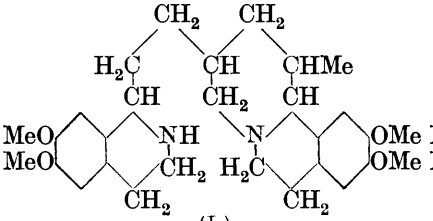
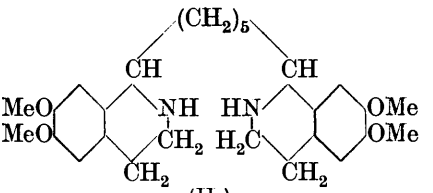
V.—1-ω-*Halogenoalkyl*isoquinolines and Their Derivatives.

By REGINALD CHILD and FRANK LEE PYMAN.

IN attempting to synthesise substances having amœbicidal properties, we have followed clues indicated by the structure assigned to emetine (I) by Brindley and Pyman (J., 1927, 1067). In our previous communication (J., 1929, 2010) we described a series of bases which resembled emetine in that they contained two 6 : 7-dimethoxy-*iso*quinoline nuclei united in the 1 : 1-positions by a chain of methylene groups, for example, the substance (II), but these had no amœbicidal properties.



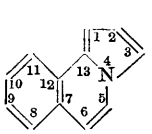
(I.)



(II.)

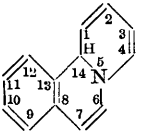
The present work was commenced with the object of synthesising 10 : 11-dimethoxy-1 : 2 : 3 : 4 : 6 : 7-hexahydrobenzpyridocoline (III),*

* The nomenclature devised by the Editor for the new ring systems described in this communication is based on the following types :



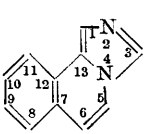
A

Benzpyrrocoline.



B

Benzpyridocoline.

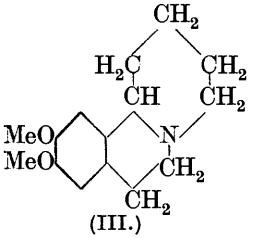


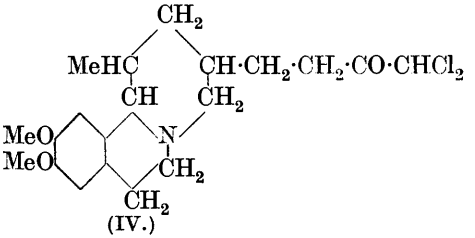
C

Benzglyoxalocoline.

A is derived from pyrrocoline (Scholtz, *Ber.*, 1912, **45**, 734) and B and C by analogy from pyridocoline and glyoxalocoline respectively.

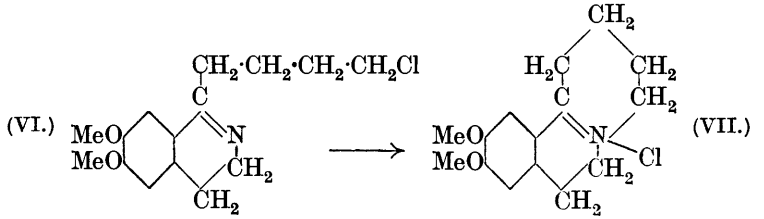
since both Späth and Leithe (*Ber.*, 1927, **60**, 688) and Brindley and Pyman (*loc. cit.*) presume that the tertiary nitrogen atom of emetine is common to a tetrahydro*iso*quinoline nucleus and an additional piperidine ring. Moreover, Pyman and Wenyon (*J. Pharm. Expt. Ther.*, 1917, **10**, 237) found that a comparatively simple derivative of cephæline having the formula $C_{20}H_{27}O_3NCl_2$ had amœbicidal properties, and Brindley and Pyman (*loc. cit.*) proposed a formula (IV) for this substance which represents it as a derivative of 10 : 11-dimethoxy-1 : 2 : 3 : 4 : 6 : 7-hexahydrobenzpyridocoline.


(III.)


(IV.)

The base (III) was readily prepared in the following manner. *δ-Chlorovalero-β-veratrylethylamide* (V) was converted by means of phosphorus oxychloride into 1-*δ-chlorobutyl*-6 : 7-*dimethoxy*-3 : 4-*dihydro*iso*quinoline* (VI), which was isolated in the form of the picrate. The corresponding base was readily converted into 5 : 14-*dehydro*-10 : 11-*dimethoxy*-1 : 2 : 3 : 4 : 6 : 7-*hexahydrobenzpyridocolinium chloride* (VII) by gentle warming, and this substance gave the required base (III) on reduction.

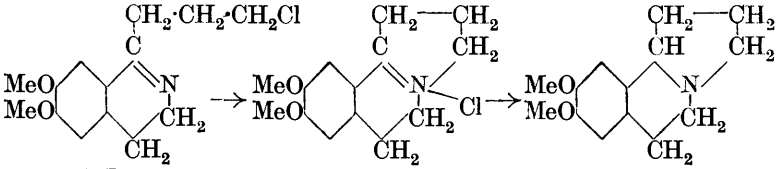
$$CH_2Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}C_6H_3(OMe)_2 \quad \text{(V.)}$$


(VI.) (VII.)

