtained by Perkin and Robinson (J., 1907, **91**, 1086) from 5 : 6-methylenedioxy-1-hydrindone (IV), which latter gives hydrastic acid on oxidation. In the first series of experiments, the lactone was converted by ammonia

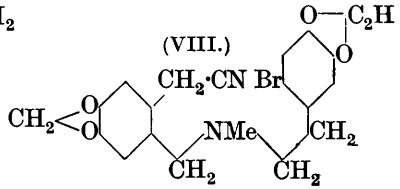
(III.)   (IV.)

into 6-*hydroxymethylhomopiperonylamide* (V), and the amide treated with phosphorus trichloride, giving 6-*chloromethylhomopiperonylonitrile* (VI). By condensing this nitrile with *N*-methyl-β-piperonylethylamine, N-*methyl*-N-β-*piperonylethyl*-6-*aminomethylhomopiperonylonitrile* (VII) was obtained, but attempts to convert this into (II) by an intramolecular Hoesch reaction were unsuccessful, only the corresponding *amide* being produced.

(V.)   (VI.)

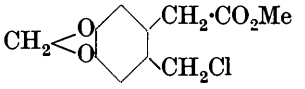
N-Methyl-β-piperonylethylamine is readily monobrominated in the 6-position, as is shown by the preparation of an identical product from 6-bromo-β-piperonylpropionamide (Haworth, Perkin, and Stevens, J., 1926, 1764) by treatment with sodium hypochlorite followed by methylation of the resulting 6-bromo-β-piperonylethylamine. The nitrile (VI) reacts with N-*methyl*-6-*bromo*-β-*piperonylethylamine*, giving N-*methyl*-N-6′-*bromo*-β-*piperonylethyl*-6-*aminomethylhomopiperonylonitrile* (VIII). It was not found possible to close the 10-membered ring, producing the substance (II), by an internal Grignard reaction involving the bromine atom and the nitrile group. As the material was invariably recovered unchanged, and therefore no organomagnesium compound was formed, it did not seem likely that better results would be obtained by preparing the ester corresponding to the nitrile (VIII), and attempting a similar ring-closure.

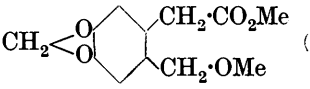
(VII.) 

(VIII.) 

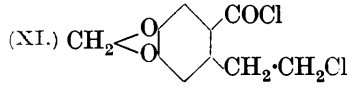
It was hoped that successive treatment with phosphorus tri-

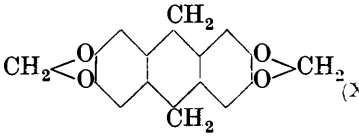
chloride and methyl alcohol would convert the lactone (III) into methyl 6-chloromethylhomopiperonylate (IX), but only the *methoxy*-ester (X) was obtained. This result provides a striking illustration of the mobility of the halogen in the methylenedioxybenzyl halides; the isomeric 6-β-chloroethylpiperonoyl chloride (XI), in which the

(IX.) 

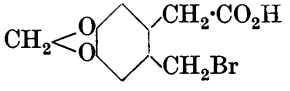
 (X.)

halogen is one position farther removed from the benzene nucleus, is smoothly converted into the corresponding chloro-ester (Perkin, J., 1890, **57**, 1032). The methoxyl group in methoxymethylhomopiperonylic acid is removed with remarkable ease: warming with dilute hydrochloric acid on the steam-bath rapidly converts the acid into the lactone (III). In the same way homopiperonyl methyl ether (Greene and Robinson, J., 1922, **121**, 2194) was found to give

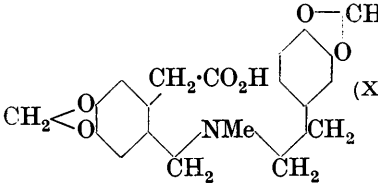
(XI.) 

 (XII.)

2 : 3 : 6 : 7-bismethylenedioxy-9 : 10-dihydroanthracene (XII), which is known to be produced from homopiperonyl alcohol under experimental conditions similar to those employed (compare Ewins, J., 1909, **95**, 1486; G. M. Robinson, J., 1915, **107**, 270).



