CCCCXVI.—*Amidines of Pharmacological Interest.*

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This paper records the details of the preparation of a number of amidines. These were prepared for pharmacological study from various points of view, as described below, but none of them has appeared to be of sufficient value to warrant clinical trial.

1. *As Local Anæsthetics.*—Many local anæsthetics contain a carboalkoxy-group, but the corresponding carboxylic acid may have no local anæsthetic properties, possibly because the lipoid-soluble character of the ester is not shared by the acid; compare, for instance, cocaine with ecgonine. Now amidines contain a group, $\cdot C(:NH)\cdot NH_2$, which is structurally similar to the carboxyl group. The free bases, although more or less soluble in water, are also soluble in immiscible solvents, whilst the salts, which contain one equivalent of acid, are neutral in reaction and readily soluble in water. It therefore appeared to be of interest to enquire whether substitution of the amidine group for the carbethoxy-group of the local anæsthetic "anæsthesin," ethyl *p*-aminobenzoate, $NH_2\cdot C_6H_4\cdot CO_2Et$, would give rise to a substance having local anæsthetic properties, and p-*aminobenzamidine*, $NH_2\cdot C_6H_4\cdot C(:NH)\cdot NH_2$, was consequently prepared. This substance and its *m*-isomeride were prepared by reduction of the corresponding nitrobenzamidines. These aminobenzamidines and also 3 : 4-*dimethoxybenzamidine*, which was prepared from veratronitrile by way of 3 : 4-*dimethoxybenzimino-*

ether, had no local anæsthetic action, but slight local anæsthetic properties were found in the case of two substituted ethyl benzoates, namely, p-*carbethoxybenzamidine*, $EtO_2C{\cdot}C_6H_4{\cdot}C(:NH){\cdot}NH_2$, which was prepared through the *imino-ether*, and p-*carbethoxyphenylguanidine*, $EtO_2C{\cdot}C_6H_4{\cdot}NH{\cdot}C(:NH){\cdot}NH_2$, which was prepared from p-*carbethoxyphenylthiocarbamide* through the S-*methyl* ether. In view of the known anæsthetic character of " holocain," ethenyldi-*p*-phenetylamidine, $EtO{\cdot}C_6H_4{\cdot}NH{\cdot}CMe{:}N{\cdot}C_6H_4{\cdot}OEt$, the preparation of similar bases containing *o*-dimethoxy-groups was attempted. *Benzenylveratrylamidine*, $NH_2{\cdot}CPh{:}N{\cdot}C_6H_3(OMe)_2$, was prepared by treating benzoylveratrylamine first with phosphorus pentachloride and then with ammonia. It proved to have well-marked local anæsthetic character. Attempts to prepare 3 : 4-dimethoxybenzenylveratrylamidine, ethenylveratrylamidine, and ethenyldiveratrylamidine in a similar manner were unsuccessful.

2. *As Antiseptics.*—Following out the plan mentioned above of comparing the effects of the amidine and carboxyl residues, o-*hydroxybenzamidine* was prepared in the form of its *sulphate* for a comparison of its antiseptic properties with those of salicylic acid. Tested against *B. coli* in broth, *o*-hydroxybenzamidine sulphate inhibited growth in a dilution of 1 in 900, but not in a dilution of 1 in 1000, whilst under similar conditions salicylic acid inhibited growth in a dilution of 1 in 2000, but not in a dilution of 1 in 2250. The inhibitive effect of *o*-hydroxybenzamidine sulphate is therefore less than that of salicylic acid, molecule for molecule, and much less weight for weight. We are indebted to Mr. C. E. Coulthard of Boots' Bacteriological Department for carrying out the tests described above.

