CLXXVII.—*Relation between Chemical Constitution and Physiological Action in Certain Substituted Aminoalkyl Esters.*

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THE desirability of producing a local anæsthetic to take the place of cocaine has led to the preparation of substances designed to possess the characteristic action of this alkaloid, whilst at the same time being free from its toxic effects. In recent years, investigation has chiefly been directed to substituted aminoalkyl esters, which contain a skeleton, $\text{:N}\cdot\dot{\text{C}}\cdot\dot{\text{C}}\cdot\text{O}\cdot\text{CO}\cdot\text{R}$, similar to that part of the cocaine molecule which is printed heavily in the formula :

and certain substances of this type, for example, "stovaine," "alypin," and "novocaine," have found application in medicine as local anæsthetics. The present paper records the preparation and the chemical, physical, and physiological properties of certain new aminoalkyl esters. Several of these possess local anæsthetic properties, some in a pronounced degree, but none are suitable for use in medicine as local anæsthetics, owing in some cases, to irritation produced on injection.

tion, in others to a relatively high general toxicity. The physiological examination of these substances (as hydrochlorides, except where otherwise stated) was carried out by Messrs. H. H. Dale and C. T. Symons, of the Wellcome Physiological Research Laboratories, to whom the author wishes to tender his best thanks.

The nitrogen atom in cocaine is connected directly to one alkyl (methyl) group and indirectly through two chains of methylene (or substituted methylene) groups to a benzoylated secondary alcoholic group. It therefore appeared of interest to prepare $\beta\beta$ -dibenzoyloxy-methyldiethylamine and $\beta\beta$ -dibenzoyloxytriethylamine,

which contain a nitrogen atom connected directly to one alkyl group and indirectly through two methylene groups to two benzoylated alcohol groups.

These substances were consequently prepared by benzoylating the corresponding amino-alcohols. The methyl derivative has no local anæsthetic action, and the ethyl derivative very little. Marked differences are shown by the two substances in other respects; in the rabbit, the ethyl derivative causes respiratory and cardiac depression, whilst the methyl derivative has no marked action on the heart or respiration, but causes marked extensor convulsions reminiscent of those produced by a small dose of strychnine; in the frog, the methyl derivative causes primarily paralysis of the brain centres, whilst the ethyl derivative causes central paralysis, primarily affecting the spinal cord.

The next point investigated was the introduction of two benzoyl groups into the molecule in a different manner, the substances prepared being respectively $\beta\gamma$ -dibenzoyloxydimethylpropylamine, $\beta\gamma$ -dibenzoyloxydiethylpropylamine, and $\beta\gamma$ -dibenzoyloxy-1-propylpiperidine,

(R = NMe_2 , NEt_2 , or $\text{C}_5\text{H}_{10}\text{N}$).

These substances possess a very considerable local anæsthetic action, but their value is discounted by the fact that they are distinctly toxic and irritant, and also acid in reaction. Here, again, the diethyl derivative has a depressant action on the heart, which is not observable in the case of the dimethyl derivative. Both the dimethyl and diethyl derivatives act on the central nervous system of the mammal, producing spasms faintly reminiscent of those caused by strychnine, the dimethyl being the most active in this respect. In the frog, the dimethyl derivative quickly paralyses the brain, but its action on the spinal cord is comparatively slight, whilst the diethyl derivative has a paralytic effect on the brain and spinal cord, the latter being at least as markedly and rapidly affected as the former.

The methobromide of the dimethyl derivative was also tested, and found to have a considerably feebler general toxicity than the hydrochloride, the central convulsant action of the latter on the mammal being replaced or obscured by a curare-like effect in the methobromide.

The above benzoates were prepared from the corresponding amino-dihydroxypropanes of C. F. Roth (*Ber.*, 1882, 15, 447). Roth's statements show that he had some difficulty in purifying dihydroxypiperidylpropane, and he does not state its melting point, but the substance may readily be purified by distillation under 80 mm. pressure, when it boils at 200—201° and solidifies on cooling; subsequent crystallisation from acetone yields the substance in large, monoclinic plates, melting at 79—80°. In the same communication, Roth gives an account of some attempts to prepare the dibenzoates of these amino-alcohols, but he was unable to isolate the dibenzoyloxy-derivatives of diethylpropylamine and 1-propylpiperidine, and only obtained $\beta\gamma$ -dibenzoyloxydimethylpropylamine in the form of its picrate, for which he gives the melting point 112°. The dibenzoyloxy-derivatives of the three bases have now been prepared by the Schotten-Baumann reaction, but $\beta\gamma$ -dibenzoyloxydimethylpropylamine picrate, prepared from the pure crystalline hydrochloride, has been found to melt at 178—179°.

Certain dialkylaminoethyl benzoates described by E. Schering (D.R.-P. 175080) have been stated to be useful local anæsthetics, and it therefore seemed of interest to prepare *piperidylethyl benzoate* (I), and *s-di- β -benzoyloxy-1:4-diethylpiperazine* (II):

These bases were obtained by benzoylating the corresponding amino-alcohols, of which one, 1:4-*diethanolpiperazine*, has not previously been described. Piperidylethyl benzoate shows some local anæsthetic property, but is distinctly irritant; its methobromide is neither anæsthetic nor irritant. *s-Di- β -benzoyloxy-1:4-diethylpiperazine* shows very distinct local anæsthetic properties, but is the most poisonous of the series, 50 milligrams causing rapid death in a rabbit weighing 1 kilogram; the appearance of the blood *post mortem* showed that the hæmoglobin was decomposed.

