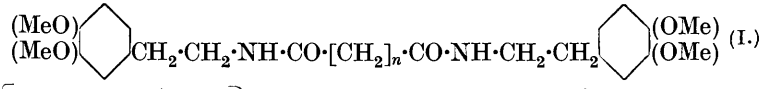
CCLXIII.—*Bases containing Two* iso*Quinoline Rings.*

By Reginald Child and Frank Lee Pyman.

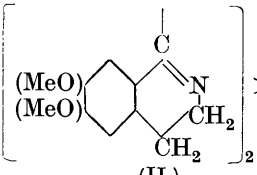
The formula recently put forward for emetine by Brindley and Pyman (J., 1927, 1069) contains two 6 : 7-dimethoxy*iso*quinoline residues connected in each case through the 1-position, and the partial formula of Späth and Leithe (*Ber.*, 1927, **60**, 688) contains the same feature.

With the hope of obtaining some substance having the amœbicidal properties characteristic of emetine, the preparation of a series of compounds containing two *iso*quinoline nuclei united through the 1 : 1′-positions by chains of methylene groups of varying length was projected. The general plan of the investigation was to prepare β-phenylethylamides and β-veratrylethylamides (I) of dibasic fatty acids, and to attempt their ring closure on the lines of the synthesis

of compounds containing a single *iso*quinoline nucleus, originated by Bischler and Napieralski (*Ber.*, 1893, **26**, 1903). The expected bis-3 : 4-dihydro*iso*quinolines (II) were then to be reduced to bistetrahydro*iso*quinolines (III, R = H) or, after methylation, to bis-2-methyltetrahydro*iso*quinolines (III, R = Me).



(I.)



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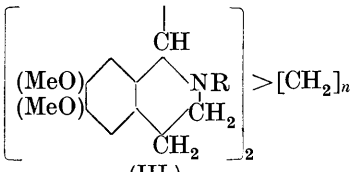
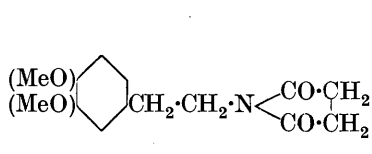
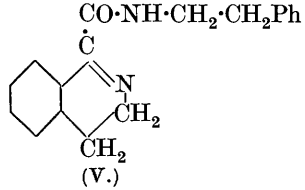


(III.)

Of the β-phenylethylamides of the dibasic fatty acids only oxalodi-β-phenylethylamide (Neubert, *Ber.*, 1886, **19**, 1826; Decker, *Annalen*, 1912, **395**, 308) and oxalodi-β-piperonylethylamide (Decker, *loc. cit.*) have been prepared previously. These and *oxalodi-β-veratrylethylamide* are formed quantitatively simply by mixing ethyl oxalate with the appropriate amine. For the preparation of the β-*phenyl-* and β-*veratryl-ethylamides* of the higher dibasic acids up to decane-1 : 10-dicarboxylic acid, it is necessary to heat the esters with the amines for some hours at 180°, whereby the amides are obtained in fair yields (50—80%). They show the alternation of m. p. and of solubility in alcohol familiar in the dibasic acid series (compare Barnicoat, J., 1927, 2927). These amides were the sole crystalline products of the reaction except in the condensations with ethyl succinate, in which N-β-*phenyl-* and N-β-*veratryl-ethyl-succinimide* (IV) were formed as by-products.



(IV.)

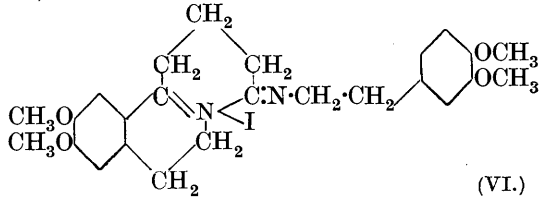


(V.)

Decker (*loc. cit.*) attempted the preparation of a bisdihydro*iso*-quinoline by treating oxalodi-β-phenylethylamide with phosphoric oxide, but was able to close only one ring with the formation of the compound (V).