3. *As Hypoglycæmic Drugs.*—The interesting properties of synthalin (diguanidinodecamethylene) led us to test the hypoglycæmic properties of the diamidines of dibasic fattyacids. Bischoff, Sahyun, and Long (*J. Biol. Chem.*, 1929, **81**, 325) have shown that in the synthalin series (I) the toxic and hypoglycæmic effects increase with the lengthening of the chain connecting the two

$$NH_2{\cdot}(NH{:})C{\cdot}NH{\cdot}[CH_2]_n{\cdot}NH{\cdot}C(:NH){\cdot}NH_2 \quad \text{(I.)}$$

$$NH_2{\cdot}(NH{:})C{\cdot}[CH_2]_n{\cdot}C(:NH){\cdot}NH_2 \quad \text{(II.)}$$

guanidine residues up to synthalin (I, $n = 10$) itself, and then decrease, the lethal dose for rabbits in mg. of base per kg. given parenterally being pentamethylene 50, octamethylene 7, decamethylene 4, and dodecamethylene 8. Any hypoglycæmic effect was usually accompanied by death.

We have consequently prepared and tested the hypoglycæmic action of a series of diamidines of basic fatty acids of varying length

of chain. Reduction of blood sugar was only observed in those animals which subsequently died. The dose required to bring about hypoglycæmia and death on injection into rabbits of about 2·9 kg. was: *azelamidine sulphate* (II, $n = 7$) between 100 and 200 mg., sebecamidine hydrochloride (II, $n = 8$) between 60 and 75 mg., and *decane*-1 : 10-*diamidine dihydrochloride* (II, $n = 10$) less than 100 mg.

Two amidines of monobasic fatty acids were also tested in this connexion, namely, *valeramidine sulphate* and lauramidine hydrochloride, but neither produced any effect in doses of 100 mg.

Two derivatives of guanidine prepared with different objects in view were incidentally tested for hypoglycæmic action, and it was found that *p*-carbethoxyphenylguanidine hydrochloride had no hypoglycæmic properties when administered to rabbits of about 2·9 kg. in a dose of 0·5 g., whilst p-*hydroxyphenylguanidine hydrochloride* had no hypoglycæmic properties in sublethal doses. In this connexion it may be recalled that Parks and Braun (*J. Biol. Chem.*, 1931, **91**, 629) have now come to the conclusion that *p*-aminophenylguanidine does not possess hypoglycæmic properties.

The experiments on the local anæsthetic and hypoglycæmic properties of the above-mentioned amidines were carried out by Mr. W. A. Broom, B.Sc., of Boots' Pharmacological Department, who will give a more detailed account of them elsewhere.

4. *As Pressor Drugs.*—It appeared to us to be of interest to determine whether the pressor effect characteristic of the phenylalkylamines was also found in similarly constituted amidines. In this connexion we prepared p-*hydroxyphenylacetamidine*,

$$HO{\cdot}C_6H_4{\cdot}CH_2{\cdot}C(:NH){\cdot}NH_2,$$

a substance analogous to *p*-hydroxyphenylethylamine, and also its N-*methyl* derivative, $HO{\cdot}C_6H_4{\cdot}CH_2{\cdot}C(:NH){\cdot}NHMe$, mandelamidine, and o- and m-*hydroxybenzamidines*, $HO{\cdot}C_6H_4{\cdot}C(:NH){\cdot}NH_2$. These substances were tested by Dr. A. St. G. Huggett and Prof. McSwiney, who found that *p*-hydroxyphenylacetamidine had a pressor effect, whilst its *N*-methyl derivative, mandelamidine, *o*- and *m*-hydroxybenzamidine were almost inactive in this respect. Their results will be reported elsewhere in due course.

5. *As Antimalarial Drugs.*—Through the courtesy of the Chemotherapy Committee of the Medical Research Council three of the above compounds were tested for antimalarial action upon canaries, 3 : 4-dimethoxybenzamidine and *p*-carbethoxyphenylguanidine by Dr. Keilin, F.R.S., and benzenylveratrylamidine by Dr. Scott McFie, but none was found to have any antimalarial properties.