In two cases the phthaloyl group had been introduced into the molecule in the place of the benzoyl group; thus *diethylaminoethyl phthalate* and *piperidylethyl phthalate*,

have been prepared by the interaction of phthaloyl chloride and the corresponding amino-alcohol in ethereal solution.

Diethylaminoethyl phthalate hydrochloride was submitted to physiological examination, and appeared to have neither anæsthetic nor irritant properties.

β-Bromo-*α*-hydroxy-3:4-methylenedioxyethylbenzene (Barger and Jowett, Trans., 1905, **87**, 970) formed the starting point of another attempt. By condensing this compound (III) with dimethylamine, *β*-hydroxy-*β*-3:4-methylenedioxyphenylethyldimethylamine (IV) was obtained, and this yielded, on benzylation, *β*-benzoyloxy-*β*-3:4-methylenedioxyphenylethyldimethylamine (V):

This substance is a substituted aminoalkyl benzoate, and has very considerable anæsthetic properties, but is unfortunately also toxic and irritant.

EXPERIMENTAL.

Those compounds described below which are aminoalkyl benzoates were prepared by the Schotten-Baumann method. The corresponding hydroxy-derivative was dissolved in a large quantity of 10 per cent. sodium hydroxide solution, and well shaken with a large excess of benzoyl chloride. The crude ester was then extracted with ether, removed from the ether with dilute hydrochloric acid, regenerated with sodium carbonate solution, and again dissolved in ether. After the ether had been dried and distilled, the resulting aminoalkyl benzoate was purified in a suitable manner in each special case.

Seventeen grams of *s*-*ββ*-dihydroxymethylethylamine gave, on benzylation, 36 grams of *s*-*ββ*-dibenzoyloxymethyldiethylamine, a yield of 77 per cent. of the theoretical. This was purified by crystallisation of the hydrogen oxalate, and regenerated from the pure salt; it formed a colourless, viscid oil which did not crystallise.

The *hydrochloride* separates from absolute alcohol in diamond-shaped plates, which melt at 132—133°. It is readily soluble in water, giving an acid solution, and sparingly so in absolute alcohol. This salt is anhydrous:

0.2474 gave 0.5692 CO_2 and 0.1328 H_2O . $\text{C} = 62.7$; $\text{H} = 6.0$.

0.2584 „ 0.1020 AgCl . $\text{Cl} = 9.8$.

$\text{C}_{19}\text{H}_{21}\text{O}_4\text{N}, \text{HCl}$ requires $\text{C} = 62.7$; $\text{H} = 6.0$; $\text{Cl} = 9.7$ per cent.

The *hydrobromide* was obtained, by evaporation of its aqueous solution, as an oil which gradually solidified, forming clusters of hard plates. After recrystallisation from dilute alcohol, it melts at $124\text{--}126^\circ$. It is anhydrous, and is almost insoluble in water, but fairly readily soluble in alcohol:

0.1150 gave 0.0540 AgBr . $\text{Br} = 20.0$.

$\text{C}_{19}\text{H}_{21}\text{O}_4\text{N}, \text{HBr}$ requires $\text{Br} = 19.6$ per cent.

The *hydrogen oxalate* crystallises from boiling water in prismatic needles, melting at $169\text{--}170^\circ$; it is anhydrous, and is very sparingly soluble in cold water or alcohol:

0.2030 gave 0.4476 CO_2 and 0.1002 H_2O . $\text{C} = 60.1$; $\text{H} = 5.5$.

$\text{C}_{19}\text{H}_{21}\text{O}_4\text{N}, \text{C}_2\text{H}_2\text{O}_4$ requires $\text{C} = 60.4$; $\text{H} = 5.6$ per cent.

The *aurichloride* separates from alcohol in clusters of hard, prismatic, yellow needles, which melt at $109\text{--}110^\circ$; it is anhydrous, and is insoluble in water, but sparingly soluble in cold alcohol:

0.1400 gave 0.0411 Au . $\text{Au} = 29.4$.

$\text{C}_{19}\text{H}_{21}\text{O}_4\text{N}, \text{HAuCl}_4$ requires $\text{Au} = 29.6$ per cent.

The *platinichloride* crystallises from alcohol in clusters of fine yellow needles, which begin to sinter at 87° and melt clearly at 95° ; it contains four molecular proportions of water of crystallisation, and is insoluble in water, but sparingly soluble in alcohol:

0.1170, air-dried, gave 0.1694 CO_2 and 0.0502 H_2O . $\text{C} = 39.5$; $\text{H} = 4.8$.

0.0978 „ lost 0.0058 at 100° . $\text{H}_2\text{O} = 5.9$.

0.0920, dried at 100° , gave 0.0167 Pt . $\text{Pt} = 18.2$.

$(\text{C}_{19}\text{H}_{21}\text{O}_4\text{N})_2\text{H}_2\text{PtCl}_6, 4\text{H}_2\text{O}$ requires $\text{C} = 40.1$; $\text{H} = 4.6$; $\text{H}_2\text{O} = 6.3$ per cent.

$(\text{C}_{19}\text{H}_{21}\text{O}_4\text{N})_2\text{H}_2\text{PtCl}_6$ requires $\text{Pt} = 18.3$ per cent.