Although numerous alkyl-, aralkyl-, and aryl-substituted 3 : 4-dihydro*iso*quinolines have been synthesised by the Bischler–Napieralski method or its variants, 1-alkyl-3 : 4-dihydro*iso*quinolines containing halogen or other reactive groups in the 1-alkyl substituent had not been prepared hitherto by this or any other method. Consequently, it appeared to us to be of interest to study further examples of similar type, and these are now described in descending order of the substituted fatty acid. The action of phosphorus oxychloride upon *γ-bromobutyro-β-veratrylethylamide* (VIII) gave very

little 1-*γ-chloropropyl*-6 : 7-*dimethoxy*-3 : 4-*dihydro*isoquinoline (IX), the main product being the resultant of its cyclisation, 4 : 13-*dehydro*-9 : 10-*dimethoxy*-1 : 2 : 3 : 5 : 6 : 13-*hexahydrobenzpyrrocolinium chloride* (X). This result, contrasted with that recorded above, adds another example to the number already known (Bennett, Heathcoat, and Mosses, J., 1929, 2567; Littmann and Marvel, *J. Amer. Chem. Soc.*, 1930, **52**, 289), where the tendency to the formation of 5-membered rings containing one hetero-atom is greater than that to the formation of 6-membered rings similarly constituted. The quaternary chloride (X) gave 9 : 10-*dimethoxy*-1 : 2 : 3 : 5 : 6 : 13-*hexahydrobenzpyrrocoline* (XI) on reduction.

(VIII.) $CH_2Br\cdot CH_2\cdot CH_2\cdot CO\cdot NH\cdot CH_2\cdot CH_2\cdot C_6H_3(OMe)_2 \longrightarrow$

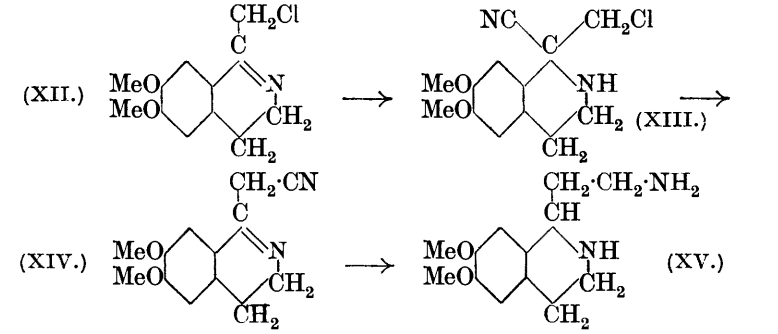


(IX.) (X.) (XI.)

The action of phosphorus oxychloride upon β-*chloropropiono*-β-*veratrylethylamide* gave basic products almost free from chlorine, which could not be crystallised. They were doubtless polymerides of 6 : 7-dimethoxy-1-vinyl-3 : 4-dihydro*iso*quinoline.

On the other hand, *chloroaceto*-β-*veratrylethylamide* was readily converted into 1-*chloromethyl*-6 : 7-*dimethoxy*-3 : 4-*dihydro*isoquinoline (XII).

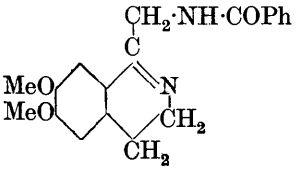
When the hydrochloride of this base was mixed with aqueous potassium cyanide, 1-*chloromethyl*-1-*cyano*-6 : 7-*dimethoxytetrahydro*isoquinoline (XIII) was precipitated. This substance when boiled with aqueous-alcoholic potassium cyanide gave 1-*cyanomethyl*-6 : 7-*dimethoxy*-3 : 4-*dihydro*isoquinoline (XIV), from which 1-β-*aminoethyl*-6 : 7-*dimethoxytetrahydro*isoquinoline (XV) was obtained on reduction.

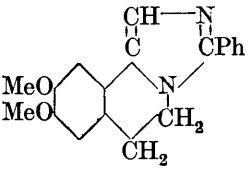


(XII.) (XIII.) (XIV.) (XV.)

Attempts to condense the substance (XII) with ethyl sodiomalonate gave only highly-coloured uninviting products, and similar results were obtained in trying to replace the chlorine atoms by the amino-group by means of ammonia and potassium phthalimide. With the hope of preparing 1-aminomethyl-6 : 7-dimethoxy-3 : 4-dihydro*iso*quinoline by the hydrolysis of its *N*-benzoyl derivative, *hippuro-β-veratrylethylamide* was dehydrated by means of phosphorus oxychloride, but in the place of the expected 1-benzamidomethyl-6 : 7-dimethoxy-3 : 4-dihydro*iso*quinoline (XVI), a substance derived from this by the loss of a molecular proportion of water was obtained. This substance is a monoacidic base, and cannot be reduced either by tin and hydrochloric acid, or by means of sodium amalgam in alcohol. These properties are consistent with its representation as 9 : 10-*dimethoxy*-3-*phenyl*-5 : 6-*dihydrobenzglyoxalocoline* (XVII), and no other formula seems equally probable.

(XVI.)





(XVII.)

Suitable salts of the compounds formulated (III), (VI), (VII), (X), (XI), (XII), (XV) and (XVII) were tested for amœbidical properties by Mr. C. A. Coulthard of Boots' Bacteriological Department, using the methods employed by Laidlaw, Dobell, and Bishop (*Parasitology*, 1928, **20**, 207) for testing the action of emetine. Of these compounds, (XVII) prevented the growth of *Entamœba histolytica* in cultures at a dilution of 1 in 25,000, whereas the control substance emetine was effective in a dilution of 1 in 500,000. All the other compounds were far less effective. By the courtesy of the Chemotherapy Committee of the Medical Research Council these salts were tested for antimalarial activity under the direction of Dr. Keilin, F.R.S., at the Molteno Institute, Cambridge, and were found to be inactive. They were also found to be devoid of trypanocidal activity by Mr. W. A. Broom, B.Sc., of Boots' Pharmacological Department.

