VIII.—N-*Substituted Derivatives of Piperazine and Ethylenediamine. Part I. The Preparation of* N-*Monosubstituted Derivatives.*

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WHEN piperazine reacts with substances capable of attacking its imino-groups, the products are almost invariably the *N*-disubstituted derivatives. For instance, dibenzoyl-, ditoluenesulphonyl-, and dicarbethoxy-piperazine are the sole products even when the reactions with the corresponding halogen compounds are carried out with an excess of piperazine. With alkyl iodides the dialkyl compounds and the quaternary derivatives $R{\cdot}N{<}C_4H_8{>}NR_2I$ and $IR_2N{<}C_4H_8{>}NR_2I$ only can be isolated (Hofmann, *Compt. rend.*, 1859, **49**, 788; van Ryl, *Dissert.*, Zürich, 1897; Strömholm, *Ber.*, 1903, **36**, 143).

Various *N*-monosubstituted derivatives being required for other work, attempts were made to find reaction conditions which would allow of their isolation, but only in one case—that of *piperazinoacetic acid*, $HN{<}C_4H_8{>}N{\cdot}CH_2{\cdot}CO_2H$—was a direct method successful. If ethyl chloroacetate (2 mols.) reacts with piperazine (3 mols.) in dry alcoholic solution, the esters of piperazinoacetic acid and of piperazinediacetic acid, $C_4H_8(N{\cdot}CH_2{\cdot}CO_2H)_2$, are both formed, together with piperazine hydrochloride. By removal of the last and hydrolysis of the esters a mixture of the hydrochlorides of the acids is obtained, and a separation is possible since the hydrochloride of the dibasic acid is practically insoluble in water; but the process is tedious and the yield small (about 30% yield of the monobasic acid). Attempts to prepare β-piperazinopropionic

acid, $HN<C_4H_8>N\cdot[CH_2]_2\cdot CO_2H$, and γ-piperazinobutyric acid, $HN<C_4H_8>N\cdot[CH_2]_3\cdot CO_2H$, by similar methods failed, for, although in each case the mixture of mono- and di-basic acids was obtained, no method of separation giving pure products could be found.

Attempts were therefore made to find conditions for the preparation of the unknown monoacyl derivatives of piperazine, since a substance of the type $HN<C_4H_8>N\cdot COR$ should allow of the preparation of the compounds $R_1N<C_4H_8>N\cdot COR$ which on hydrolysis would give $R_1N<C_4H_8>NH$, where R_1 is any desired substituent.

Since ethyl chloroformate even with excess of piperazine produces only the dicarbethoxy-compound, it is evident that the rate of reaction of the chloroformic ester with monocarbethoxypiperazine, which, presumably, is the first product, is specifically very much greater than the rate of reaction of the ester with piperazine; for otherwise some monocarbethoxypiperazine must remain in the solution. And the same must be true of the relative rates of reaction with piperazine and with the monosubstituted piperazine of all the compounds which produce only disubstituted derivatives. This relation seemed so remarkable that later, when the mono-substituted derivatives had been prepared and their properties were known, special experiments were made to find out whether, in fact, monosubstituted derivatives were formed under ordinary conditions, but had escaped isolation; no such derivatives could be detected.

The following considerations show that the possibility of survival of a monosubstituted derivative is much increased if the reaction is carried out in acid solution. A salt of a diacid base, such as piperazine, undergoes hydrolysis in aqueous solution in two stages represented by the equations (anions omitted)

$$H_2\dot{N}<C_4H_8>\dot{N}H_2 + H_2O \rightleftharpoons H_2\dot{N}<C_4H_8>NH_2\cdot OH + \dot{H} \rightleftharpoons H_2\dot{N}<C_4H_8>NH + \dot{H} + H_2O \quad . \quad . \quad . \quad . \quad (1)$$

$$\underset{y}{H_2\dot{N}<C_4H_8>NH} + H_2O \rightleftharpoons \underset{x_1}{HO\cdot H_2N<C_4H_8>NH} + \dot{H} \rightleftharpoons \underset{x_2}{HN<C_4H_8>NH} + \dot{H} + H_2O \quad . \quad . \quad . \quad . \quad (2)$$

These equations represent respectively the hydrolysis corresponding to the second and the first dissociation constant of the base itself; and since the second dissociation constant of a diacid base must be much smaller than the first—just as in dibasic acids—the degree of hydrolysis corresponding to equation (1) will be much greater than that corresponding to equation (2). We have not the data necessary for finding the separate values of x_1 and x_2 in equation

(2), but putting $x = x_1 + x_2$, we find that y/x is given by the expression $[H] . K_b/K_w$, where [H] is the concentration of hydrion, K_b is the "apparent" first dissociation constant of piperazine, and K_w is the ionic product of water. Using the known values of K_b and K_w (Landolt–Börnstein, "Tabellen," 1923), the value of y/x is found to be $[H] \times 10^{10}$ and is thus very large even in weakly acid solution.