(XIII.)

 (XIV.)

By treatment with hydrogen bromide, the substance (III) is converted into 6-*bromomethylhomopiperonylic acid* (XIII), which is reconverted into the lactone by primary or secondary bases but readily forms the *methyl* ester with diazomethane. This ester yields N-*methyl*-N-β-*piperonylethyl*-6-*aminomethylhomopiperonylic acid* (XIV) on condensation with *N*-methyl-β-piperonylethylamine and subsequent hydrolysis. It was not found possible to transform this into the compound (II) by conversion into the acid chloride and treatment with aluminium chloride.

Experimental.

Homopiperonylic Acid.—Much of the homopiperonylic acid used in this investigation was prepared by the following method, which

is more convenient and much cheaper than that described by Buck and Perkin (J., 1924, **125**, 1679). Ethyl 3 : 4-methylenedioxymandelate (Barger and Ewins, J., 1909, **95**, 554), when boiled with 5—10% sodium hydroxide solution (10 parts), dissolves at once; the acid is obtained from the cooled and acidified solution: the troublesome hydrolysis with alcoholic alkali described by these authors is unnecessary. The acid (50 g.) is dissolved in acetic acid (500 c.c.) at 50—60°, and dry hydrogen bromide (50 g.) passed in. After 2 hours, the piperonylbromoacetic acid (not isolated) is reduced by addition of zinc dust (50 g.). The mixture is heated for 1½—2 hours on the steam-bath, hydrochloric acid (200 c.c.) added, and, when reaction ceases, the solution is filtered and cautiously diluted with water. Most of the homopiperonylic acid crystallises on standing, and a further quantity is obtained by extraction with chloroform. Yield, 75%.

Lactone of 6-Hydroxymethylhomopiperonylic Acid (III).—Homopiperonylic acid (10 g.), dissolved in hot acetic acid (30 c.c.), is mixed with hydrochloric acid (10 c.c.) and formalin (10 c.c. of 40%) and heated on the steam-bath for 45 minutes. The mixture is poured into water, extracted with chloroform, and the extract concentrated after being washed with sodium bicarbonate solution. The *lactone* separates on cooling and crystallises from alcohol in colourless leaflets, m. p. 137° (Found: C, 62·8; H, 4·2. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%). It is readily soluble in chloroform, less soluble in alcohol or benzene, very sparingly soluble in hot water, and almost insoluble in light petroleum. Cold sodium carbonate solution has no action on the lactone, but this dissolves readily in warm sodium hydroxide solution, and rapidly separates unchanged in the crystalline condition on acidification.

4 : 5-*Methylenedioxyhomophthalic Acid*.—To a solution of the lactone (2 g.) in warm dilute sodium hydroxide solution kept at 30—40°, potassium permanganate (3 g.), in aqueous solution, is gradually added. The mixture is treated with sulphur dioxide, concentrated, and strongly acidified; the acid then rapidly crystallises. It is freed from any unchanged lactone by solution in sodium carbonate and reprecipitation, and recrystallised from acetic acid, being obtained in small, colourless prisms, m. p. about 240° (decomp.). Perkin and Robinson (*loc. cit.*) give 236° (decomp.) (Found: C, 53·3; H, 3·7. Calc. for $C_{10}H_8O_6$: C, 53·6; H, 3·6%). The isomeric 3 : 4-methylenedioxyhomophthalic acid melts at 203—204° (decomp.) (Haworth, Perkin, and Stevens, *loc. cit.*). More drastic treatment of the lactone with permanganate, in the hope of obtaining hydrastic acid, gave oxalic acid as the only isolable product; further experiments on its oxidation, which are still in progress,

have led, among other results, to the indirect conversion of the lactone (III) into hydrastic acid, thus confirming the constitution assigned to it.

6-*Hydroxymethylhomopiperonylamide* (V).—The lactone (III) (10 g.) is dissolved in hot alcohol (80 c.c.), mixed with ammonia (250 c.c.; *d* 0·880), and warmed on the steam-bath for ½ hour. The solid which separates soon redissolves, and the *amide* (7 g.) crystallises on cooling. It forms fine, white needles from water or alcohol; m. p. 164—167° (Found: C, 57·7; H, 5·5; N, 6·5. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3; N, 6·7%). The substance is readily soluble in hot water or alcohol, very sparingly soluble in chloroform or benzene, and decomposes above its m. p. with evolution of ammonia and regeneration of the original lactone. It is readily hydrolysed by boiling with sodium carbonate solution.