We desire to express our thanks to all the above investigators of the physiological properties of these compounds.

Experimental.

The acyl-phenylethylamides required as intermediates in the preparation of the *iso*quinoline derivatives to be described were prepared, unless otherwise stated, by the gradual addition of the corresponding acid chloride (1 mol.) to a well-stirred solution of the amine (2 mols.) in dry ether. After being kept for 1 hour, the

ethereal solution was washed with water to remove amine hydrochloride and the amide was collected either by filtration or after drying and distillation of the ethereal solution. After recrystallisation the pure amide was obtained in yields averaging about 75% of the theoretical. These amides were insoluble in water, but readily soluble in the usual organic solvents with the exception of light petroleum and in some cases ether.

Chloroaceto-β-phenylethylamide, long needles from ether at 0°, has m. p. 67° (corr.) (Found : C, 60·6; H, 6·3; N, 7·1. $C_{10}H_{12}ONCl$ requires C, 60·7; H, 6·1; N, 7·1%).

Chloroaceto-β-m-methoxyphenylethylamide, plates from ether, has m. p. 56—57° (corr.) (Found: C, 58·0; H, 6·5. $C_{11}H_{14}O_2NCl$ requires C, 58·0; H, 6·2%).

Chloroaceto-β-piperonylethylamide, fine needles from ether–light petroleum, has m. p. 72° (corr.) (Found : C, 54·6; H, 5·2. $C_{11}H_{12}O_3NCl$ requires C, 54·6; H, 5·0%).

Chloroaceto-β-veratrylethylamide, prismatic needles from alcohol, has m. p. 96° (corr.) (Found : C, 55·7; H, 6·3; N, 5·5; Cl, 13·8. $C_{12}H_{16}O_3NCl$ requires C, 55·9; H, 6·3; N, 5·4; Cl, 13·8%).

Bromoaceto-β-veratrylethylamide, from β-veratrylethylamine and bromoacetyl bromide, separated from alcohol in minute needles, m. p. 115° (corr.) (Found : C, 47·7; H, 5·4; N, 4·7. $C_{12}H_{16}O_3NBr$ requires C, 47·7; H, 5·3; N, 4·6%).

Cyanoaceto-β-veratrylethylamide, prepared by mixing equimolecular quantities of β-veratrylethylamine and ethyl cyanoacetate, crystallised from alcohol in needles, which melted at 115° (corr.), but after resolidifying did not melt until 127—128° (corr.) (Found : C, 62·8; H, 6·9; N, 11·3. $C_{13}H_{16}O_3N_2$ requires C, 62·9; H, 6·5; N, 11·3%).

Hippuro-β-phenylethylamide, needles from alcohol, has m. p. 161° (corr.) (Found : C, 72·3; H, 6·5; N, 9·8. $C_{17}H_{18}O_2N_2$ requires C, 72·3; H, 6·4; N, 9·9%).

Hippuro-β-veratrylethylamide, clusters of needles from moist acetone, contains $1H_2O$, and melts between 85° and 95° (Found : C, 63·1; H, 6·7; N, 7·9. $C_{19}H_{22}O_4N_2,H_2O$ requires C, 63·3; H, 6·7; N, 7·8%).

β-Chloropropiono-β-veratrylethylamide, needles from alcohol, has m. p. 102—103° (corr.) (Found : N, 4·9. $C_{13}H_{18}O_3NCl$ requires N, 5·2%).

γ-Bromobutyro-β-veratrylethylamide, prepared from the amine and γ-bromobutyryl chloride (b. p. 86—87°/15mm.), crystallised from ether–light petroleum in matted needles, m. p. 65° (corr.) (Found : C, 51·0; H, 6·3; Br, 24·4. $C_{14}H_{20}O_3NBr$ requires C, 50·9; H, 6·1; Br, 24·3%). This substance decomposes very readily, especially when moist, with the formation of butyrolactone, b. p. 205—207°,

and β-*veratrylethylamine hydrobromide*, m. p. 179—180° (corr.), readily soluble in water, sparingly soluble in cold absolute alcohol (Found : C, 46·0; H, 6·0; N, 5·3. $C_{10}H_{15}O_2N$,HBr requires C, 45·8; H, 6·2; N, 5·3%).

δ-*Chlorovalero*-β-*veratrylethylamide* was prepared from β-veratrylethylamine and δ-chlorovaleryl chloride (b. p. 75—80°/5—8 mm., from the acid and thionyl chloride). It formed needles from ether, m. p. 60—62° (corr.) (Found : C, 60·3; H, 7·6. $C_{15}H_{22}O_3NCl$ requires C, 60·1; H, 7·4%).

δ-*Bromovaleryl*-β-*veratrylethylamide*, feathery needles from ether–light petroleum, has m. p. 70—72° (corr.) (Found : C, 52·5; H, 6·6; N, 4·0; Br, 23·4. $C_{15}H_{22}O_3NBr$ requires C, 52·3; H, 6·5; N, 4·1; Br, 23·2%).