If a reactive halogen compound, *e.g.*, ethyl chloroformate, is added to a solution of piperazine hydrochloride, it can react with $H_2\dot{N}{<}C_4H_8{>}NH$ to form $H_2\dot{N}{<}C_4H_8{>}N{\cdot}CO_2Et$, the kation of the salt of the monocarbethoxy-compound. Comparatively very little reaction can occur with $HN{<}C_4H_8{>}NH$, since its concentration is relatively small. But the salt of the monocarbethoxy-compound will itself undergo hydrolysis according to the equation

$$\underset{m}{H_2\dot{N}{<}C_4H_8{>}N{\cdot}CO_2Et} + H_2O \rightleftharpoons \underset{l_1}{HO{\cdot}H_2N{<}C_4H_8{>}N{\cdot}CO_2Et} + \dot{H}$$

$$\rightleftharpoons \underset{l_2}{HN{<}C_4H_8{>}N{\cdot}CO_2Et} + H_2O + \dot{H} \quad . \quad . \quad . \quad (3)$$

The extent of this hydrolysis depends on the dissociation constant of the monocarbethoxy-compound, which will probably be smaller than, but at any rate of an order of magnitude not very different from, the first dissociation constant of piperazine, so that the ratio m/l, where $l = l_1 + l_2$ in equation (3), will be of much the same order as the ratio y/x, *i.e.*, very large. Thus, of the four substances in the solution containing iminic hydrogen, which are therefore capable of reacting with ethyl chloroformate, *viz.*, $H_2\dot{N}{<}C_4H_8{>}NH$, $HO{\cdot}H_2N{<}C_4H_8{>}NH$, $HN{<}C_4H_8{>}NH$, and $HN{<}C_4H_8{>}N{\cdot}CO_2Et$, the first has a concentration very large compared with the concentrations of the other three, so long as the solution is acid. When half the piperazine has reacted, and if the solution is $N/1000$ with regard to hydrion, the concentration of $H_2\dot{N}{<}C_4H_8{>}NH$ is probably more than a million times the concentration of $HN{<}C_4H_8{>}N{\cdot}CO_2Et$. So that even though the specific rate of reaction of ethyl chloroformate with monocarbethoxypiperazine is so much greater than its rate of reaction with piperazine, the ratio of the concentration of $HN{<}C_4H_8{>}N{\cdot}CO_2Et$ to that of $H_2\dot{N}{<}C_4H_8{>}NH$ in acid solution is so small, and therefore so unfavourable to the former reaction, that a considerable quantity of monocarbethoxypiperazine should remain in the solution as hydrochloride.

Although concentration ratios become more favourable for the purpose in view the higher the hydrion concentration is maintained during the reaction, there must be an upper limit to the useful concentration of hydrion, since the concentrations of both

$H_2\dot{N}<C_4H_8>NH$ and $HN<C_4H_8>N{\cdot}CO_2Et$ diminish with increasing hydrion concentration, and a point must be reached when the rate of reaction would become inconveniently small. Other things being equal, the halogen compound which has the greatest rate of reaction with piperazine should therefore give the best results in practice, since for a given duration of the experiment it will allow of the highest hydrion concentration.

Preliminary experiments showed that of ethyl chloroformate, benzoyl chloride, and toluenesulphonyl chloride, the first reacts most quickly with piperazine; and that the rate of reaction of the ester with piperazine becomes too small for preparative purposes if the acidity exceeds approximately $0{\cdot}0015N$ ($p_H = 2{\cdot}8$). The procedure found successful was the following. To a concentrated solution of piperazine containing some bromophenol-blue (p_H 2·8 — 4·6), 2*N*-hydrochloric acid was added until the neutral tint of the indicator appeared. Small quantities of ethyl chloroformate and 2*N*-sodium hydroxide were run in at intervals, with vigorous stirring, each addition of ester being allowed to disappear before the addition of the alkali, and only sufficient of the latter being added at one time to bring the colour of the indicator back to the neutral tint. The process was continued until a test showed that no piperazine remained. The solution so obtained contains both mono- and di-carbethoxypiperazines, of which the latter is readily extracted by ether after addition of excess of alkali, whereas the *monocarbethoxypiperazine* is hardly extracted at all until the solution has been saturated with potassium carbonate. The yields of the mono- and the di-derivative correspond to 70% and 12%, respectively, of the piperazine used. The proportion of mono- to di-carbethoxypiperazine falls either if a less acid indicator is used, or if the additions of alkali are made before the previous addition of ethyl chloroformate has been used up—no doubt on account of the momentary alkalinity where the drops of alkali enter the solution.