6-*Chloromethylhomopiperonylonitrile* (VI).—Hydroxymethylhomopiperonylamide (10 g.), chloroform (50 c.c.), and phosphorus trichloride (15 c.c.) are boiled for 3 hours. The amide changes to an insoluble syrup, which is slowly converted into a yellow solid. The liquid is decanted cautiously into cold water, and the residue washed with chloroform and dissolved by agitation with successive small quantities of acetone, finally with addition of sodium bicarbonate solution. After filtering, the united liquors are extracted with chloroform, the extract is washed with sodium bicarbonate, dried, and evaporated, and the residue extracted repeatedly with light petroleum. The *nitrile* separates on cooling in long, colourless needles, m. p. 83—85°, which are very soluble in benzene, but rather sparingly soluble in light petroleum (Found: C, 56·9; H, 4·2; Cl, 17·3. $C_{10}H_8O_2NCl$ requires C, 57·3; H, 3·8; Cl, 16·9%).

N-*Methyl*-β-*piperonylethylamine* was prepared by Decker and Becker's method (*Annalen*, 1913, **395**, 335), piperonylidene-β-piperonylethylamine (Decker and Becker, *ibid.*, p. 349), which crystallises more readily and gives a purer product, being used instead of the benzylidene derivative.

N-*Methyl*-N-β-*piperonylethyl*-6-*aminomethylhomopiperonylonitrile* (VII).—The nitrile (VI) (1 g.) is boiled for 12 hours in benzene solution with methyl-β-piperonylethylamine (2·6 g.), and the liquid shaken with dilute hydrochloric acid (10 c.c. of 2*N*), a brown resin forming. The acid layer is separated, the resin and benzene are repeatedly extracted with hot water, and the united washings and acid layer are treated with concentrated hydrochloric acid, which precipitates the hydrochloride of the product as a gum. The liquid (containing the excess of methyl-β-piperonylethylamine) is decanted, the gum decomposed by ammonia, and the base extracted with chloroform and recrystallised from light petroleum. It forms fine,

white needles, m. p. 74—76°, giving a violet solution in warm concentrated sulphuric acid (Found: C, 68·5; H, 5·9; N, 7·9. $C_{20}H_{20}O_4N_2$ requires C, 68·2; H, 5·7; N, 8·0%). The *nitrate* forms minute crystals, m. p. *ca.* 150° with effervescence, which are very sparingly soluble in cold water and almost insoluble in cold dilute nitric acid.

N-*Methyl*-N-β-*piperonylethyl*-6-*aminomethylhomopiperonylamide*.—The base (VII) (0·6 g.) was mixed with dry ether (30 c.c.) and powdered zinc chloride (2·4 g.), stirred, cooled to −20°, and saturated with dry hydrogen chloride. After 12 hours, the mixture was again cooled and saturated with hydrogen chloride, and on the following day it was cautiously poured into water and heated until the ether had evaporated and no more of the gum would dissolve. Ammonia was added, and the base extracted with chloroform and recrystallised from methyl alcohol; it then formed small, white needles, m. p. 140°, very soluble in chloroform or hot methyl alcohol, which gave a violet solution in strong sulphuric acid and were not noticeably attacked by boiling for a short time with strong alkali. Analysis showed it to be the *amide* as stated, not the desired substance (II) [Found: C, 64·8; H, 6·0. $C_{20}H_{22}O_5N_2$ requires C, 64·9; H, 5·9%. $C_{20}H_{19}O_5N$ (II) requires C, 68·0; H, 5·4%]. The same amide is obtained when the substance (VII) is warmed for some time in methyl-alcoholic solution with excess of alkali and 2% hydrogen peroxide. The *picrate* crystallises from methyl alcohol in minute, orange-yellow plates, m. p. 210° (decomp.) after previous softening. Attempts to bring about the intended ring-closure under other conditions, including the use of aluminium chloride as condensing agent, gave no better result.