Action of Phosphorus Oxychloride upon Chloroaceto-β-*veratrylethylamide.*—Chloroaceto-β-veratrylethylamide (30 g.), toluene (90 c.c.), and phosphorus oxychloride (30 c.c.) were heated under reflux in an oil-bath at 120—130° for 1 hour. After cooling, the product was diluted with light petroleum and the nearly colourless mixture of solvents was decanted and rejected. The remaining brown gum was dissolved in water, and traces of non-basic material were removed by ether. The aqueous liquor was basified with ammonia and extracted with ether. The ethereal solution was extracted with dilute hydrochloric acid, and this extract was concentrated to a syrup and mixed with acetone; 1-*chloromethyl*-6 : 7-*dimethoxy*-3 : 4-*dihydroisoquinoline hydrochloride* (24·0 g.) then separated in canary-yellow elongated plates (darkens from about 210°, effervesces at 217°), and a further quantity (6·1 g.) of almost equally pure material was isolated from the mother-liquors. The total yield (30·1 g.) is 93·8% of the theoretical. This salt is easily soluble in water, giving an acid solution. It is anhydrous and has sternutatory properties (Found : C, 52·5; H, 5·6; Cl, 25·9. $C_{12}H_{14}O_2NCl$,HCl requires C, 52·2; H, 5·5; Cl, 25·7%).

The *picrate* is sparingly soluble in alcohol; it separates from glacial acetic acid in yellow needles, m. p. 196° (corr.; decomp.) (Found : Cl, 7·5. $C_{12}H_{14}O_2NCl,C_6H_3O_7N_3$ requires Cl, 7·6%).

1-*Chloromethyl*-1-*cyano*-6 : 7-*dimethoxytetrahydroisoquinoline* is prepared as a gummy mass, which quickly becomes crystalline, when aqueous solutions of potassium cyanide and 1-chloromethyl-6 : 7-dimethoxy-3 : 4-dihydro*iso*quinoline hydrochloride are mixed. It softens at 122° and melts at 125° (corr.; decomp.) (Found : N, 10·3; Cl, 13·4. $C_{13}H_{15}O_2N_2Cl$ requires N, 10·5; Cl, 13·3%). It is insoluble in water, very dilute hydrochloric acid or ether. It is readily soluble in hot alcohol, but the solution quickly darkens on heating.

1-*Cyanomethyl*-6 : 7-*dimethoxy*-3 : 4-*dihydro*isoquinoline.—To 1-chloromethyl-6 : 7-dimethoxy-3 : 4-dihydro*iso*quinoline hydrochloride (20 g.) in water (200 c.c.), potassium cyanide (15 g.) in water (75 c.c.) was added. The gummy precipitate of 1-chloromethyl-1-cyano-6 : 7-dimethoxytetrahydro*iso*quinoline was transferred moist to a solution of potassium cyanide (25 g.) in water (70 c.c.) and alcohol (100 c.c.). The solution was boiled under reflux for ½ hour and filtered hot; pure 1-*cyanomethyl*-6 : 7-*dimethoxy*-3 : 4-*dihydro*isoquinoline (9·7 g.; m. p. 173°, corr.) was thus obtained in very pale buff, sandy crystals. The mother-liquor deposited on cooling a crop (4·1 g.; brown; m. p. 171°) and on concentration another crop (2·1 g.; dark brown; m. p. 165°). The total yield is thus 95%. The compound separates from alcohol in pale yellow, almost colourless needles, m. p. 173° (corr.) (Found: C, 67·5; H, 6·0; N, 12·4. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H, 6·1; N, 12·2%). The *hydrochloride*, pale yellow rhombs from alcohol, m. p. 205—206° (corr.), is readily dissociated by water with deposition of the free base (Found: N, 10·6; Cl, 13·1. $C_{13}H_{14}O_2N_2$,HCl requires N, 10·5; Cl, 13·3%). The *picrate* is sparingly soluble in alcohol and crystallises from glacial acetic acid in orange-yellow needles, m. p. 225° (decomp.) (Found: C, 49·5; H, 3·9. $C_{13}H_{14}O_2N_2$,$C_6H_3O_7N_3$ requires C, 49·6; H, 3·7%).

1-Cyanomethyl-6 : 7-dimethoxy-3 : 4-dihydro*iso*quinoline was also obtained (in 40% yield) by the interaction of cyanoaceto-β-veratrylethylamide and phosphorus oxychloride in toluene; it melted at 173° (corr.) alone or mixed with the base prepared as above described.

1-β-*Aminoethyl*-6 : 7-*dimethoxytetrahydro*isoquinoline.—To 1-cyanomethyl-6 : 7-dimethoxy-3 : 4-dihydro*iso*quinoline (11·7 g.), suspended in absolute alcohol (200 c.c.), sodium (60 g.) and more absolute alcohol (400 c.c.) were added in the course of 1½ hours. After heating for ½ hour on the steam-bath, the sodium had dissolved completely. The solution was mixed with water (100 c.c.), acidified with hydrochloric acid (300 c.c. conc.), filtered from sodium chloride, and concentrated to a volume of about 200 c.c. It was then mixed with a large excess of sodium hydroxide and extracted, first with ether and then with chloroform. Each solvent removed gummy bases, which were dissolved in dilute hydrochloric acid and precipitated by aqueous picric acid. The amorphous picrates obtained were crystallised fractionally from alcohol; 14·3 g. of pure 1-β-*aminoethyl*-6 : 7-*dimethoxytetrahydro*isoquinoline *dipicrate* were then obtained (yield, 40%). It crystallises from alcohol in glistening yellow needles, containing 1 mol. C_2H_5·OH, and after drying has m. p. 205° (corr.). It is sparingly soluble in water or alcohol, even when hot (Found in air-dried salt: loss at 115°, 6·3; C, 43·5; H, 5·0; N, 15·0.