The authors desire to express their thanks to all the investigators, named above, of the pharmacology of these amidines.

EXPERIMENTAL.

m-*Aminobenzamidine Monohydrochloride.*—*m*-Nitrobenzamidine hydrochloride, prepared by the method of Forsyth, Nimkar, and Pyman (J., 1926, 800), was reduced to *m*-aminobenzamidine dihydrochloride (monohydrate) by the method of Pinner (*Ber.*, 1895, **28**, 473). This salt had m. p. 265—266° (corr.); Pinner gives m. p. 260°. This salt (35 g.) and 150 c.c. of 1·035*N*-sodium hydroxide were evaporated to dryness under diminished pressure, and the monohydrochloride was extracted from the residue with absolute alcohol. After recrystallisation from water m-*aminobenzamidine monohydrochloride dihydrate* (25 g.; yield, 87%) was obtained in long fibrous needles, m. p. 79—85° (Found : H_2O, 16·9; N, 19·8; Cl, 17·2. $C_7H_9N_3,HCl,2H_2O$ requires H_2O, 17·3; N, 20·2; Cl, 17·1%). The saturated aqueous solution contains 15% of the anhydrous salt at the ordinary temperature and is neutral to litmus. The dihydrate is readily soluble in alcohol and slightly soluble in acetone. The water of crystallisation is lost almost completely by keeping in a vacuum over sulphuric acid, and completely at 100°. The anhydrous salt crystallises from methyl alcohol in needles, m. p. 162—163° (corr.). It is hygroscopic and slowly absorbs two molecules of water when exposed to the air.

p-*Aminobenzamidine Salts.*—18·3 G. of *p*-nitrobenzamidine hydrochloride (prepared according to Pinner and Gradenwitz, *Annalen*, 1888, **248**, 47, and having m. p. 294—296°, corr. decomp.) were added to stannous chloride (66 g.) in concentrated hydrochloric acid (92 c.c.). Granulated tin (37 g.) was added, and the mixture boiled for 1 hour. After removal of tin as sulphide, p-*aminobenzamidine dihydrochloride* (13·1 g.; 70%) was obtained. It crystallises from water, in which it is readily soluble, in needles, m. p. about 320° (decomp.) (Found : C, 40·2; H, 5·5; N, 20·5; Cl, 33·8. $C_7H_9N_3,2HCl$ requires C, 40·4; H, 5·3; N, 20·2; Cl, 34·1%). The *monohydrochloride*, prepared in the same way as the *m*-isomeride, crystallises from water with $1H_2O$, which is lost in a vacuum over sulphuric acid (Found : H_2O, 8·7, 10·8. $C_7H_9N_3,HCl,H_2O$ requires H_2O, 9·5%). The anhydrous salt is non-hygroscopic, and has m. p. 225—226° (corr.) (Found : C, 48·6; H, 5·7; Cl, 20·6. $C_7H_9N_3,HCl$ requires C, 49·0; H, 5·8; Cl, 20·7%). It is soluble in alcohol. The saturated aqueous solution contains 35% of the anhydrous salt, the solution being neutral to litmus.

The *monopicrate* crystallises from glacial acetic acid in small leaflets, m. p. 231—232° (corr. decomp.) (Found : C, 43·1; H, 3·2. $C_7H_9N_3,C_6H_3O_7N_3$ requires C, 42·8; H, 3·3%).

The free base was obtained as an amorphous powder, m. p.

(decomp.) about 125°; it is easily soluble in water or alcohol, and slightly soluble in ether or chloroform; its aqueous solution when warmed decomposes with evolution of ammonia.