We were unable to convert the unsubstituted β-phenylethylamides of the dibasic fatty acids from malonic up to sebacic into bisdihydro-*iso*quinolines, or even to close one of the two rings, by any of the known methods, using phosphoric oxide after Pictet and Kay (*Ber.*,

1909, **42**, 1973), phosphorus pentachloride and aluminium chloride after Decker and Kropp (*Ber.*, 1909, **42**, 2075), or phosphorus oxychloride after Buck and Perkin (J., 1924, **125**, 1680, 1695). More successful results were obtained with the β-veratrylethylamides, for *adipo-*, *pimelo-*, and *sebaco-di-β-veratrylethylamides* readily gave *bisdihydro*isoquinolines of type II (n = 4, 5, and 8) on dehydration by phosphorus oxychloride, and test-tube experiments showed that *azelao-*, *subero-*, *nonane*-1 : 9-*dicarboxy-*, and *decane*-1 : 10-*dicarboxy-di-β-veratrylethylamides* also underwent this type of condensation. *Adipodi-β-piperonylethylamide* behaved similarly. The β-veratrylethylamides of the lower dibasic fatty acids, however, behaved differently on treatment with phosphorus oxychloride. *Succino-di-β-veratrylethylamide* underwent such extensive decomposition that no basic products could be isolated, whilst *glutaro-di-β-veratrylethylamide* gave a poor yield of a monoacid base, isolated as its *hydriodide*, $C_{25}H_{31}O_4N_2I$, and traces of a second *hydriodide*, $C_{25}H_{32}O_5N_2,HI$. The latter is probably analogous in structure to the substance (V), whilst the former may possibly be a quaternary salt of formula (VI). On treatment with alkali it gave an unstable tertiary base, of which the formation may be explained by the assumption that the iodine was removed together with a hydrogen atom from the methylene group attached to the carbon atom in the 1-position with consequent rearrangement of the linkings, as in the formation of *N*-methyl*iso*-papaverine from papaverine methiodide (Decker and Klauser, *Ber.*, 1904, **37**, 520).



(VI.)

The reduction of bases of type II to bases of type III would be expected to yield two stereoisomeric (*dl-* and *meso-*) forms owing to the two carbon atoms in the 1 : 1′-position being rendered asymmetric. In the reduction of αδ-*bis*-(6 : 7-*dimethoxy*-3 : 4-*dihydro*isoquinolyl-1-)*butane* and of αε-bis-(6 : 7-dimethoxy-3 : 4-dihydro*iso*quinolyl-1-)pentane, however, only a single *bistetrahydro*-derivative was isolated in each case, but the reduction of the *dimethiodide* of the former base gave a mixture of αδ-*bis*-(6 : 7-*dimethoxy*-2-*methyltetrahydro*isoquinolyl-1-)*butanes*, only one of which was isolated in a pure state.

The following substances have been submitted to physiological examination :

A. αδ-Bis-(6 : 7-dimethoxy-3 : 4-dihydro*iso*quinolyl-1-)butane.
B. αδ-Bis-(6 : 7-dimethoxytetrahydro*iso*quinolyl-1-)butane.
C. αδ-Bis-(6:7-dimethoxy-2-methyltetrahydro*iso*quinolyl-1-)butane.
D. αε-Bis-(6 : 7-dimethoxy-3 : 4-dihydro*iso*quinolyl-1-)pentane.
E. αε-Bis-(6 : 7-dimethoxytetrahydro*iso*quinolyl-1-)pentane.
F. αθ-Bis-(6 : 7-dimethoxy-3 : 4-dihydro*iso*quinolyl-1-)octane.
G. The hydrochloride, $C_{25}H_{30}O_4N_2$,HCl, from glutarodi-β-veratrylethylamide.

By the courtesy of the Chemotherapy Committee of the Medical Research Council, these seven substances were tested for amœbicidal properties by Mr. Tate and Miss Vincent, working under Dr. Keilin's direction, at the Molteno Institute at Cambridge, using the methods employed by Laidlaw, Dobell, and Bishop (*Parasitology*, 1928, **20**, 207) for testing the action of emetine. None of these substances prevented the growth of *Entamoeba histolytica* in cultures at a dilution of 1 in 5000, whereas the control substance, emetine, was effective in a dilution of 1 in 500,000. Also by the courtesy of the Chemotherapy Committee, the above compounds were tested for antimalarial activity, B by Dr. Scott McFie and the remainder in Dr. Keilin's laboratory, and were found to be inactive. The substances A, B, C, D, E, and F were examined for toxicity and trypanocidal activity by Mr. W. A. Broom, B.Sc., of Boots Pharmacological Department. The maximum tolerated doses to mice (in mg. per g.) were A, 0·1; B, 0·35; C, 0·7; D, 0·5; E, 0·2—0·4; F, 0·10—0·15. None of the six substances had curative properties against *Trypanosoma equiperdum* in doses of half the maximum tolerated dose.

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

Experimental.