The *picrate* crystallises from alcohol in long, slender, yellow needles, which melt at $136\text{--}137^\circ$.

The *methobromide* was obtained in long, fine needles by the addition of methyl bromide to a cold alcoholic solution of the base. After crystallisation from alcohol, it formed long, fine needles, which melted at $170\text{--}171^\circ$. It is insoluble in water, but sparingly soluble in cold alcohol:

0.1676 gave 0.0744 AgBr . $\text{Br} = 18.9$.

$\text{C}_{19}\text{H}_{21}\text{O}_4\text{N}, \text{CH}_3\text{Br}$ requires $\text{Br} = 18.9$ per cent.

Ten grams of *s*- β -dihydroxytriethylamine gave, on benzylation, 18 grams of *s*- β -dibenzoyloxytriethylamine, the yield being 70 per cent. of the theoretical. This was purified by crystallisation of the hydrogen oxalate, and regenerated from the pure salt; it formed a colourless, viscid oil, which did not crystallise.

The *hydrochloride* separated from its aqueous solution as a viscid oil, which gradually solidified, after the addition of a little alcohol, on evaporation in a vacuum over sulphuric acid. On recrystallisation from benzene, it was obtained in matted clusters of fine needles, which melted at 110—111°, and contained half a molecular proportion of alcohol of crystallisation; the alcohol is gradually lost at 110°, but is not entirely removed before further decomposition of the salt commences. This salt is very readily soluble in water, giving an acid solution, and readily so in alcohol:

0.1410 gave 0.3260 CO_2 and 0.0874 H_2O . $\text{C} = 63.1$; $\text{H} = 6.9$.

0.2582 „ 0.0960 AgCl . $\text{Cl} = 9.2$.

$\text{C}_{20}\text{H}_{23}\text{O}_4\text{N}, \text{HCl}, \frac{1}{2}\text{C}_2\text{H}_6\text{O}$ requires $\text{C} = 62.9$; $\text{H} = 6.8$; $\text{Cl} = 8.8$ per cent.

The *hydrogen oxalate* crystallises from boiling water in glistening needles, which melt at 157—158°; it is anhydrous, and is very sparingly soluble in cold water or alcohol:

0.2106 gave 0.4734 CO_2 and 0.1096 H_2O . $\text{C} = 61.3$; $\text{H} = 5.8$.

$\text{C}_{20}\text{H}_{23}\text{O}_4\text{N}, \text{C}_2\text{H}_2\text{O}_4$ requires $\text{C} = 61.2$; $\text{H} = 5.7$ per cent.

The *aurichloride* separates from alcohol in hard, yellow nodules of prismatic needles, which melt at 115—116°. It is anhydrous, and is insoluble in water, but sparingly soluble in cold alcohol:

0.2940 gave 0.0850 Au . $\text{Au} = 28.9$.

$\text{C}_{20}\text{H}_{23}\text{O}_4\text{N}, \text{HAuCl}_4$ requires $\text{Au} = 28.9$ per cent.

The *platinichloride* crystallises from alcohol in fine, yellowish-brown needles, which have no definite melting point, but commence to soften and lose alcohol at 60°, and are completely molten at 95°. It contains one and a-half molecular proportions of alcohol of crystallisation, and is insoluble in water, and very sparingly soluble in alcohol:

0.0978, air-dried, gave 0.1594 CO_2 and 0.0416 H_2O . $\text{C} = 44.4$; $\text{H} = 4.8$.

0.1020 „ lost 0.0064 at 100°. $\text{C}_2\text{H}_6\text{O} = 6.3$.

0.1354, dried at 100°, gave 0.0244 Pt . $\text{Pt} = 18.0$.

$(\text{C}_{20}\text{H}_{23}\text{O}_4\text{N}_2)_2, \text{H}_2\text{PtCl}_6, 1\frac{1}{2}\text{C}_2\text{H}_6\text{O}$ requires $\text{C} = 44.4$; $\text{H} = 4.8$; $\text{C}_2\text{H}_6\text{O} = 6.0$ per cent.

$(\text{C}_{20}\text{H}_{23}\text{O}_4\text{N}_2)_2, \text{H}_2\text{PtCl}_6$ requires $\text{Pt} = 17.8$ per cent.

The *picrate* crystallises from alcohol in microscopic rosettes of yellow needles, which melt at 136—137°.

Eighteen grams of *βγ*-dihydroxydimethylpropylamine gave, on benzoylation, 37 grams of *βγ*-dibenzoyloxydimethylpropylamine, a yield of 75 per cent. of the theoretical. The substance was purified by crystallisation of the picrate and regeneration from the pure salt, when it formed a colourless, viscid oil which did not crystallise.

The *hydrochloride* crystallises from ethyl acetate in long needles, which melt at 179—180°. It is anhydrous, and is very readily soluble in water, giving an acid solution, but fairly readily so in alcohol :

0·1967 gave 0·4493 CO₂ and 0·1079 H₂O. C = 62·3 ; H = 6·1.

0·2076 „ 0·0794 AgCl. Cl = 9·5.

C₁₉H₂₁O₄N, HCl requires C = 62·7 ; H = 6·1 ; Cl = 9·7 per cent.

The *nitrate* separates from absolute alcohol in large, acicular crystals, which melt at 111—112°. It is anhydrous, and is sparingly soluble in cold water or alcohol :

0·1408 gave 0·3004 CO₂ and 0·0722 H₂O. C = 58·2 ; H = 5·7.