3 : 4 - *Dimethoxybenziminoether Hydrochloride.*—Veratronitrile (49 g.) was dissolved in a mixture of absolute alcohol (14·2 g.) and sufficient dry benzene to give a homogeneous solution. Dry hydrogen chloride (11·5 g.) was led in, with cooling. The mixture was kept in the ice-chest over-night and then for 48 hours at room temperature. The *imino-ether hydrochloride* separated in greenish fibrous needles. Dry ether was stirred into the mixture and the crystals were collected, washed with ether, and dried in a vacuum over caustic soda. The imino-ether hydrochloride had m. p. 142—143° (efferv.) (Found: C, 53·1; H, 6·3; N, 5·6; Cl, 14·2. $C_{11}H_{15}O_3N$,HCl requires C, 53·7; H, 6·5; N, 5·7; Cl, 14·5%). Yield, 28 g., *i.e.*, 38%. Unchanged nitrile was recovered from the filtrate and ether washings.

3 : 4-*Dimethoxybenzamidine Hydrochloride.*—The finely powdered imino-ether hydrochloride (24·5 g.) was treated with alcoholic ammonia in the manner described by Pinner ("Die Imidoäther," p. 86). The mixture was kept at 37° for 48 hours. The almost clear solution which was formed yielded 21 g. (96%) of the *amidine hydrochloride*, which crystallised from alcohol in fine needles, m. p. 237° (corr., decomp.) (Found: C, 49·5; H, 6·4; N, 12·9; Cl, 16·8. $C_9H_{12}O_2N_2$,HCl requires C, 49·8; H, 6·0; N, 12·9; Cl, 16·4%). The saturated solution contains 60% of the salt at the ordinary temperature. The picrate forms yellow needles from alcohol, m. p. 217—218° (corr.). The free base, extracted from a strongly alkaline mixture with ether containing a little alcohol, separated on evaporation of the solvent in a vacuum, at room temperature, in long, pale yellow needles, m. p. 110—120°. It is readily soluble in water and in alcohol, fairly readily soluble in chloroform, and sparingly soluble in ether.

p-*Carbethoxybenziminoether Hydrochloride.*—*p*-Carbethoxybenzonitrile (17 g.) was dissolved in a mixture of dry benzene (22 c.c.) and absolute alcohol (4·5 g.), and dry hydrogen chloride (3·6 g.) led into the solution with cooling. The mixture was kept for several days in the ice-chest. The *imino-ether hydrochloride* separated in long fine needles (17·3 g.), m. p. 179°. Yield, 69% (Found: Cl, 13·8. $C_{12}H_{15}O_3N$,HCl requires Cl, 13·8%).

p - *Carbethoxybenzamidine Hydrochloride.* — *p* - Carbethoxybenziminoether hydrochloride (14·5 g.) was treated with a very small excess of alcoholic ammonia. After 3 days, the ammonium chloride had been replaced by thick colourless prisms consisting of the *amidine hydrochloride* (11·1 g.; 90%). The salt crystallised from

alcohol in long transparent prisms, m. p. 217—218° (corr., decomp.) (Found : C, 52·6; H, 6·1; N, 12·6; Cl, 15·6. $C_{10}H_{12}O_2N_2$,HCl requires C, 52·5; H, 5·7; N, 12·3; Cl, 15·5%). The free base separated from a strongly basified concentrated solution of the hydrochloride as an oil which slowly solidified. The oil was readily soluble in ether. Crystallisation did not take place when the ethereal solution was evaporated in a vacuum. Decomposition with evolution of ammonia occurred when the ethereal solution was kept. The oil was readily soluble in water, the solution being alkaline.

p-*Carboxyphenylthiocarbamide.*—An aqueous solution of *p*-aminobenzoic acid hydrochloride (20 g.) and ammonium thiocyanate (12 g.) was evaporated to dryness on the steam-bath. The residue was dissolved in caustic soda, and the solution filtered and acidified. The fine white powder precipitated was washed with water (yield, 16·5 g.; 73%). The substance could not be crystallised, as it was only very slightly soluble in water, alcohol, or acetone, and apparently insoluble in benzene, ether, chloroform, ethyl acetate, carbon disulphide or glacial acetic acid. It did not melt below 330° (Found : N, 14·6; S, 15·4. $C_8H_8O_2N_2S$ requires N, 14·3; S, 16·3%).