β-*Veratrylethylamine.*—The β-veratrylethylamine employed in this investigation was prepared essentially by the method of Buck and Perkin (J., 1924, **125**, 1679), but the method was improved considerably at one stage, namely the conversion of 3 : 4-dimethoxyphenylpropionic acid into its amide. These authors did not obtain good results by the action of ammonia upon either the ethyl ester or the acid chloride, prepared by means of either phosphorus pentachloride (Pictet and Finkelstein, *Ber.*, 1909, **42**, 1986) or thionyl chloride. Finally, they employed the method used by Decker (*Annalen*, 1913, **395**, 290) for the preparation of piperonylacetamide, *i.e.*, passage of dry ammonia through the molten acid at 220—230° for two hours; they did not state the yield, but in our hands it varied from 31 to 36%. Haworth and Perkin (J.,

1926, 1775) and Ray (*J. Indian Chem. Soc.*, 1927, **4**, 403) used the thionyl chloride method, and the latter author claims a yield of about 55%, which we confirm. The following is a more convenient method.

Ethyl β-3 : 4-*dimethoxyphenylpropionate* was prepared in the usual manner in 80% yield, b. p. 193°/20 mm., m. p. 13°, $d_{15\cdot5°}^{15\cdot5°}$ 1·1123 (Found : C, 65·5; H, 7·8. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%). When 100 g. of this ester were shaken for 4 days with ammonia (1 kg.; *d* 0·880), it gradually dissolved and was replaced by the pure amide. This was collected, and the filtrate was treated successively with four further amounts of ester (104 g., 98 g., 102 g., and 55 g.), whereby 305 g. of the amide were obtained (yield 75%), and a quantity of 3 : 4-dimethoxyphenylpropionic acid was recovered from the final mother-liquor.

Methyl β-3 : 4-*dimethoxyphenylpropionate*, b. p. 174—175°/12 mm., 194°/30 mm., m. p. 38—39° (Found : C, 64·2; H, 7·1. $C_{12}H_{16}O_4$ requires C, 64·2; H, 7·2%), is less suitable for conversion into the amide owing to its higher m. p.

Amides.—The amides of the dibasic fatty acids (except oxalic acid) were prepared by heating the ester (1 mol.) with the amine (2 mols.) in an open vessel for 4 hours at 180°. On cooling, crystalline masses were obtained, which after washing with alcohol gave the nearly pure amide, except in cases involving ethyl succinate, in which both the amide and the imide were formed. The following amides,* which were all insoluble in water, were prepared.

Oxalodi-β-phenylethylamide, m. p. 186° (Neubert, *loc. cit.*, gives m. p. 180°; Decker, *loc. cit.*, gives m. p. 186°).

Malonodi-β-phenylethylamide, silky needles from alcohol, m. p. 129—130°; yield 83% (Found : C, 73·4; H, 7·4; N, 8·9. $C_{19}H_{22}O_2N_2$ requires C, 73·5; H, 7·2; N, 9·0%).

Succin-amide and -imide. β-Phenylethylamine (5·15 g.) and ethyl succinate (3·75 g.) gave a crystalline product (4 g.; m. p. 130—160°), which was separated by boiling water into an insoluble fraction, *succinodi-β-phenylethylamide* (2 g.), long, silky needles from alcohol, m. p. 200° (Found : C, 74·6; H, 7·6; N, 8·5. $C_{20}H_{24}O_2N_2$ requires C, 74·0; H, 7·5; N, 8·6%), and N-β-*phenylethylsuccinimide* (1 g.), hard prisms from water, m. p. 133—134° (Found : C, 71·1; H, 6·5; N, 6·8. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·5; N, 6·9%). Prolonged heating favours the production of the imide, the succinamide derivative losing a molecule of phenylethylamine. Thus, in a second experiment, 6·1 g. of amine and 4·5 g. of ester gave 1·8 g. of imide and 1·8 g. of amide when heated for 6 hours at 190°.

* These, and all other compounds described in this paper, are colourless, and their m. p.'s are corrected, except where otherwise stated.

Glutarodi-β-phenylethylamide, needles from alcohol, m. p. 159—160°, was obtained in 70% yield, no formation of imide being detected (Found : C, 74·8; H, 7·7; N, 8·15. $C_{21}H_{26}O_2N_2$ requires C, 74·5; H, 7·75; N, 8·3%).

Adipodi-β-phenylethylamide, needles from alcohol, m. p. 184°, yield 66% (Found : C, 74·6; H, 8·1; N, 7·8. $C_{22}H_{28}O_2N_2$ requires C, 74·9; H, 8·0; N, 8·0%).

Pimelodi-β-phenylethylamide, silky matted needles from alcohol or benzene, m. p. 147—148°, yield 60% (Found : C, 75·6; H, 8·5; N, 7·7. $C_{23}H_{30}O_2N_2$ requires C, 75·4; H, 8·3; N, 7·7%).