C₁₉H₂₁O₄N, HNO₃ requires C = 58·4 ; H = 5·7 per cent.

The *aurichloride* separates from alcohol in clusters of glistening, golden-yellow needles, which melt at 161—162°. It is anhydrous, and is insoluble in water, but sparingly soluble in cold alcohol :

0·1417 gave 0·0416 Au. Au = 29·4.

C₁₉H₂₁O₄N, HAuCl₄ requires Au = 29·6 per cent.

The *platinichloride* crystallises from water in clusters of pale yellow needles, which melt at 174—176°. It is anhydrous, and is insoluble in water, but very sparingly soluble in cold alcohol :

0·1275 gave 0·0230 Pt. Pt = 18·0.

(C₁₉H₂₁O₄N)₂, HPtCl₆ requires Pt = 18·3 per cent.

The *methobromide* crystallises from ethyl acetate in clusters of monoclinic plates, which melt at 94—95°. It contains one molecule of water of crystallisation, and is readily soluble in water or alcohol :

0·1334, air-dried, gave 0·2660 CO₂ and 0·0710 H₂O. C = 54·4 ; H = 6·0.

0·2288 „ „ 0·0966 AgBr. Br = 18·0.

C₁₉H₂₁O₄N, CH₃Br, H₂O requires C = 54·5 ; H = 6·0 ; Br = 18·2 per cent.

The picrate has already been described by Roth (*loc. cit.*), and characterised as yellow, silky plates (from water) which melted at 112°. For comparison, it has been prepared from the pure hydrochloride by precipitation with picric acid, and recrystallised from alcohol. It formed glistening, yellow scales, which melted at

178—179°. After recrystallisation from water, the substance melted at the same temperature, and, on analysis, proved to be the normal salt:

0.2004 gave 0.3952 CO_2 and 0.0784 H_2O . $\text{C} = 53.8$; $\text{H} = 4.4$.

$\text{C}_{19}\text{H}_{21}\text{O}_4\text{N}_3\cdot\text{C}_6\text{H}_5\text{O}_7\text{N}_3$ requires $\text{C} = 53.9$; $\text{H} = 4.4$ per cent.

Twenty grams of $\beta\gamma$ -dihydroxydiethylpropylamine gave, on benzoylation, 40 grams of $\beta\gamma$ -dibenzoyloxydiethylpropylamine, a yield of 83 per cent. of the theoretical. The substance was purified by crystallisation of the picrate, and regeneration from the pure salt, when it formed a colourless, viscid oil which did not crystallise.

The *hydrochloride* crystallises from ethyl acetate in colourless, highly-refracting plates, which melt at 125—126°. It is anhydrous, and is very readily soluble in water, giving an acid solution, but sparingly so in cold alcohol or ethyl acetate:

0.2678 gave 0.6334 CO_2 and 0.1572 H_2O . $\text{C} = 64.5$; $\text{H} = 6.6$.

0.2324 „ 0.0854 AgCl . $\text{Cl} = 9.1$.

$\text{C}_{21}\text{H}_{25}\text{O}_4\text{N}_3\cdot\text{HCl}$ requires $\text{C} = 64.3$; $\text{H} = 6.7$; $\text{Cl} = 9.1$ per cent.

The *nitrate* crystallises from ethyl acetate in clusters of short needles, which melt at 123—124°. It is anhydrous, and is sparingly soluble in water, but fairly readily so in cold alcohol or ethyl acetate:

0.1502 gave 0.3292 CO_2 and 0.0818 H_2O . $\text{C} = 59.8$; $\text{H} = 6.1$.

$\text{C}_{21}\text{H}_{25}\text{O}_4\text{N}_3\cdot\text{HNO}_3$ requires $\text{C} = 60.2$; $\text{H} = 6.3$ per cent.

The *hydrogen oxalate* separates from boiling water in clusters of imperfectly-formed, acicular crystals, which melt at 120—121°. It is anhydrous, and is sparingly soluble in water, but very sparingly so in alcohol:

0.1346 gave 0.3058 CO_2 and 0.0744 H_2O . $\text{C} = 62.0$; $\text{H} = 6.2$.

$\text{C}_{21}\text{H}_{25}\text{O}_4\text{N}_3\cdot\text{C}_2\text{H}_2\text{O}_4$ requires $\text{C} = 62.0$; $\text{H} = 6.1$ per cent.

The *aurichloride* crystallises from alcohol in clusters of long, yellow, silky needles, which melt at 121—122°. It is anhydrous, and is insoluble in water, but sparingly soluble in cold alcohol:

0.3138 gave 0.0900 Au . $\text{Au} = 28.7$.

$\text{C}_{21}\text{H}_{25}\text{O}_4\text{N}_3\cdot\text{HAuCl}_4$ requires $\text{Au} = 28.4$ per cent.

The *platinichloride* crystallises from alcohol in hard clusters of yellowish-brown, monoclinic plates, which melt at 176—177°. It is anhydrous, and is insoluble in water, but sparingly soluble in cold alcohol:

0.1028 gave 0.0176 Pt . $\text{Pt} = 17.1$.

$(\text{C}_{21}\text{H}_{25}\text{O}_4\text{N}_3)_2\cdot\text{H}_2\text{PtCl}_6$ requires $\text{Pt} = 17.4$ per cent.