$C_{13}H_{20}O_2N_2,2C_6H_3O_7N_3,C_2H_5{\cdot}OH$ requires $C_2H_5{\cdot}OH$, 6·2; C, 43·8; H, 4·4; N, 15·1%. Found in dried salt: C, 43·0; H, 4·1; N, 16·3. $C_{13}H_{20}O_2N_2,2C_6H_3O_7N_3$ requires C, 43·2; H, 3·8; N, 16·1%).

The *dihydrochloride* crystallises from aqueous acetone in cream-coloured plates, m. p. 276—277° (corr.; efferv.). It is readily soluble in water, giving a neutral solution (Found in air-dried salt: loss at 120°, 6·8, 7·0. $C_{13}H_{20}O_2N_2,2HCl,H_2O$ requires H_2O, 5·5%. Found in dried salt: C, 50·1; H, 7·5; Cl, 22·4. $C_{13}H_{20}O_2N_2,2HCl$ requires C, 50·5; H, 7·2; Cl, 22·9%).

Action of Phosphoric Oxide upon Bromoaceto-β-veratrylethylamide.—Bromoaceto-β-veratrylethylamide (5 g.) was dissolved in xylene (50 c.c.) and phosphoric oxide (15 g.) was added at intervals in three equal portions to the boiling solution (compare Pictet and Kay, *Ber.*, 1909, **42**, 1973). The gelatinous residue remaining after decantation of the hot liquor was dissolved in water, and non-basic material removed by means of ether. The addition of picric acid precipitated 5·7 g. of picrate (yield, 70%), m. p. 177° (uncorr.; decomp.).

1-*Bromomethyl*-6 : 7-*dimethoxy*-3 : 4-*dihydro*isoquinoline *picrate* is sparingly soluble in alcohol (about 1 in 120 parts of boiling alcohol). It was obtained, after two crystallisations from acetone, in which it is more soluble, as orange-yellow needles, m. p. 190—191° (corr.; decomp.) (Found: C, 42·0; H, 3·6; Br, 15·6.

$C_{12}H_{14}O_2NBr,C_6H_3O_7N_3$

requires C, 42·1; H, 3·3; Br, 15·6%).

On heating bromoaceto-β-veratrylethylamide with phosphorus oxychloride in toluene, 1-chloromethyl-6 : 7-dimethoxy-3 : 4-dihydro-*iso*quinoline was obtained in 80% yield, the bromine substituent having been replaced by chlorine.

Action of Phosphorus Oxychloride upon Chloroaceto-β-m-methoxyphenylethylamide.—Chloroaceto-β-*m*-methoxyphenylethylamide (7 g.) was treated with phosphorus oxychloride and the basic products were taken into hydrochloric acid in the usual way. The hydrochloride solution on concentration, and addition of acetone, gave 3·1 g. of buff-coloured hard crystals, which softened at 130° and had m. p. *ca.* 170° and appeared to contain solvent of crystallisation; these were collected and the hydrochloride remaining in the mother-liquor was converted into picrate, 3·8 g., m. p. 162—165°, by the addition of aqueous picric acid.

1-*Chloromethyl*-6-*methoxy*-3 : 4-*dihydro*isoquinoline *picrate* separated from acetone in fine yellow needles, m. p. 169—170° (uncorr.) (Found: C, 46·5; H, 4·0; N, 13·2. $C_{11}H_{12}ONCl,C_6H_3O_7N_3$ requires C, 46·5; H, 3·45; N, 12·8%).

Action of Phosphorus Oxychloride upon Chloroaceto-β-piperonyl-

ethylamide.—Chloroaceto-β-piperonylethylamide (9 g.) was treated with phosphorus oxychloride in the usual manner; the residue, after dilution with light petroleum and decantation of the supernatant liquid, consisted of a semi-crystalline reddish mass. This was dissolved in water and basified; the base was transferred to hydrochloric acid by means of chloroform, since it was more readily soluble in this solvent than in ether.

The solution of hydrochloride was evaporated to small bulk under diminished pressure and treated with acetone, which gave 8 g. (82%) of crude hydrochloride, m. p. 190° (decomp.). The salt, recrystallised from aqueous acetone, had m. p. between 150° and 170° and contained solvent; after drying at 100°, it darkened at 195° and decomposed with effervescence at 204°; it was less readily soluble in water than the other hydrochlorides prepared. On the addition of picric acid it gave 1-*chloromethyl*-6 : 7-*methylenedioxy*-3 : 4-*dihydro*-iso*quinoline picrate,* orange-red needles from acetone, m. p. 179—180° (corr.; decomp.) (Found: C, 45·2; H, 3·2. $C_{11}H_{10}O_2NCl,C_6H_3O_7N_3$ requires C, 45·1; H, 2·9%).