Suberodi-β-phenylethylamide, needles from alcohol, m. p. 166°, yield 55% (Found : C, 75·7; H, 8·5; N, 7·3. $C_{24}H_{32}O_2N_2$ requires C, 75·7; H, 8·5; N, 7·4%).

Azelaodi-β-phenylethylamide, feathery crystals from alcohol, m. p. 151°, yield 55% (Found : C, 76·1; H, 8·6; N, 7·1. $C_{25}H_{34}O_2N_2$ requires C, 76·1; H, 8·7; N, 7·1%).

Sebacodi-β-phenylethylamide, needles from alcohol, m. p. 159°, yield 60% (Found : C, 76·5; H, 9·0. $C_{26}H_{36}O_2N_2$ requires C, 76·4; H, 8·9%).

Nonane-1 : 9-*dicarboxydi-β-phenylethylamide*, from ethyl nonane-1 : 9-dicarboxylate (b. p. 184°/14 mm.), short needles from alcohol, m. p. 151—152° (Found : N, 6·6. $C_{27}H_{38}O_2N_2$ requires N, 6·6%).

Decane-1 : 10-*dicarboxydi-β-phenylethylamide*, from ethyl decane-1 : 10-dicarboxylate (b. p. 192—193°/14 mm.), needles from alcohol, m. p. 157°, yield 50% (Found : N, 6·5. $C_{28}H_{40}O_2N_2$ requires N, 6·4%).

Oxalodi-β-veratrylethylamide, fine needles from alcohol, m. p. 173—174°; yield theoretical (Found : C, 63·2; H, 7·0. $C_{22}H_{28}O_6N_2$ requires C, 63·4; H, 6·8%).

Malonodi-β-veratrylethylamide could not be isolated in the pure state.

Succin-amide and -imide. β-Veratrylethylamine (17·1 g.) and ethyl succinate (8·2 g.) heated for 4 hours at 180—190° gave a crystalline product (13 g.), which boiling water partly separated into an insoluble portion (7·8 g.; m. p. 168—170°) and a soluble fraction (4·55 g.; m. p. 124—128°). Crystallisation of the former gave *succinodi-β-veratrylethylamide*, needles from alcohol, m. p. 174—175° (Found : C, 65·0; H, 7·5; N, 6·2. $C_{24}H_{32}O_6N_2$ requires C, 64·8; H, 7·3; N, 6·3%); and repeated crystallisation of the water-soluble fraction was necessary for the purification of N-β-*veratrylethylsuccinimide*, hard crystals from alcohol or benzene, m. p. 129° (Found : C, 63·8; H, 6·3. $C_{14}H_{17}O_4N$ requires C, 63·8; H, 6·5%).

Glutarodi-β-veratrylethylamide, felted needles from benzene, or hard crystals from a little alcohol, m. p. 131°, yield 74% (Found :

C, 65·6; H, 7·7; N, 6·0. $C_{25}H_{34}O_6N_2$ requires C, 65·5; H, 7·5; N, 6·1%); soluble in cold alcohol, about 1 g. in 40 c.c., and sparingly soluble in ether.

Adipodi-β-veratrylethylamide, needles from alcohol, m. p. 169°, yield 81·6% (Found: C, 65·8; H, 7·8; N, 5·9. $C_{26}H_{36}O_6N_2$ requires C, 66·1; H, 7·7; N, 5·9%); soluble in cold alcohol, about 1 g. in 300 c.c.

Pimelodi-β-veratrylethylamide, short needles from alcohol, m. p. 143—144°; yield 67% (Found: C, 66·5; H, 8·1. $C_{27}H_{38}O_6N_2$ requires C, 66·6; H, 7·9%); solubility in cold alcohol, about 1 g. in 60 c.c.

Suberodi-β-veratrylethylamide, thin needles from alcohol, m. p. 161°, yield 61% (Found: C, 67·3; H, 8·3; N, 5·6. $C_{28}H_{40}O_6N_2$ requires C, 67·2; H, 8·1; N, 5·6%); solubility in cold alcohol, about 1 g. in 160 c.c.

Azelaodi-β-veratrylethylamide, needles, m. p. 148—149°, yield 65% (Found: C, 67·6; H, 8·5; N, 5·45. $C_{29}H_{42}O_6N_2$ requires C, 67·6; H, 8·2; N, 5·4%); solubility in cold alcohol, 1 g. in 120 c.c.