p-*Carboxyphenyl*-S-*methyl*isothiocarbamide *Hydriodide.*—A mixture of *p*-carboxyphenylthiocarbamide (14·2 g.), absolute alcohol (100 c.c.), and methyl iodide (10·5 g.) was refluxed for an hour. The fine powder gradually dissolved and a greenish-yellow crystalline substance separated. The mixture was cooled and the precipitation completed by addition of dry ether. Yield, 20·8 g. (85%). The *hydriodide* formed prisms from absolute alcohol, m. p. 238—239° (corr., decomp.), easily soluble in water (Found : C, 31·8; H, 3·3; N, 8·3. $C_9H_{10}O_2N_2S$,HI requires C, 32·0; H, 3·3; N, 8·3%).

p-*Carbethoxyphenylguanidine.*—A mixture of the above hydriodide (67 g.) with an excess of concentrated aqueous ammonia was warmed gently until refluxing began and boiled for 3 hours. The hydriodide quickly dissolved and mercaptan was evolved. The solution was concentrated on the steam-bath until crystallisation began, cooled, and the *p*-carboxyphenylguanidine filtered off and washed with water. Yield, 30 g. of m. p. about 310°; 85%. The nitrate of this guanidino-acid is less soluble in water than the parent substance. The crude acid (20·5 g.) was esterified by boiling with absolute alcohol (260 c.c.) and alcoholic hydrogen chloride (20·5 c.c. of 33%) for 12 hours. The ester was extracted from the evaporated basified solution with ethyl acetate, the extract evaporated with excess of alcoholic hydrogen chloride, and the residue digested with anhydrous ether and filtered. The crude p-*carbethoxyphenylguanidine hydrochloride* thus obtained (16 g.) had m. p. 150—160°. After recrystallisation from alcohol it formed rectangular prisms, m. p. 166—167°

(corr.). Yield, 11·0 g. (50%) (Found: C, 49·1; H, 6·0; N, 16·9; Cl, 14·7. $C_{10}H_{13}O_2N_3$,HCl requires C, 49·3; H, 5·8; N, 17·2; Cl, 14·6%). The saturated aqueous solution contains about 48% of the salt at the ordinary temperature, the solution being neutral. The free base separates from ethyl acetate in thin prisms, m. p. 162—163° (corr.), which are readily soluble in alcohol and in ethyl acetate, but sparingly soluble in ether and in water. The picrate forms yellow prisms from alcohol, m. p. 224—225° (corr.); the nitrate, thin prisms from water, m. p. 201—202° (corr. decomp.).

p-*Hydroxyphenyl*-S-*methyl*isothiocarbamide *Hydriodide*.—A mixture of *p*-hydroxyphenylthiocarbamide (23·8 g.), absolute alcohol (50 c.c.), and methyl iodide (22 g.) was refluxed for an hour; a clear solution, miscible with water, was then formed. From this the *hydriodide* was obtained in 95% yield (42·2 g.), m. p. 176—181°. It is very readily soluble in water and in alcohol, and readily soluble in acetone (Found: I, 41·1; S, 10·1. $C_8H_{10}ON_2S$,HI requires I, 41·0; S, 10·3%).

p-*Hydroxyphenylguanidine Hydrochloride*.—The above hydriodide (45 g.) was refluxed with 200 c.c. of aqueous ammonia (*d* 0·880) for 3 hours. The solution was then heated in an open dish for an hour, to remove mercaptan and ammonia. The hydroxyphenylguanidine was precipitated as the picrate, which was converted into the *hydrochloride* (18·2 g.; 66%). This separates from alcohol in stout transparent prisms, m. p. 197—198° (corr.) (Found: N, 22·2; Cl, 18·6. $C_7H_9ON_3$,HCl requires N, 22·4; Cl, 18·9%). It is readily soluble in water. The picrate crystallises from dilute alcohol in needles, m. p. 235—236° (corr.); the nitrate, from dilute alcohol in prisms, m. p. 205—206° (corr.).