Action of Phosphorus Oxychloride upon β-*Chloropropiono*-β-*veratrylethylamide.*—β-Chloropropiono-β-veratrylethylamide (9·5 g.) was boiled gently under reflux with phosphorus oxychloride (28·5 c.c.) in toluene (100 c.c.) for 45 minutes. The residue after addition of light petroleum and decantation of the supernatant liquor was dissolved in water. Addition of excess of aqueous picric acid to the solution precipitated 14 g. of an amorphous picrate, which melted over a wide range of temperature. All attempts to obtain a homogeneous crystalline substance from the latter failed; but acetone (500 c.c.) effected a partial separation of the picrate from two experiments (24·7 g.) into a high-melting fraction, A (5·2 g.; m. p. 235°, uncorr.), and a more soluble fraction, B (19 g.; m. p. 145—185°, uncorr.; decomp.). A contained no chlorine, and B only a trace.

Action of Phosphorus Oxychloride upon γ-*Bromobutyro*-β-*veratrylethylamide.*—(1) γ-Bromobutyro-β-veratrylethylamide (9 g.) was boiled gently with phosphorus oxychloride (25 c.c.) in toluene (90 c.c.) for 30 minutes. After cooling, light petroleum was added and the supernatant liquor decanted. The dark oily residue was dissolved in water and precipitated with saturated aqueous picric acid (500 c.c.), giving 11·5 g. of picrates, m. p. 152—154° to a turbid fluid, clearing at 164°. This product proved to be a mixture of 1-γ-chloropropyl-6 : 7-dimethoxy-3 : 4-dihydro*iso*quinoline picrate and 4 : 13-dehydro-9 : 10-dimethoxy-1 : 2 : 3 : 5 : 6 : 13-hexahydrobenzpyrrocolinium picrate, which were difficult to separate, but after fractionation from acetone 1 g. of the quaternary picrate was isolated in a nearly pure state (m. p. 190—192°) and a specimen (0·7 g.) of crude 1-γ-chloropropyl-

6 : 7-dimethoxy-3 : 4-dihydro*iso*quinoline picrate (m. p. 163—164°) was obtained with Cl = 5·6 instead of the calculated 7·1%. It was found that the mixed picrates were very readily converted into the quaternary cyclic compound through the base, and in a second experiment cyclisation was completed before the products of the reaction were isolated.

(2) γ-Bromobutyro-β-veratrylethylamide (27·7 g.) was treated with phosphorus oxychloride in the usual way, and the aqueous solution of the reaction product was basified with ammonia and extracted with ether. The ethereal extract was concentrated and rapidly deposited the crystalline quaternary chloride (6·2 g.; m. p. 119—120°); the ethereal filtrate on evaporation left a residue which gave with picric acid 0·7 g. of the quaternary picrate. The aqueous liquor gave with picric acid, 26·7 g. of the quaternary picrate, m. p. 188—193°. The yield of crude quaternary salts is thus 95% of the theoretical.

4 : 13-*Dehydro*-9 : 10-*dimethoxy*-1 : 2 : 3 : 5 : 6 : 13-*hexahydrobenzpyrrocolinium chloride* separates from alcohol–ether as a crystalline powder, m. p. 120—122° (corr.), containing $2H_2O$ (Found : loss at 120°, 10·7; C, 55·2; H, 7·6. $C_{14}H_{18}O_2NCl,2H_2O$ requires $2H_2O$, 11·9; C, 55·3; H, 7·3%). After prolonged drying at 100°, it is rendered anhydrous and melts at 204—205° (corr.) (Found : C, 62·7; H, 7·1. $C_{14}H_{18}O_2NCl$ requires C, 62·8; H, 6·8%). The dry salt is hygroscopic and easily soluble in water or alcohol.

The *picrate* is best recrystallised by dissolving 10 g. in acetone (2 l.) and concentrating the solution to 750 c.c. It separates on cooling in short yellow prisms, m. p. 201—202° (corr.). Difficulty was experienced in its combustion owing to its explosive nature (Found : C, 51·3; H, 4·7; picric acid, 49·5. $C_{20}H_{20}O_9N_4$ requires C, 52·1; H, 4·4; picric acid, 49·8%).

9 : 10-*Dimethoxy*-1 : 2 : 3 : 5 : 6 : 13-*hexahydrobenzpyrrocoline*.—To 4 : 13-dehydro-9 : 10-dimethoxy-1 : 2 : 3 : 5 : 6 : 13-hexahydrobenzpyrrocolinium chloride (5 g.) in alcohol (50 c.c.) and hydrochloric acid (30 c.c.), tinfoil (9 g.) and more acid (20 c.c.) were added in the course of 4 hours. Tin was removed by hydrogen sulphide, and the filtrate was concentrated, basified, and extracted with ether. On distillation of the ether, the *base* was obtained as an oil, which rapidly crystallised (m. p. crude 78—80°), in yields of 80—85%. It crystallises from light petroleum in broad needles, m. p. 88—89° (corr.), which are readily soluble in other organic solvents. It is slightly soluble in water, giving a solution which is alkaline to phenolphthalein (Found : C, 71·8; H, 8·2. $C_{14}H_{19}O_2N$ requires C, 72·0; H, 8·2%).

The *hydrobromide* forms rhombs from absolute alcohol; it has m. p.

186° (corr.) and is readily soluble in water, giving a neutral solution (Found: C, 53·4; H, 6·7; Br, 25·3. $C_{14}H_{19}O_2N$,HBr requires C, 53·5; H, 6·4; Br, 25·4%). The *picrate* crystallises from alcohol (100 pts.) in fine yellow needles, m. p. 187° (corr.; decomp.) (Found: N, 12·0. $C_{14}H_{19}O_2N$,$C_6H_3O_7N_3$ requires N, 12·1%).