Sebacodi-β-veratrylethylamide, m. p. 156°, yield 65% (Found: C, 68·4; H, 8·7; N, 5·3. $C_{30}H_{44}O_6N_2$ requires C, 68·1; H, 8·4; N, 5·3%); solubility in cold alcohol, about 1 g. in 250 c.c.

Nonane-1 : 9-*dicarboxydi-β-veratrylethylamide*, feathery needles from alcohol–ether, m. p. 152—153° (Found: C, 68·5; H, 8·8. $C_{31}H_{46}O_6N_2$ requires C, 68·6; H, 8·55%), readily soluble in alcohol.

Decane-1 : 10-*dicarboxydi-β-veratrylethylamide*, needles from alcohol, m. p. 155—156°, yield 55% (Found: C, 69·0; H, 9·0; N, 5·0. $C_{32}H_{48}O_6N_2$ requires C, 69·0; H, 8·7; N, 5·0%).

Adipodi-β-piperonylethylamide formed plates from glacial acetic acid, m. p. 208° (Found: C, 65·2; H, 6·7; N, 6·6. $C_{24}H_{28}O_6N_2$ requires C, 65·4; H, 6·4; N, 6·4%), very sparingly soluble in alcohol or benzene.

αδ-*Bis*-(6 : 7-*dimethoxy*-3 : 4-*dihydro*isoquinolyl-1-)*butane*.—Adipodi-β-veratrylethylamide (5 g.) in dry toluene (50 c.c.) and freshly distilled phosphorus oxychloride (15 c.c.) were boiled gently under reflux for 1 hour. Hydrogen chloride was evolved and a granular yellow deposit of the phosphate of the base separated. After cooling, the toluene was decanted off, and the residue washed with light petroleum and dried; it was then dissolved in 80—100 c.c. of alcohol and basified with 20% aqueous sodium hydroxide. On the addition of water, the free base (4·1 g.) separated as a mass of felted needles; yield 89%.

αδ-*Bis*-(6 : 7-*dimethoxy*-3 : 4-*dihydro*isoquinolyl-1-)*butane* separated from 70—100 times its weight of dry ethyl acetate in hard needles, m. p. 172—173°, and from alcohol or benzene in felted needles

(Found : C, 71·6, 71·8; H, 7·6, 7·7. $C_{26}H_{32}O_4N_2$ requires C, 71·5; H, 7·4%). It is insoluble in water or light petroleum, very readily soluble in chloroform, but sparingly soluble in ether. The *hydrochloride* crystallises from water in hydrated rhombs which soften between 90° and 100°. The *anhydrous* salt had m. p. 263—264° (decomp.) (Found, in air-dried salt : loss at 120°, 22·1, 22·1; C, 47·6; H, 7·9. $C_{26}H_{32}O_4N_2,2HCl,8H_2O$ requires loss, 22·1; C, 47·7; H, 7·6%. Found, in salt dried at 120° : C, 61·0; H, 6·9; Cl, 13·8. $C_{26}H_{32}O_4N_2,2HCl$ requires C, 61·2; H, 6·7; Cl, 13·9%). The *hydriodide* is sparingly soluble in water, from which it crystallises in pale yellow anhydrous needles, m. p. 260—261° (decomp.) (Found : C, 45·1; H, 5·1; I, 36·6. $C_{26}H_{32}O_4N_2,2HI$ requires C, 45·1; H, 5·0; I, 36·7%). The *hydrogen sulphate* separates from aqueous alcohol as a microcrystalline powder, m. p. 255—260° (decomp.), easily soluble in water (Found : SO_4, 29·8.

$$C_{26}H_{32}O_4N_2,2H_2SO_4$$

requires SO_4, 30·4%). The *succinate* crystallises from alcohol in plates, m. p. 202—203° (decomp.). It is soluble in twice its weight of water at the ordinary temperature, giving a solution neutral to litmus; soluble in hot alcohol, sparingly soluble in cold alcohol, but insoluble in ether (Found : C, 64·8; H, 7·1. $C_{26}H_{32}O_4N_2,C_4H_6O_4$ requires C, 64·9; H, 6·9%).

Dimethiodide. The base was heated under reflux with a large excess of methyl iodide for 3 hours, and the crude product recrystallised from 40—50 times its weight of water, being obtained in long pale yellow needles, m. p. 240—241° (decomp.), containing $1H_2O$, which is lost at 120°, but readily regained by the dried substance on exposure to moist air (Found, in air-dried salt : loss at 120°, 2·5; C, 45·5; H, 5·7; I, 34·4. $C_{28}H_{38}O_4N_2I_2,H_2O$ requires loss, 2·4; C, 45·5; H, 5·5; I, 34·4%. Found, in dried salt : I, 35·0. $C_{28}H_{38}O_4N_2I_2$ requires I, 35·3%).