Benzenylveratrylamidine.—Benzoylveratrylamine (18 g.), phosphorus pentachloride (20 g.), and a little dry benzene were refluxed for 2 hours. Hydrogen chloride was evolved and a dark brown solution formed. Phosphorus oxychloride was removed by distillation in a vacuum, and the clear syrupy residue (which did not crystallise and did not distil unchanged) digested with dry ether. After removal of a small quantity of insoluble solid, the filtrate was shaken with concentrated aqueous ammonia. A voluminous precipitate soon formed and the whole set to a semi-solid mass. After standing for an hour with occasional shaking, the precipitate was filtered off, washed with water, and dissolved in dilute hydrochloric acid, and the solution neutralised and washed with chloroform. The aqueous solution was warmed to expel chloroform, cooled, and basified. The crude amidine was precipitated as a pale yellow rubber-like mass (7·2 g.) which solidified completely in a few minutes. After crystallisation from alcohol–benzene, 5·5 g. of the pure base

were obtained; yield, 27%. It has m. p. 121° (corr.) and is readily soluble in alcohol, chloroform, or acetone, slightly soluble in ether and in water. The picrate separates from alcohol in stellate clusters of yellow needles, m. p. 217—218° (corr.). The *hydrochloride* crystallises from methyl alcohol in small needles, m. p. 217—218° (corr.) (Found : C, 61·0; H, 5·8; N, 9·3; Cl, 12·2. $C_{15}H_{16}O_2N_2$,HCl requires C, 61·5; H, 5·8; N, 9·6; Cl, 12·2%).

Veratroylveratrylamine was prepared by the interaction of veratrylamine and veratroyl chloride in ethereal solution in the presence of potassium carbonate. It crystallised from moist acetone in felted needles, m. p. 192—193° (corr.) (Found : C, 64·5; H, 6·5; N, 4·6. $C_{17}H_{19}O_5N$ requires C, 64·4; H, 6·0; N, 4·4%). No pure product could be isolated from the reaction mixture of this amide with phosphorus pentachloride and ammonia.

p-*Hydroxyphenylacetiminoether Hydrochloride.*—Into a solution of *p*-hydroxyphenylacetonitrile (35·3 g.) in absolute alcohol (13 g.) and dry benzene (37 c.c.), dry hydrogen chloride (10 g.) was led, with cooling. The solution separated into two layers. The mixture was kept in the ice-chest for 4 hours; the lower layer had then crystallised completely. The solid was broken up under dry ether, filtered off, washed with dry ether, and kept over caustic soda in a vacuum for 12 hours. Yield, 55·5 g. (97%). It was a powder with a faint reddish tinge, m. p. 145—148° (efferv.) (Found : C, 55·6; H, 6·8; Cl, 16·0. $C_{10}H_{13}O_2N$,HCl requires C, 55·6; H, 6·5; Cl, 16·5%).

p-*Hydroxyphenylacetamidine Salts.*—The imino-ether hydrochloride (55·5 g.) was mixed with slight excess of alcoholic ammonia. The reaction was complete in 5 hours at 40°, the ammonium chloride being replaced by the crystalline amidine hydrochloride. Yield, 41·6 g. (87%). The *hydrochloride* crystallised from alcohol in needles, m. p. 253—254° (corr.). The cold saturated aqueous solution contained 10% of the salt (Found : C, 51·1; H, 6·1; N, 14·8; Cl, 18·8. $C_8H_{10}ON_2$,HCl requires C, 51·5; H, 5·9; N, 15·0; Cl, 19·0%). The picrate formed long yellow needles from water, m. p. 212—213° (corr.), and the nitrate, leaflets from alcohol, m. p. 175—176° (corr.).