Action of Phosphorus Oxychloride upon δ-Chlorovalero-β-veratrylethylamide.—δ-Chlorovalero-β-veratrylethylamide (4·5 g.) was boiled with phosphorus oxychloride (15 c.c.) in toluene (50 c.c.) for 30 minutes. The product was worked up in the usual way and precipitated as picrate, the yield of crude salt, m. p. 150—156°, being 7·1 g., *i.e.*, 93%. δ-Bromovalero-β-veratrylethylamide, when similarly treated, gave the same product, and when larger quantities were worked up it was possible to isolate from the mother-liquor a small quantity of the corresponding quaternary picrate of m. p. 183°.

1-δ-*Chlorobutyl*-6 : 7-*dimethoxy*-3 : 4-*dihydroisoquinoline picrate* crystallises from alcohol (80 pts.) in yellow needles, m. p. 156—157° (corr.) (Found: C, 49·3; H, 4·8; N, 10·8; Cl, 6·9; picric acid, 44·4. $C_{15}H_{20}O_2NCl$,$C_6H_3O_7N_3$ requires C, 49·3; H, 4·8; N, 11·0; Cl, 6·9; picric acid, 44·8%). The *hydrochloride* was prepared by treating the picrate with hydrochloric acid and removing picric acid by ether. It forms hard rhombs from 90% acetone, m. p. 172—173° (corr.; decomp.). It is readily soluble in water, giving a solution neutral to litmus and having a marked blue fluorescence (Found: Cl, 22·2. $C_{15}H_{20}O_2NCl$,HCl requires Cl, 22·3%).

5 : 14-*Dehydro*-10 : 11-*dimethoxy*-1 : 2 : 3 : 4 : 6 . 7-*hexahydrobenzpyridocolinium Salts.*—1-δ-Chlorobutyl-6 : 7-dimethoxy-3 : 4-dihydro*iso*quinoline picrate (34 g.) was converted into the hydrochloride. The latter was not isolated, but the solution after removal of picric acid was basified with ammonia and extracted three times with ether. The extract was dried over sodium sulphate, filtered, and concentrated. As evaporation proceeded, the at first clear ethereal solution became turbid; when the solution reached small bulk, exothermic reaction set in and the last traces of ether came off rapidly. The residue was dissolved in water, and the solution was filtered and treated with an excess of picric acid, which precipitated the quaternary picrate (23·9 g., m. p. 182—184°). Acidification of the alkaline mother-liquor and addition of picric acid gave a further 4·5 g. of the same picrate (total yield, 28·4 g. or 90%).

5 : 14-*Dehydro*-10 : 11-*dimethoxy*-1 : 2 : 3 : 4 : 6 : 7-*hexahydrobenzpyridocolinium picrate* separates from alcohol (80 pts.) in beautiful golden spangles, m. p. 185—186° (corr.) (Found: C, 53·1; H, 5·1; N, 12·0; picric acid, 48·5. $C_{21}H_{22}O_9N_4$ requires C, 53·2; H, 4·7; N, 11·8; picric acid, 48·3%). The corresponding *chloride*, when prepared from the picrate, is obtained by the gradual addition of

ether to its solution in 5 parts of alcohol as a microcrystalline, pale yellow powder which after air-drying retains an additional molecule of hydrogen chloride and 2 molecules of water; both of these are lost on prolonged drying first over sulphuric acid in a vacuum and finally at 115°. The air-dried salt effervesces at 103° after softening from 90°; the dried salt has m. p. 197—198° (corr.) and is hygroscopic [Found in air-dried salt: C, 51·1, 51·2; H, 7·3, 7·1; Cl (total), 18·5; Cl (as free HCl, by titration), 8·8; total loss on drying, 19·9. $C_{15}H_{20}O_2NCl,HCl,2H_2O$ requires C, 50·8; H, 7·1; Cl (total), 20·0; Cl (as free HCl), 10·0; total loss, 20·4%. Found in dried salt: C, 63·5; H, 7·3. $C_{15}H_{20}O_2NCl$ requires C, 63·9; H, 7·2%]. The iodide separates from water, in which it is moderately easily soluble, in large yellow rhombs, m. p. 210—212°.

10 : 11-*Dimethoxy*-1 : 2 : 3 : 4 : 6 : 7-*hexahydrobenzpyridocoline.*—Thirty grams of the above quaternary picrate were converted into hydrochloride; the syrupy residue of the latter was dissolved in 100 c.c. of alcohol and reduced by means of concentrated hydrochloric acid (75 c.c.) and tinfoil (28 g.), the foil being added gradually to the gently boiling solution over a period of 6 hours.

After distillation of the alcohol, the residue was diluted with water and treated with hydrogen sulphide, and the filtrate from tin sulphide was evaporated to dryness under reduced pressure. The residue was dissolved in a little water, basified with ammonia, and extracted with ether. The extract, dried over potassium carbonate and evaporated, left an oil, which rapidly crystallised; m. p. 54°. Yield, 14·5 g. (92·7%).