6-*Bromo*-β-*piperonylethylamine*.—(a) β-Piperonylethylamine hydrochloride is dissolved in water, and a slight excess of bromine, diluted with a little acetic acid, gradually added. The mixture is rendered strongly alkaline, and the oily base is washed by decantation, dissolved in a moderate excess of 2*N*-hydrochloric acid, boiled with charcoal, and concentrated hydrochloric acid added; the hydrochloride of the brominated base soon separates in nearly colourless prisms. The washings from the crude base yield a further small quantity on extraction with benzene, in which the substance is too sparingly soluble for the main portion to be extracted.

(b) 6-Bromo-β-piperonylpropionamide (Haworth, Perkin, and Stevens, *loc. cit.*) (5 g.) is finely powdered and heated to 70° with a solution prepared by passing the chlorine from potassium permanganate (1·2 g.) and excess of hydrochloric acid into aqueous sodium hydroxide (40 c.c. of 10%). After 2 hours, the aqueous layer is decanted, the oil extracted with hot dilute hydrochloric acid,

and the cold filtered solution treated with potassium iodide. The hydriodide which is precipitated, and the benzoyl derivative prepared from it, were shown by mixed m. p. determinations to be identical with those made from the base obtained by process (a); the yield by method (b) is rather poor.

The *hydrochloride* dissolves readily in hot water or alcohol and gives a claret-coloured solution in concentrated sulphuric acid; it melts at 208—210° after sintering and losing its water of crystallisation at 110—120° (Found: C, 36·1; H, 4·3. $C_9H_{10}O_2NBr,HCl,H_2O$ requires C, 36·2; H, 4·4%. 0·1234 gave 0·1382 silver halides. Theory demands 0·1371). The base is a colourless oil, which could not be made to solidify, and absorbs carbon dioxide from the air. The *hydriodide* forms white microcrystals, m. p. 221°, which are fairly easily soluble in water, but much less soluble in potassium iodide solution. The *benzoyl* derivative is prepared in the usual manner and crystallises from methyl alcohol in fine, white needles, m. p. 138—140° (Found: C, 55·4; H, 4·3; Br, 23·3. $C_{16}H_{14}O_3NBr$ requires C, 55·2; H, 4·0; Br, 23·0%).

Piperonylidene-6-bromo-β-piperonylethylamine.—A solution of bromo-β-piperonylethylamine hydrochloride in hot alcohol is rendered just alkaline to phenolphthalein by alcoholic sodium ethoxide and filtered from sodium chloride, a slight excess of piperonal is added, and the mixture boiled for 2 hours. The Schiff's base crystallises on cooling in colourless prisms, m. p. 108—112° (Found: C, 53·9; H, 3·8; N, 3·7. $C_{17}H_{14}O_4NBr$ requires C, 54·3; H, 3·7; N, 3·7%).

N-Methyl-6-bromo-β-piperonylethylamine. — (a) Piperonylidenebromopiperonylethylamine (5 g.) is heated with methyl iodide (3 c.c.) for 5 hours at 100° and the product is dissolved in 90—95% alcohol and boiled for 10 minutes. The hydriodide, which separates on addition of ether, is recrystallised from alcohol–ethyl acetate. In several experiments, apparently carried out under the usual conditions, a considerable quantity of a sparingly soluble salt was obtained, which crystallised from water in white needles, m. p. 260°, behaved like the iodide of a quaternary base, and would appear to be trimethyl-6-bromo-β-piperonylethylammonium iodide (Found: C, 34·6; H, 4·1. $C_{12}H_{17}O_2NBrI$ requires C, 34·8; H, 4·1%). The *picrate* crystallises from alcohol in minute, bright yellow plates, m. p. 151—153°. On boiling the quaternary iodide with 20% potassium hydroxide solution, a volatile oil was formed, presumably *6-bromopiperonylethylene*, but this rapidly polymerised to a plastic resin, insoluble in the ordinary solvents, which was not further investigated.