p-*Hydroxyphenyl*-N-*methylacetamidine.*—A mixture of *p*-hydroxyphenylacetiminoether hydrochloride (15·6 g.) with a slight excess of a 33% absolute alcoholic solution of methylamine was kept at about 40° for 3 days. The mixture was precipitated with dry ether, and the precipitate crystallised from a mixture of water, alcohol, and acetone. Yield, 8·7 g. (60%). It crystallised from water in prisms, m. p. 229—230° (corr.) (Found : C, 53·5; H, 6·6; Cl, 17·8. $C_9H_{12}ON_2$,HCl requires C, 53·8; H, 6·5; Cl, 17·7%). The picrate crystallised from alcohol in rhombs, m. p. 167—168° (corr.).

o-*Hydroxybenziminoether Hydrochloride.*—A mixture of *o*-hydroxybenzonitrile (20 g.), absolute alcohol (8·6 g.), dry benzene (4 c.c.), and hydrogen chloride (6·2 g.) was kept at room temperature for 15 days. The *imino-ether hydrochloride* (14·0 g., m. p. 150° with decomp.; yield, 41%) was filtered off and washed with dry ether. After crystallisation from alcohol, it formed small needles, m. p. 150—151° (corr., decomp.) (Found: Cl, 17·4. $C_9H_{11}O_2N$,HCl requires Cl, 17·6%).

o-*Hydroxybenzamidine Salts.*—The ammonium chloride formed when the imino-ether hydrochloride (6·5 g.) was mixed with alcoholic ammonia was almost completely redissolved in 2 hours. The solution was kept at 40° for a few days, filtered, and evaporated. The syrupy residue was treated with silver sulphate, and the o-*hydroxybenzamidine sulphate* obtained crystallised twice from water (needles, m. p. 285° with decomp.) (Found: S, 8·4. $C_7H_8ON_2,\frac{1}{2}H_2SO_4$ requires S, 8·6%). The cold saturated aqueous solution, which was neutral to litmus, contained 1·5% of the salt. The *picrate* separated from glacial acetic acid in small yellow needles, m. p. 245—246° (corr.) (Found: C, 42·6; H, 3·2; N, 19·4. $C_7H_8ON_2,C_6H_3O_7N_3$ requires C, 42·7; H, 3·0; N, 19·2%).

m-*Hydroxybenziminoether Hydrochloride.*—A solution of *m*-hydroxybenzonitrile (17·4 g.) in dry benzene (25 c.c.), absolute alcohol (6·6 g.), and hydrogen chloride (5·3 g.) was kept over-night, and dry ether added. The crystals (27·5 g.; yield, 93%) were filtered off and washed with dry ether; m. p. 161—164° (decomp.).

m-*Hydroxybenzamidine Salts.*—The *sulphate* was prepared in exactly the same manner as the *o*-isomeride. It crystallised with 3—4 molecules of water of crystallisation. On drying at 100°, the crystals disintegrated into a white powder, m. p. 245° (decomp.) (Found in anhydrous salt: C, 45·2; H, 5·0; S, 8·6.

$$C_7H_8ON_2,\frac{1}{2}H_2SO_4$$

requires C, 45·4; H, 4·9; S, 8·6%). The *picrate* crystallised from glacial acetic acid in deep yellow needles, m. p. 260—261° (corr.) (Found: C, 43·2; H, 3·4; N, 18·7. $C_7H_8ON_2,C_6H_3O_7N_3$ requires C, 42·7; H, 3·0; N, 19·2%).

Diamidines of Dibasic Acids.—Considerable difficulties were encountered in the synthesis of these compounds. The iminoethyl ether hydrochlorides were prepared from the corresponding dinitriles by keeping these, usually for 3 to 14 days, with 2 mols. of alcohol and 2 of hydrogen chloride. They were not isolated, since they were very hygroscopic and not always crystalline. The syrupy reaction mixtures were treated with alcoholic ammonia either at 40° or at the b. p. under reflux (compare Eitner and Wetz, *Ber.*, 1893, **26**, 2841). After removal of water-insoluble oils by

means of chloroform the diamidines were isolated in the form of salts, but always in poor or very poor yields.