The *picrate* crystallises from dilute alcohol in radial clusters of yellow needles, which melt at 139—140°.

Twenty grams of $\beta\gamma$ -dihydroxy-1-propylpiperidine gave, on benzylation, 40 grams of $\beta\gamma$ -dibenzoyloxy-1-propylpiperidine in the form of a colourless, viscid oil; this solidified on stirring with a little alcohol, and, after recrystallisation from the same solvent, yielded 30 grams of pure base, that is, 65 per cent. of the theoretical.

The base crystallises from alcohol in clusters of long, white, glistening needles, which melt at 64—65°; it is insoluble in water, and somewhat sparingly soluble in cold alcohol:

0.1630 gave 0.4320 CO_2 and 0.1010 H_2O . $\text{C} = 72.3$; $\text{H} = 6.9$.

$\text{C}_{22}\text{H}_{25}\text{O}_4\text{N}$ requires $\text{C} = 71.9$; $\text{H} = 6.9$ per cent.

The *hydrochloride* crystallises from benzene in clusters of monoclinic plates, which melt at 118—119°. It is anhydrous, and is readily soluble in water and alcohol, giving an acid solution:

0.2444 gave 0.0834 AgCl . $\text{Cl} = 8.4$.

$\text{C}_{22}\text{H}_{25}\text{O}_4\text{N}\cdot\text{HCl}$ requires $\text{Cl} = 8.8$ per cent.

The *nitrate* separates from alcohol in glistening, diamond-shaped plates, which melt and decompose at 158°. It is anhydrous, and is very sparingly soluble in water, but sparingly so in cold alcohol:

0.1504 gave 0.3384 CO_2 and 0.0810 H_2O . $\text{C} = 61.4$; $\text{H} = 6.0$.

$\text{C}_{22}\text{H}_{25}\text{O}_4\text{N}\cdot\text{HNO}_3$ requires $\text{C} = 61.3$; $\text{H} = 6.1$ per cent.

The *aurichloride* crystallises from alcohol in golden-yellow, monoclinic plates, which melt at 162—163°. It is anhydrous, and is insoluble in water, but sparingly soluble in cold alcohol:

0.2097 gave 0.0585 Au . $\text{Au} = 27.9$.

$\text{C}_{22}\text{H}_{25}\text{O}_4\text{N}\cdot\text{HAuCl}_4$ requires $\text{Au} = 27.9$ per cent.

The *picrate* crystallises from alcohol in yellow, diamond-shaped plates, which melt at 167—168°.

Ten grams of piperidylethyl alcohol gave, on benzylation, 14.5 grams of piperidylethyl benzoate, a yield of 82 per cent. of the theoretical. The substance was purified by crystallisation of the hydrochloride, and regeneration from the pure salt, when it formed a colourless, viscid oil which did not crystallise.

The *hydrochloride* crystallises from absolute alcohol in large, monoclinic plates, which melt at 175—176°. It is anhydrous, and is easily soluble in water, giving a neutral solution, but sparingly so in alcohol:

0.1782 gave 0.4074 CO_2 and 0.1164 H_2O . $\text{C} = 62.3$; $\text{H} = 7.3$.

0.3116 „ 0.1647 AgCl . $\text{C} = 13.1$.

$\text{C}_{14}\text{H}_{19}\text{O}_2\text{N}$, HCl requires $\text{C} = 62.3$; $\text{H} = 7.5$; $\text{Cl} = 13.1$ per cent.

The *hydrobromide* separates from its alcoholic solution in glistening plates, which melt at 168 — 169° . It is anhydrous, and is fairly readily soluble in water, but sparingly so in alcohol:

0.2042 gave 0.1214 AgBr . $\text{Br} = 25.9$.

$\text{C}_{14}\text{H}_{19}\text{O}_2\text{N}$, HBr requires $\text{Br} = 25.4$ per cent.

The *aurichloride* crystallises from alcohol in serrated needles, which melt at 119 — 120° . It is anhydrous, and is insoluble in water, but somewhat sparingly soluble in cold alcohol:

0.1226 gave 0.0422 Au . $\text{Au} = 34.4$.

$\text{C}_{14}\text{H}_{19}\text{O}_2\text{N}$, HAuCl_4 requires $\text{Au} = 34.4$ per cent.

The *picrate* crystallises from alcohol in clusters of yellow needles, which melt at 160 — 161° .

The *methobromide* crystallises from a mixture of alcohol and light petroleum in slender needles, which melt at 144 — 147° . It is anhydrous, and is readily soluble in water or alcohol:

0.2138 gave 0.4318 CO_2 and 0.1260 H_2O . $\text{C} = 55.1$; $\text{H} = 6.6$.

0.1050 „ 0.0600 AgBr . $\text{Br} = 24.3$.

$\text{C}_{14}\text{H}_{19}\text{O}_2\text{N}$, CH_3Br requires $\text{C} = 54.8$; $\text{H} = 6.8$; $\text{Br} = 24.4$ per cent.

1:4-Diethanolpiperazine,

Six grams of piperazine and 14 grams of ethylene chlorohydrin were heated together for four hours at 105° . The resulting dark brown oil was made alkaline with 50 per cent. aqueous sodium hydroxide, diluted with 150 c.c. of alcohol, saturated with carbon dioxide, and filtered. The alcoholic filtrate was then dried with anhydrous sodium sulphate, filtered, and distilled. After the removal of the alcohol, the distillation was continued under 50 mm. pressure, when the base passed over at 215 — 220° ; after crystallisation from absolute alcohol, 5 grams of pure base were obtained; this yield represents 41 per cent. of the theoretical.