(b) *N*-Methyl-β-piperonylethylamine is dissolved in 7—10 parts

of dilute hydrochloric acid, treated with the theoretical quantity of bromine diluted with a little acetic acid, and the product precipitated as hydriodide by the addition of a strong solution of potassium iodide.

Methylbromopiperonylethylamine is a colourless oil, readily soluble in benzene. The *hydrochloride* crystallises from alcohol–ether in small, stout needles, m. p. 162—164°, which give a claret-coloured solution in sulphuric acid, turned brown by potassium nitrate. The *hydriodide* forms small, white prisms, m. p. 175°, which dissolve readily in water or alcohol (Found : C, 31·5; H, 3·6. $C_{10}H_{12}O_2NBr,HI$ requires C, 31·1; H, 3·4%). The *benzoyl* derivative, obtained in the usual manner, crystallises from dilute methyl alcohol in clusters of colourless needles, m. p. 98—100° (Found : C, 56·4; H, 4·6. $C_{17}H_{16}O_3NBr$ requires C, 56·4; H, 4·4%).

N-Methyl-N-6′-bromo-β-piperonylethyl-6-aminomethylhomopiperonylonitrile (VIII).—The preparation is similar to that of the halogen-free compound (VII). As the hydrochloride is very sparingly soluble, it is best to evaporate the benzene, dissolve the residue in acetic acid, and pour the solution into hot, very dilute hydrochloric acid (100 c.c.). The mixture is treated with charcoal, and concentrated hydrochloric acid added; the hydrochloride then crystallises, on cooling, in colourless needles, m. p. 205° (Found : C, 51·2; H, 4·3. $C_{20}H_{19}O_4N_2Br,HCl$ requires C, 51·3; H, 4·3%. 0·1154 gave 0·0818 silver halides; theory demands 0·0818). It is sparingly soluble in water or alcohol and gives an emerald-green solution in concentrated sulphuric acid. The *nitrate* separates from dilute nitric acid, in which it is very difficultly soluble, as a microcrystalline powder which decomposes with effervescence at about 160° (Found : Br, 16·2. $C_{20}H_{19}O_4N_2Br,HNO_3$ requires Br, 16·2%).

Repeated attempts were made to bring about an internal Grignard reaction with this substance, but it could not be induced to react with magnesium under any conditions, and the bromine atom was not removed even by prolonged boiling in ligroin with " molecular " potassium.

6-Methoxymethylhomopiperonylic Acid.—(a) The lactone (3 g.) is boiled with chloroform (12 c.c.) and phosphorus trichloride (6 c.c.) for 5 hours, and the mixture is poured into excess of methyl alcohol and warmed on the steam-bath for 2 hours. After dilution with water, the *ester* (X) is extracted with chloroform and distilled in a vacuum; the greater part passes over at 199°/21 mm. as a colourless oil which solidifies in a freezing mixture. It crystallises from dilute methyl alcohol in white needles, m. p. 41—43° (Found : C, 60·2; H, 5·9. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). The free *acid*, obtained by hydrolysis with methyl-alcoholic potassium hydroxide,

forms colourless needles from benzene–light petroleum, m. p. 93—95°. The *silver* salt is sparingly soluble in hot water (Found : Ag, 32·5. $C_{11}H_{11}O_5Ag$ requires Ag, 32·6%). When the acid is heated with dilute hydrochloric acid (15%) for an hour on the steam-bath, a pink solution is produced which deposits the lactone (III) in an impure condition on cooling.

For purposes of comparison, homopiperonyl methyl ether was mixed with concentrated hydrochloric acid and enough acetic acid to give a homogeneous solution and heated on the steam-bath; crystals soon began to separate, and the ether was finally completely converted into 2 : 3 : 6 : 7-bismethylenedioxydihydroanthracene (XII), which was identified by its insolubility and high m. p., and its conversion, by treatment with nitric acid, into 6 : 6′-dinitro-3 : 4 : 3′ : 4′-bismethylenedioxydiphenylmethane (Ewins, *loc. cit.*; G. M. Robinson, *loc. cit.*), which did not depress the m. p. of an authentic specimen. Both samples of the dinitro-compound crystallised from acetic acid in yellow needles, and not in prisms, as described by Ewins, but gave the correct m. p. (217°).