αδ-Bis-(6 : 7-*dimethoxytetrahydro*iso*quinolyl*-1-)*butane.*—The foregoing dihydro*iso*quinoline base (5 g.), alcohol (25 c.c.), concentrated hydrochloric acid (25 c.c.), and tin-foil (12 g.) were heated under reflux for 24 hours with a further addition of hydrochloric acid after 16 hours. After dilution of the solution, and removal of tin as sulphide, the filtrate was evaporated to dryness under reduced pressure and the residue crystallised from 100 c.c. of water, giving 3·1 g. of a crystalline *hydrochloride*. The air-dried salt attained constant weight only after several days and then appeared to contain $1H_2O$. After drying at 120°, it had m. p. 268—270° (decomp.) (Found : loss at 120°, 3·3; C, 58·2; H, 8·1; Cl, 13·3.

$$C_{26}H_{36}O_4N_2,2HCl,H_2O$$

requires loss, 3·4; C, 58·6; H, 7·7; Cl, 13·3%).

The base, *αδ-bis-*(6 : 7-*dimethoxytetrahydro*isoquinolyl-1-)*butane*, crystallised from ethyl acetate in rosettes of minute needles, m. p. 127°, insoluble in water (Found : C, 70·2; H, 8·3; N, 6·5. $C_{26}H_{36}O_4N_2$ requires C, 70·9; H, 8·2; N, 6·4%). The *lactate* is precipitated from alcoholic solution by ether as a microcrystalline powder, m. p. 212—213° (decomp.) (Found : C, 61·7; H, 7·9. $C_{26}H_{36}O_4N_2,2C_3H_6O_3$ requires C, 61·9; H, 7·8%); this salt is soluble in twice its weight of water at the ordinary temperature, giving a solution neutral to litmus, and is slightly soluble in alcohol, but insoluble in ether.

αδ-Bis-(6 : 7-*dimethoxy*-2-*methyltetrahydro*isoquinolyl-1-)*butane*.—The above dimethiodide (35 g.) in hot water (1 l.) was digested with silver chloride from 40 g. of silver nitrate, and the solution evaporated to dryness under diminished pressure. This product, with alcohol (150 c.c.) and concentrated hydrochloric acid (200 c.c.), was digested with tin-foil (40 g.) for 7 hours. After removal of tin as sulphide, the filtrate was concentrated, basified with ammonia, and extracted with ether. This left a nearly colourless varnish (20 g.), which slowly crystallised when moistened with acetone. This product melted at about 84—90° to a turbid liquid which became clear about 103°; it gave satisfactory figures on analysis (Found : C, 71·5; H, 8·7%), and was doubtless a mixture of stereoisomerides. It was mixed with oxalic acid (10 g.) in hot alcohol (100 c.c.) and kept; the acid oxalate which separated was collected, boiled with water (100 c.c.), and kept. An acid oxalate (7·5 g., m. p. 232°) was deposited, and a further quantity of 1·7 g. of the same m. p. was recovered from the mother-liquors. After treatment with sodium hydroxide and extraction in ether, this gave *αδ-bis-*(6 : 7-*dimethoxy*-2-*methyltetrahydro*isoquinolyl-1-)*butane* (4·0 g.; m. p. 105°), which crystallises from alcohol in elongated prisms, m. p. 108—109°, and is insoluble in water but readily soluble in hot alcohol (Found : C, 71·9; H, 8·7. $C_{28}H_{40}O_4N_2$ requires C, 71·7; H, 8·6%).

The *hydrochloride* separates from alcohol in minute needles, m. p. 244—245°, soluble in two parts of water at the ordinary temperature, giving a neutral solution (Found, in salt dried at 100° : C, 61·4; H, 8·2. $C_{28}H_{40}O_4N_2,2HCl$ requires C, 62·1; H, 7·8%). The hydriodide and acid oxalate are sparingly soluble in water. The mother-liquors from the crystallisation of the acid oxalates in the above preparation were basified and extracted with ether. This left an oil which slowly crystallised, m. p. about 85—88°, and was doubtless a stereoisomeride of the base of m. p. 108—109°, but attempts to purify it were unsuccessful owing to its ready solubility.

αε-Bis-(6 : 7-dimethoxy-3 : 4-dihydro*iso*quinolyl-1-)pentane was prepared from pimelodi-β-veratrylethylamide in the same way as the

butane analogue (p. 2016), except that the crude base did not crystallise. It was collected by means of chloroform, and converted through the hydrochloride and potassium iodide into the hydriodide; yield 83%. The base crystallised from benzene–light petroleum in rosettes, m. p. 57—58°. It is soluble in the usual media, with the exception of water and light petroleum. It is somewhat unstable and tends to decompose to a non-basic resinous material.