10 : 11-*Dimethoxy*-1 : 2 : 3 : 4 : 6 : 7-*hexahydrobenzpyridocoline* is insoluble in water, but is easily soluble in the usual organic solvents, with the exception of light petroleum, from which it separates in nodular crystals, m. p. 59—60° (corr.). It may be distilled under diminished pressure without decomposition, b. p. 225°/15 mm. (Found: C, 72·7; H, 8·3; N, 5·9. $C_{15}H_{21}O_2N$ requires C, 72·8; H, 8·5; N, 5·7%). The *hydrochloride* separates from alcohol in small colourless crystals, m. p. 235—237° (corr.; decomp.), easily soluble in water, giving a solution neutral to litmus (Found: Cl, 12·6. $C_{15}H_{21}O_2N,HCl$ requires Cl, 12·5%). The picrate forms bright yellow needles, m. p. 172—174° (corr.), from 40 parts of alcohol.

Methiodides. The base (2 g.) was boiled under reflux for 5 hours with an excess of methyl iodide. The product (3·2 g., m. p. 236°) was separated by fractional crystallisation from water into the sparingly soluble β-*methiodide*, colourless rosettes of needles, m. p. 244—245° (corr.) (Found: C, 49·3; H, 6·5; I, 32·8. $C_{16}H_{24}O_2NI$ requires C, 49·3; H, 6·2; I, 32·6%), and the more soluble α-*methiodide*, colourless glistening plates from water, m. p. 228° (corr.) (Found:

I, 32·5%). The α-methiodide is largely converted into the β-salt on being heated at 250°.

Action of Phosphorus Oxychloride upon Hippuro-β-veratrylethylamide.—Crude hippuro-β-veratrylethylamide (15·6 g.) (prepared by heating equimolecular proportions of ethyl hippurate and β-veratrylethylamine for 5 hours at 180°) was boiled gently under reflux for ½ hour with toluene (160 c.c.) and phosphorus oxychloride (48 c.c.). The product was mixed with light petroleum, and the precipitated dark resinous material was dissolved in water. After treatment with charcoal this solution was basified, and the crude precipitated base (yield, 90%) was purified by several crystallisations from alcohol, the pure base being obtained in about 60% yield.

9 : 10-*Dimethoxy*-3-*phenyl*-5 : 6-*dihydrobenzglyoxalocoline* crystallises from alcohol (12 pts.) in large striated plates, m. p. 187° (corr.). It is insoluble in water or ether, but readily soluble in chloroform (Found : C, 74·5; H, 5·8. $C_{19}H_{18}O_2N_2$ requires C, 74·5; H, 5·9%). The *hydrochloride* crystallises from aqueous alcohol in plates, m. p. 286—287° (corr.; decomp.). It is soluble in 25—30 parts of cold water (Found : Cl, 10·4. $C_{19}H_{18}O_2N_2$,HCl requires Cl, 10·35%). The *hydrobromide* forms colourless anhydrous needles, m. p. 293° (corr.), from water (80 parts) (Found : Br, 20·7; N, 7·25. $C_{19}H_{18}O_2N_2$,HBr requires Br, 20·6; N, 7·2%). The *methiodide*, obtained by refluxing the powdered base with a large excess of methyl iodide for several hours, formed pale cream-coloured feathery needles, m. p. 255° (corr.), from a large volume of water (Found : C, 53·4; H, 5·0; I, 27·6. $C_{19}H_{18}O_2N_2$,CH_3I requires C, 53·5; H, 4·7; I, 28·3%). The picrate, sparingly soluble in alcohol or acetone, was obtained from glacial acetic acid as matted clusters of yellow needles, m. p. 226—227° (corr.).

Nitro-derivative. The base (1·0 g., m. p. 187°) was added to 50 c.c. of *N*-nitric acid; on warming, the sparingly soluble nitrate gradually dissolved. As the temperature was raised, the solution began to turn yellow and between 60° and 70° it became turbid with the separation of an orange-yellow solid. After 1 hour's heating on the steam-bath, the solid was removed, washed well with water, and dried at 100°. Yield, 1·05 g. M. p. 193—194° (uncorr.).

The *nitro*-derivative formed long orange-yellow needles, m. p. 202° (corr.), from 150 parts of alcohol (Found : C, 64·5, 64·6; H, 5·2, 5·3; N, 12·05. $C_{19}H_{17}O_4N_3$ requires C, 64·9; H, 4·9; N, 12·0%). It is soluble in concentrated hydrochloric acid, but is thrown out of solution by addition of water. The orange-coloured solution in hydrochloric acid is reduced by tinfoil to a colourless solution, which, after dilution and removal of tin as sulphide, gives a diazo-reaction for a free amino-group.

Demethylation. The base (1 g.) was heated in a sealed tube with concentrated hydrochloric acid (15 c.c.) for 5 hours at 160°. The resulting mass of crystals (hydrochloride of the demethylated base) was collected, washed with water, and dried (yield, 1 g.).

9 : 10-*Dihydroxy*-3-*phenyl*-5 : 6-*dihydrobenzglyoxalocoline hydrochloride* crystallises from water (80 parts) in small needles, containing $3H_2O$. After drying at 120°, it has m. p. 293° (corr.) (Found : loss at 120°, 13·3. $C_{17}H_{14}O_2N_2,HCl,3H_2O$ requires loss, 14·7%. Found in dried salt : C, 64·6; H, 5·2. $C_{17}H_{14}O_2N_2,HCl$ requires C, 64·8; H, 4·8%). The salt in dilute aqueous solution affords a deep green colour with a drop of ferric chloride solution.

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NOTTINGHAM. [*Received, December 1st*, 1930.]