(b) The methoxy-acid is also formed, along with much of the lactone (III), when bromomethylhomopiperonylic acid (XIII; *vide infra*) is boiled for 2 hours with excess of methyl alcohol, and any ester formed hydrolysed by means of potassium hydroxide.

6-*Bromomethylhomopiperonylic Acid* (XIII).—The lactone (III) is dissolved in a little hot acetic acid, and excess of a strong solution of hydrogen bromide in the same solvent added. After some hours, the white needles that have separated are collected, washed, and recrystallised from benzene. The acid is moderately easily soluble in warm acetic acid, less soluble in benzene or ether, melts at 146—149°, and decomposes at about 180° with evolution of hydrogen bromide (Found : Br, 29·7. $C_{10}H_9O_4Br$ requires Br, 29·3%). On treatment with sodium bicarbonate solution, it is reconverted into the lactone without dissolving completely. Attempts were made to condense the substance with β-piperonylethylamine or its *N*-methyl derivative, but under all conditions tried, even in presence of acetic acid, the lactone (III) was produced : with quinoline, on the other hand, a quaternary salt appeared to be formed, but this was not further investigated. The *methyl* ester is obtained by adding a solution of the acid in warm benzene to excess of diazomethane in well-cooled ether. After several hours, the solvents are evaporated and the residue is extracted several times with light petroleum. The ester separates from the concentrated extract, cooled in ice, and is recrystallised from benzene–light petroleum. It forms hard prisms, m. p. 68—70° with previous softening at about 64°, which are readily soluble in benzene, but sparingly soluble in light petroleum

(Found: Br, 28·1. $C_{11}H_{11}O_4Br$ requires Br, 27·9%). Both bromomethylhomopiperonylic acid and its ester very slowly turn pink on keeping.

N-*Methyl*-N-β-*piperonylethyl*-6-*aminomethylhomopiperonylic Acid* (XIV).—Methyl bromomethylhomopiperonylate (1 mol.), dissolved in benzene, is gradually added to a benzene solution of methyl-β-piperonylethylamine (2 mols.); heat is evolved and a solid rapidly separates. After the benzene has been evaporated, the ester group is hydrolysed by boiling for 1 hour with methyl-alcoholic potassium hydroxide, the liquid diluted, and the excess of methylpiperonylethylamine extracted with benzene. The aqueous layer is acidified, rendered alkaline with ammonia, concentrated, and a solution of oxalic acid added. On standing, the *oxalate* separates and is recrystallised from alcohol–ether and dried at 110°, forming warty aggregates of minute prisms, softening at 173° and melting with effervescence at 178° [Found: C, 60·8; H, 5·6. $(C_{20}H_{21}O_6N)_2,C_2H_2O_4$ requires C, 60·6; H, 5·3%]. Considerable difficulty was experienced in obtaining the free amino-acid in a crystalline condition. The oxalate is dissolved in alcohol, treated with alcoholic ammonia, the ammonium oxalate removed by filtration, and the residue evaporated to dryness and dried in a vacuum. A hard glassy mass remains which slowly crystallises on warming on the steam-bath. In this condition, the substance melts at 136—140°, and is readily soluble in methyl or ethyl alcohol, moderately soluble in chloroform or hot water, and almost insoluble in ether or benzene; it dissolves readily in ammonia, and gives a violet solution in concentrated sulphuric acid. From most of the solvents tried, the amino-acid separates as a gum, but it forms a microcrystalline powder, from chloroform–ether, which contains chloroform of crystallisation (carbylamine reaction), not removed in a steam-oven, and melts to a yellow froth at about 100°. In view of the small quantity available and the intractability of the substance it was not purified for analysis. By the action of thionyl chloride, it was converted into the acid chloride (not isolated), and the latter treated in nitrobenzene solution with aluminium chloride with a view to obtain the compound (II). Considerable decomposition took place, and no pure substance could be isolated in several experiments.

The author's thanks are due to the Ramsay Memorial Trustees for a Fellowship, and to Professor W. H. Perkin for suggesting this investigation and for his kindly interest in its progress.

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[*Received, November 24th*, 1926.]