The *hydrochloride* crystallises from 90% alcohol as a microcrystalline powder, m. p. 235—236° (eff.), soluble in five parts of cold water, very slightly soluble in absolute alcohol, and insoluble in acetone (Found, in air-dried salt : loss at 120°, 3·6.

$$C_{27}H_{34}O_4N_2,2HCl,H_2O$$

requires loss, 3·3. Found, in dried salt : C, 61·6; H, 7·2.

$$C_{27}H_{34}O_4N_2,2HCl$$

requires C, 61·9; H, 6·9%). The *hydriodide* separates from 40 times its weight of methyl alcohol in hard, pale yellow crystals, m. p. 220—222° (decomp.) (Found : C, 46·0; H, 5·4; I, 35·95.

$$C_{27}H_{34}O_4N_2,2HI$$

requires C, 45·9; H, 5·1; I, 35·9%). The *hydrogen tartrate* separates as a microcrystalline powder, m. p. 189—190° (eff.), when 10% alcoholic solutions of the base and the acid are mixed, and this procedure is a convenient method of purifying this base; this salt is readily soluble in water, giving a solution acid to litmus, and is sparingly soluble in alcohol (Found : C, 56·0; H, 6·4.

$$C_{27}H_{34}O_4N_2,2C_4H_6O_6$$

requires C, 56·0; H, 6·2%).

Dimethiodide. The crude base was heated under reflux with an excess of methyl iodide for 5 hours; the crude *dimethiodide* was recrystallised twice from methyl alcohol, and formed large yellow crystals containing methyl alcohol of crystallisation, which was lost rapidly at 100°, or gradually on keeping; m. p. of dried salt, 236—237° (decomp.) (Found : loss at 100°, 9·88.

$$C_{27}H_{34}O_4N_2,2CH_3I,2\tfrac{1}{2}CH_3\cdot OH$$

requires loss, 9·83. Found, in dried salt : I, 34·6.

$$C_{27}H_{34}O_4N_2,2CH_3I$$

requires I, 34·6%).

αε-*Bis*-(6 : 7-*dimethoxytetrahydro*isoquinolyl-1-)*pentane.*—5 G. of the foregoing dihydro*iso*quinoline base were dissolved in alcohol (20 c.c.) and heated under reflux for 24 hours with concentrated hydrochloric acid (20 c.c.) and tin-foil (12 g.). Further additions of hydrochloric acid were made after 5 and after 20 hours. The solution was diluted, and tin was removed as sulphide. The filtrate was evaporated to dryness and gave a crystalline *hydro-*

chloride (4·8 g.), which was recrystallised from alcohol–ether and obtained as a crystalline powder, m. p. 225—227°, readily soluble in water (1 part in 4 parts) to a neutral solution, and fairly readily soluble in alcohol (Found, in salt dried at 100° : Cl, 13·3. $C_{27}H_{38}O_4N_2$ requires Cl, 13·5%).

αθ-Bis-(6 : 7-dimethoxy-3 : 4-dihydroisoquinolyl-1-)octane was prepared from sebacodi-β-veratrylethylamide in the same way as the butane analogue (p. 2016); yield 85%. It crystallises from 25 parts of ethyl acetate in needles, m. p. 116°, insoluble in water but soluble in the usual organic solvents except light petroleum (Found : C, 72·9; H, 8·4. $C_{30}H_{40}O_4N_2$ requires C, 73·1; H, 8·2%).

The *hydrochloride* crystallises from 90% alcohol in small needles, m. p. 172° (eff.), containing $1H_2O$. The *anhydrous* salt has m. p. 208—210° (decomp.), is soluble in 5 parts of cold water, giving a solution neutral to litmus, and is sparingly soluble in alcohol (Found : loss at 120°, 3·1. $C_{30}H_{40}O_4N_2,2HCl,H_2O$ requires loss, 3·1. Found, in dried salt : Cl, 12·6. $C_{30}H_{40}O_4N_2,2HCl$ requires Cl, 12·5%). The *hydriodide* formed orange needles from water, m. p. 208—209° (eff.) (Found : C, 48·0; H, 6·0; I, 33·9. $C_{30}H_{40}O_4N_2,2HI$ requires C, 48·1; H, 5·7; I, 33·9%); and the *succinate* separated from alcohol as a microcrystalline powder, m. p. 187°, soluble in 80 parts of cold water, giving a solution neutral to litmus and having a slight green fluorescence (Found, by titration to phenolphthalein : $C_4H_6O_4$, 19·3, 19·5. $C_{30}H_{40}O_4N_2,C_4H_6O_4$ requires $C_4H_6O_4$, 19·3%).