The base separates from absolute alcohol in large, tetragonal pyramids, which melt at 134 — 135° . It is very readily soluble in water, and readily so in chloroform, but sparingly so in the other usual organic solvents:

0.1702 gave 0.3446 CO_2 and 0.1618 H_2O . $\text{C} = 55.2$; $\text{H} = 10.6$.

$\text{C}_8\text{H}_{18}\text{O}_2\text{N}_2$ requires $\text{C} = 55.1$; $\text{H} = 10.4$ per cent.

The *hydrochloride* crystallises from absolute alcohol in prismatic

plates, which contain two molecules of water of crystallisation. It is very easily soluble in water, but sparingly so in absolute alcohol. After drying at 120° , this salt melts at $200-202^{\circ}$:

0.1940, air-dried, lost 0.0242 at 120° . $H_2O = 12.5$.

0.1628, dried at 120° , gave 0.1886 AgCl. $Cl = 28.7$.

$C_8H_{18}O_2N_2 \cdot 2HCl \cdot 2H_2O$ requires $H_2O = 12.7$ per cent.

$C_8H_{18}O_2N_2 \cdot 2HCl$ requires $Cl = 28.7$ per cent.

The *hydrobromide* crystallises from acetone in highly-refracting, prismatic plates, which contain two molecules of water of crystallisation. It is very readily soluble in water, but sparingly so in alcohol or acetone. After drying at 120° , this salt melts at $190-192^{\circ}$:

0.2622, air-dried, lost 0.0250 at 120° . $H_2O = 9.5$.

0.1494, dried at 120° , gave 0.1674 AgBr. $Br = 47.7$.

$C_8H_{18}O_2N_2 \cdot 2HBr \cdot 2H_2O$ requires $H_2O = 9.7$ per cent.

$C_8H_{18}O_2N_2 \cdot 2HBr$ requires $Br = 47.6$ per cent.

The *nitrate* crystallises from absolute alcohol in diamond-shaped plates, which melt at $177-178^{\circ}$. It is anhydrous, and is readily soluble in water, but sparingly so in absolute alcohol:

0.1968 gave 0.2302 CO_2 and 0.1134 H_2O . $C = 31.9$; $H = 6.5$.

$C_8H_{18}O_2N_2 \cdot 2HNO_3$ requires $C = 32.0$; $H = 6.7$ per cent.

The *aurichloride* separates from very dilute hydrochloric acid in long, light yellow, prismatic needles, which melt and decompose at $205-207^{\circ}$. It is anhydrous, and is sparingly soluble in cold water, but moderately so in alcohol:

0.1240 gave 0.0570 Au. $Au = 46.0$.

$C_8H_{18}O_2N_2 \cdot 2HAuCl_4$ requires $Au = 46.2$ per cent.

The *picrate* crystallises from alcohol in fine yellow needles, which melt and decompose at $245-246^{\circ}$.

s-Di-β-benzoyloxy-1:4-diethylpiperazine,

Three grams of 1:4-diethanolpiperazine gave, on benzylation, a quantity of solid *s-di-β-benzoyloxy-1:4-diethylpiperazine*; this was collected, washed with water, dried on a porous plate, and purified by crystallisation from absolute alcohol; the yield was 6 grams, that is, 91 per cent. of the theoretical.

The base crystallises from ether in long, prismatic needles, which melt at $104-105^{\circ}$; it is insoluble in water, fairly readily soluble in alcohol, and sparingly so in ether:

0.1998 gave 0.5076 CO_2 and 0.1234 H_2O . $C = 69.3$; $H = 6.9$.

$C_{22}H_{26}O_4N_2$ requires $C = 69.1$; $H = 6.9$ per cent.

The *hydrochloride* separates from boiling water in colourless needles, which melt and decompose at 260° . It is anhydrous, and is very sparingly soluble in cold water or alcohol:

0.1078 gave 0.0667 AgCl. $\text{Cl} = 15.3$.

$\text{C}_{22}\text{H}_{26}\text{O}_4\text{N}_2 \cdot 2\text{HCl}$ requires $\text{Cl} = 15.6$ per cent.

The *hydrobromide* crystallises from dilute hydrobromic acid in rosettes of feathery needles, which melt and decompose at 264 — 265° . It is anhydrous, and is very sparingly soluble in cold water or alcohol:

0.1476 gave 0.1006 AgBr. $\text{Br} = 29.0$.

$\text{C}_{22}\text{H}_{26}\text{O}_4\text{N}_2 \cdot 2\text{HBr}$ requires $\text{Br} = 29.4$ per cent.

The *sulphate* crystallises from water in clusters of glistening needles, which melt and decompose at 219 — 220° . It is anhydrous, and is very sparingly soluble in cold water or alcohol:

0.1346 gave 0.0662 BaSO_4 . $\text{SO}_4 = 20.3$.

$\text{C}_{22}\text{H}_{26}\text{O}_4\text{N}_2 \cdot \text{H}_2\text{SO}_4$ requires $\text{SO}_4 = 20.0$ per cent.