Pimelamidine was isolated as the picrate and converted into the *hydrochloride*, which crystallised from slightly diluted alcohol in needles (yield, 19%), m. p. 218—219° (corr.) (Found : C, 36·9; H, 8·3; N, 24·4; Cl, 30·2. $C_7H_{16}N_4,2HCl$ requires C, 36·7; H, 7·9; N, 24·4; Cl, 31·0%). The picrate crystallised from much water in prisms, m. p. 249—250° (decomp., sintering at 245°). It is very sparingly soluble in glacial acetic acid and insoluble in most other solvents.

Azelamidine sulphate crystallised from water in small needles, m. p. 310—315° (decomp.) (Found : C, 38·0; H, 8·4; N, 20·2; S, 11·3. $C_9H_{20}N_4,H_2SO_4$ requires C, 38·2; H, 7·8; N, 19·9; S, 11·4%). Solubility in cold water, 35%. The picrate separated from a mixture of alcohol, acetone, and water in long felted needles, m. p. 260—261° (corr.).

Sebacamidine was isolated as the hydrochloride (yield, 15%). This salt has been described by Eitner and Wetz (*loc. cit.*). The solubility in cold water is 60%. The *picrate* separates from glacial acetic acid as a microcrystalline powder, m. p. 249—250° (corr.) (Found : N, 21·8. $C_{10}H_{22}N_4,2C_6H_3O_7N_3$ requires N, 21·4%).

Nonane-1 : 9-*diamidine picrate*. In the preparation of the dinitrile of nonane-1 : 9-dicarboxylic acid, the hitherto undescribed *acid chloride* of this acid was isolated, b. p. 191—192°/22 mm. (corr.) (0·1944 g. required 30·3 c.c. *N*/10-NaOH for hydrolysis and neutralisation. $C_{11}H_{18}O_2Cl_2$ requires 30·7 c.c.). The *amidine picrate* separated from glacial acetic acid as a microcrystalline powder, m. p. 245—246° (corr.) (Found : N, 20·6. $C_{11}H_{24}N_4,2C_6H_3O_7N_3$ requires N, 20·9%).

Decane-1 : 10-diamidine was isolated as the *hydrochloride* (yield, 24%), which was crystallised from a mixture of alcohol, acetone, and water. This salt had m. p. 174—175° (corr.) (Found : Cl, 23·4. $C_{12}H_{26}N_4,2HCl$ requires Cl, 23·7%). Its solubility in cold water is 80%. The *picrate* separated from glacial acetic acid as a fine yellow powder, m. p. 227—228° (corr.) (Found : C, 42·0; H, 4·9; N, 20·4. $C_{12}H_{26}N_4,2C_6H_3O_7N_3$ requires C, 42·1; H, 4·7; N, 20·5%).

Undecane-1 : 11-*diamidine picrate* crystallised from glacial acetic acid as a fine yellow powder, m. p. 192—193° (corr.) (Found : C, 42·8; H, 5·6; N, 19·9. $C_{13}H_{28}N_4,2C_6H_3O_7N_3$ requires C, 43·0; H, 4·9; N, 20·1%).

Valeramidine.—The preparation of this is similar to that of the dibasic aliphatic amidines. It was isolated as the picrate, which was converted into the *sulphate* (yield, 10%). This crystallised

from water in leaflets, m. p. 272—274° (corr., decomp.) (Found : C, 39·7; H, 9·3; N, 18·7; SO_4'', 32·6. $C_5H_{12}N_2,\frac{1}{2}H_2SO_4$ requires C, 40·2; H, 8·7; N, 18·8; SO_4'', 32·2%). The picrate separates from alcohol in thin prisms, m. p. 195—196° (corr.).

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