αδ-Bis-(6 : 7-methylenedioxy-3 : 4-dihydroisoquinolyl-1-)butane was prepared from adipodi-β-piperonylethylamide in the same way as the dimethoxy-analogue; yield, 87% of crude base, m. p. 197—201° (decomp.). After crystallisation from benzene or from 200 parts of alcohol it formed minute needles, m. p. 210—211°, sparingly soluble in the usual solvents (Found : C, 71·0; H, 6·1. $C_{24}H_{24}O_4N_2$ requires C, 71·25; H, 6·0%).

The *hydrochloride* crystallises from water (20 parts) in cream-coloured needles containing $2H_2O$, m. p. 270° (decomp.) (Found : loss at 120°, 7·2. $C_{24}H_{24}O_4N_2,2HCl,2H_2O$ requires loss, 7·0%); the *hydriodide* crystallises from water (100 parts) in golden-yellow crystals, m. p. 277—280° (decomp.) (Found : I, 38·4. $C_{24}H_{24}O_4N_2,2HI$ requires I, 38·5%). The *dimethiodide*, prepared by heating the base for 5 hours under reflux with excess of methyl iodide, crystallised from water (100 parts) in yellow needles, m. p. 285—287° (decomp.) (Found : C, 45·5; H, 4·5. $C_{24}H_{24}O_4N_2,2CH_3I$ requires C, 45·3; H, 4·4%).

Action of Phosphorus Oxychloride upon Glutarodi-β-veratrylethylamide.—The amide was treated with phosphorus oxychloride for various periods, but even under the most favourable conditions

upwards of 50% was converted into non-crystallisable resinous material, which appears to result from decomposition of the products primarily formed (see below); consequently prolonged heating with phosphorus oxychloride is to be avoided.

Glutarodi-β-veratrylethylamide (10 g.) in toluene (100 c.c.) was heated gently under reflux for 30 minutes with phosphorus oxychloride (30 c.c.). No deposit of phosphate was formed, so the product was mixed with light petroleum, which precipitated a resinous material. After removal of the liquor by decantation, the residue was dissolved in water (100 c.c.) and the solution filtered. Sodium iodide (12 g.) in water (20 c.c.) was added, and after 1 hour the supernatant aqueous liquor was decanted from the sticky precipitate, which was triturated with 20 c.c. of cold methyl alcohol and filtered, leaving a granular, nearly colourless residue. 30 G. of the amide treated in this way gave 14·05 g. of solid hydriodide and the methyl-alcoholic filtrates on evaporation gave a resin (21 g.). The sparingly soluble material (14·05 g.) was extracted (Extract E) with 100 c.c. of hot (not boiling) methyl alcohol, leaving a residue (10·2 g.; m. p. 238°). This was recrystallised from boiling methyl alcohol (solubility, 1 g. in 120 c.c.) and obtained in cream-coloured plates, m. p. 239—240° (Found: C, 54·4, 54·3; H, 6·1, 6·0; I, 23·1; N, 5·05. $C_{25}H_{31}O_4N_2I$ requires C, 54·4; H, 5·7; I, 23·1; N, 5·1%). This *hydriodide* (? VI) can be extracted from aqueous solution by means of chloroform. When digested with silver chloride in boiling water, it yields the *hydrochloride*, which is precipitated from alcohol by ether as a colourless microcrystalline powder, m. p. 199—200°, readily soluble in water, giving a solution neutral to litmus, and soluble in 5 parts of cold alcohol, but insoluble in ether (Found: C, 64·7; H, 7·2; N, 6·0. $C_{25}H_{30}O_4N_2$,HCl requires C, 65·4; H, 6·8; N, 6·1%). The hydrochloride darkens in colour on drying at 100° or on keeping. The aqueous solution gives with sodium hydroxide an insoluble base (m. p. about 103°), which is unstable and is rapidly converted in air to a brown resin, especially in alcoholic or ethyl acetate solution.

The methyl-alcoholic extract (E) deposited, on cooling, a *hydriodide* (1·45 g.) in yellow crystals which, when recrystallised from 30 c.c. of methyl alcohol, had m. p. 203—204° (Found: C, 52·3; H, 6·3; I, 22·0. $C_{25}H_{32}O_5N_2$,HI requires C, 52·8; H, 5·9; I, 22·3%).

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