The *aurichloride* crystallises from alcohol in monoclinic plates, which melt and decompose at 205° . It is anhydrous, and is insoluble in water, but very sparingly soluble in alcohol:

0.0818 gave 0.0302 Au. $\text{Au} = 36.9$.

$\text{C}_{22}\text{H}_{26}\text{O}_4\text{N}_2 \cdot 2\text{HAuCl}_4$ requires $\text{Au} = 37.1$ per cent.

The *picrate* crystallises from methyl alcohol in pale yellow, prismatic needles, which melt and decompose at 265 — 267° .

The *methobromide* crystallises from water in prismatic needles, which melt at 228 — 229° . It is very sparingly soluble in cold water, and insoluble in alcohol:

0.2582 gave 0.1678 AgBr. $\text{Br} = 27.7$.

$\text{C}_{22}\text{H}_{26}\text{O}_4\text{N}_2 \cdot 2\text{CH}_3\text{Br}$ requires $\text{Br} = 27.9$ per cent.

Diethylaminoethyl Phthalate,

Eighteen grams of phthaloyl chloride were diluted with 50 c.c. of anhydrous ether, and added to a solution of 18 grams of β -hydroxy-triethylamine in 50 c.c. of anhydrous ether. A white, crystalline precipitate of diethylaminoethylphthalate hydrochloride was immediately produced; this was allowed to stand for half an hour, collected, dissolved in water, and the aqueous solution extracted with ether to remove impurities; the solution was then rendered alkaline with solid sodium carbonate, and extracted with chloroform; on distilling the chloroform, 21 grams of the base were obtained as a colourless, viscid oil, the yield representing 75 per cent. of the theoretical.

The *hydrobromide* crystallises from acetone in bushy crystals, which,

after drying at 100° , melt at 157 — 159° . It is very readily soluble in water, and fairly readily so in alcohol:

0.1486, dried at 100° , gave 0.2470 CO_2 and 0.0842 H_2O . $\text{C} = 45.3$; $\text{H} = 6.3$.

0.1802, dried at 100° , gave 0.1286 AgBr . $\text{Br} = 30.4$.

$\text{C}_{20}\text{H}_{32}\text{O}_4\text{N}_2 \cdot 2\text{HBr}$ requires $\text{C} = 45.6$; $\text{H} = 6.5$; $\text{Br} = 30.4$ per cent.

The *platinichloride* crystallises from water in clusters of fine needles, which melt at 191 — 193° . It contains one molecule of water of crystallisation, and is fairly readily soluble in hot water, but sparingly so in cold water:

0.1240, air-dried, lost 0.0030 at 100° . $\text{H}_2\text{O} = 2.4$.

0.1210, dried at 100° , gave 0.0300 Pt . $\text{Pt} = 24.8$.

$\text{C}_{20}\text{H}_{32}\text{O}_4\text{N}_2 \cdot \text{H}_2\text{PtCl}_6 \cdot \text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 2.3$ per cent.

$\text{C}_{20}\text{H}_{32}\text{O}_4\text{N}_2 \cdot \text{H}_2\text{PtCl}_6$ requires $\text{Pt} = 25.1$ per cent.

The *picrate* separates from boiling alcohol in yellow, prismatic crystals, which melt at 146 — 147° . It is anhydrous, and is very sparingly soluble in water or alcohol:

0.1884 gave 0.3246 CO_2 and 0.0848 H_2O . $\text{C} = 47.0$; $\text{H} = 5.0$.

$\text{C}_{20}\text{H}_{32}\text{O}_4\text{N}_2 \cdot 2\text{C}_6\text{H}_3\text{O}_7\text{N}_3$ requires $\text{C} = 46.7$; $\text{H} = 4.7$ per cent.

Piperidylethyl Phthalate,

This base was prepared in a similar manner to diethylaminoethyl phthalate. Twenty-eight grams of phthaloyl chloride and 36 grams of piperidylethyl alcohol gave 37 grams of the base as a colourless, viscid oil, the yield representing 68 per cent. of the theoretical.

The *hydrochloride* crystallises from a mixture of absolute alcohol and ether in rosettes of long, white needles, which, after drying at 100° , melt at 190 — 191° . Before drying at 100° , the salt is very deliquescent, and probably contains solvent of crystallisation, but the nature and amount of this were not determined. The salt is very readily soluble in water or absolute alcohol:

0.2464, dried at 100° , gave 0.1553 AgCl . $\text{Cl} = 15.6$.

$\text{C}_{22}\text{H}_{32}\text{O}_4\text{N}_2 \cdot 2\text{HCl}$ requires $\text{Cl} = 15.4$ per cent.

The *hydrobromide* crystallises from absolute alcohol in radiating, prismatic needles, which melt at 205 — 206° to a red liquid. It is anhydrous, and is very readily soluble in water, but moderately so in absolute alcohol:

0.1638 gave 0.2864 CO_2 and 0.0916 H_2O . $\text{C} = 47.7$; $\text{H} = 6.3$.

0.1968 „ 0.1352 AgBr . $\text{Br} = 29.2$.

$\text{C}_{22}\text{H}_{32}\text{O}_4\text{N}_2 \cdot 2\text{HBr}$ requires $\text{C} = 48.0$; $\text{H} = 6.2$; $\text{Br} = 29.1$ per cent.

The *nitrate* crystallises from absolute alcohol in rosettes of fine

prismatic needles, which melt at 169—170°. It contains one-half a molecular proportion of water of crystallisation, and is very readily soluble in water, and moderately so in alcohol:

0.1896, air-dried, gave 0.3504 CO₂ and 0.1138 H₂O. C = 50.4; H = 6.7.

0.2646 „ lost 0.0048 at 130°. H₂O = 1.8.

(C₂₂H₃₂O₄N₂, 2HNO₃)₂, H₂O requires C = 50.5; H = 6.8; H₂O = 1.7 per cent.

The *platinichloride* crystallises from water in rosettes of fine reddish-yellow needles, which melt at 205—206°. It contains one molecule of water of crystallisation, and is sparingly soluble in cold water, but very sparingly so in alcohol:

0.0990, air-dried, lost 0.0028 at 140°. H₂O = 2.8.

0.0962, dried at 140°, gave 0.0236 Pt. Pt = 24.5.

C₂₂H₃₂O₄N₂, H₂PtCl₆, H₂O requires H₂O = 2.2 per cent.

C₂₂H₃₂O₄N₂, H₂PtCl₆ requires Pt = 24.4 per cent.

The *picrate* crystallises from methyl alcohol in fine yellow needles, which melt at 182—183°.

β-Hydroxy-β-3:4-methylenedioxyphenylethyl dimethylamine,

Seventeen grams of *β*-bromo-*α*-hydroxy-3:4-methylenedioxyethylbenzene were dissolved in 80 c.c. of absolute alcohol, and boiled for two hours under reflux with 50 c.c. of a 33 per cent. aqueous solution of dimethylamine. After distillation of the alcohol, the product was rendered alkaline and extracted with ether. The base was then withdrawn from the ether by dilute hydrochloric acid, regenerated with sodium carbonate, and again dissolved in ether. The ethereal solution gave, on evaporation, 13 grams of base, that is, 90 per cent. of the theoretical.

The base was purified by crystallisation of the picrate and regeneration from the pure salt, when it formed a viscid, colourless oil which did not crystallise.

The *hydrochloride* crystallises from absolute alcohol in prismatic needles, which melt at 151—153°. It is anhydrous, and is readily soluble in water or hot alcohol:

0.1512 gave 0.2954 CO₂ and 0.0902 H₂O. C = 53.3; H = 6.7.

0.1242 „ 0.0732 AgCl. Cl = 14.6.

C₁₁H₁₅O₃N, HCl requires C = 53.7; H = 6.6; Cl = 14.4 per cent.

The *aurichloride* crystallises from alcohol in dark brown nodules, which melt at 111—112°. It is anhydrous, and is readily soluble in hot water or alcohol:

0.1768 gave 0.0642 Au. Au = 36.3.

$C_{11}H_{15}O_3N, HAuCl_4$ requires Au = 35.9 per cent.

The *picrate* crystallises from water in fine prismatic needles, which melt at 98—100°, and contain one molecule of water of crystallisation. It is readily soluble in hot water :

0.1130, air-dried, gave 0.1858 CO_2 and 0.0452 H_2O . C = 44.8 ; H = 4.5.

0.1446 „ lost 0.0052 at 125°. H_2O = 3.6.

$C_{11}H_{15}O_3N, C_6H_5O_7N_3, H_2O$ requires C = 44.7 ; H = 4.4 ; H_2O = 3.9 per cent.

β-Benzoyloxy-β-3 : 4-methylenedioxyphenylethyldimethylamine,

Five grams of *β*-hydroxy-β-3 : 4-methylenedioxyphenylethyldimethylamine gave, on benzylation, 5 grams of the benzyolated base ; the yield represents 78 per cent. of the theoretical. The substance was purified by crystallisation of the hydrochloride and regeneration from the pure salt, when it formed a colourless, viscid oil which did not crystallise.

The *hydrochloride* crystallises from hot water in glistening prisms, which melt at 216°. It is anhydrous, and is sparingly soluble in cold water or alcohol :

0.1786 gave 0.0716 AgCl. Cl = 9.9.

$C_{18}H_{19}O_4N, HCl$ requires Cl = 10.1 per cent.

The *hydrogen sulphate* crystallises from absolute alcohol in irregular, lustrous plates, which melt at 89—90°. It contains one molecule of water of crystallisation, and is readily soluble in water or absolute alcohol :

0.1082, air-dried, gave 0.1996 CO_2 and 0.0542 H_2O . C = 50.3 ; H = 5.6.

0.1330 „ lost 0.0050 at 100°. H_2O = 3.8.

0.1466, dried at 100°, gave 0.0834 $BaSO_4$. SO_4 = 23.4.

$C_{18}H_{19}O_4N, H_2SO_4, H_2O$ requires C = 50.3 ; H = 5.4 ; H_2O = 4.2 per cent.

$C_{18}H_{19}O_4N, H_2SO_4$ requires SO_4 = 23.3 per cent.

The *platinichloride* was obtained as a granular precipitate which could not be crystallised. It was purified by dissolution in acetone, and precipitated with ether, when it formed a granular precipitate, which melted and decomposed at 151—153°. It is readily soluble in acetone, but insoluble in water, alcohol, or ether :

0.0748, dried at 100°, gave 0.0140 Pt. Pt = 18.7.

$(C_{18}H_{19}O_4N)_2, H_2PtCl_6$ requires Pt = 18.8 per cent.

The *picrate* crystallises from absolute alcohol in rosettes of fine yellow needles, which melt at 184—185°.

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