In later experiments the necessary degree of acidity was maintained by addition of a strong solution of sodium acetate, instead of sodium hydroxide. On account of the buffering action of the sodium acetate–acetic acid mixture, the concentration of hydrion rises only slowly as hydrochloric acid is liberated during the reaction, so that it is kept nearer the most favourable point. The yields were practically unaltered, but the duration of the experiment was reduced from about 4½ hours to about 2½ hours, and less ethyl chloroformate, of which a considerable amount is lost by evaporation and hydrolysis, was required.

With benzoyl chloride under similar conditions the yield of *monobenzoylpiperazine* was only 22% of the theoretical; with toluene-

sulphonyl chloride the reaction was exceedingly slow, and no monotoluenesulphonyl compound could be isolated.

Since the method should apply in general to diacid bases, experiments were carried out with ethylenediamine, another base of which no *N*-mono-alkyl or -acyl derivatives have yet been described. The most favourable hydrion concentration for the reaction with ethyl chloroformate in this case is approximately $0{\cdot}0001N$ ($p_H = 4$), corresponding to the acidic end of the range covered by bromocresol-green. With sodium hydroxide the experiment takes 7 hours, and with sodium acetate 3½ hours, but the yields are slightly better with the former and are 60—70% of the theoretical yield of *monocarbethoxyethylenediamine*, $H_2N{\cdot}C_2H_4{\cdot}NH{\cdot}CO_2Et$, and 10% of the dicarbethoxy-compound.

The preparation of compounds $RN{<}C_4H_8{>}N{\cdot}CO_2Et$ from carbethoxypiperazine offered little difficulty. The carbethoxy-group is removed from these compounds rapidly (2 hours) by boiling alkali, but only very slowly (2—3 days) by boiling hydrochloric acid. Nevertheless the latter method is in many cases more convenient, for several of the products are best isolated as hydrochlorides. If R is an acidic radical, it is usually removed with the carbethoxy-group, so that, except for the toluenesulphonyl derivative, the monoacyl compounds cannot be prepared through the carbethoxy-compounds. But it should be possible to prepare such derivatives directly, in acid solution, and this has been done in the case of monobenzoylpiperazine.

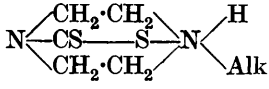
The solubilities of the compounds $RN{<}C_4H_8{>}N{\cdot}CO_2Et$ are somewhat remarkable. When R is benzoyl or toluenesulphonyl, the compounds are readily soluble in the common organic solvents, but are practically insoluble in water; when R is C_2H_5, $C_2H_4{\cdot}OH$, $CH_2{\cdot}CO_2Et$ or $[CH_2]_2{\cdot}CO_2Et$, the compounds are liquids miscible in all proportions with water, as well as with organic solvents (benzene, ether, chloroform) at the ordinary temperature, but the aqueous solution of *carbethoxyethylpiperazine* separates into two phases on warming.

Of the compounds $HN{<}C_4H_8{>}NR$ which have been prepared, all except *toluenesulphonylpiperazine* are exceedingly soluble in water. Thus carbethoxy- and *ethyl-piperazine* are practically not extracted from aqueous solution by ether, with which, however, they are both completely miscible; benzoylpiperazine is not extracted from aqueous solution by ether, in which it is very soluble; and all three compounds mix with or dissolve in benzene. On the other hand, the acids $HN{<}C_4H_8{>}N{\cdot}[CH_2]_n{\cdot}CO_2H$ (where $n = 1$, 2, or 3) are practically insoluble in organic liquids except that they are sparingly soluble in hot alcohol—no doubt because they exist as internal salts

$HN<C_4H_8>\overset{+}{N}H\cdot[CH_2]_n\cdot C\bar{O}_2$ or $H_2\overset{+}{N}<C_4H_8>N\cdot[CH_2]_n\cdot C\bar{O}_2$. From aqueous solution piperazinoacetic acid crystallises, or is precipitated by alcohol, as hydrated crystals, which retain one molecule of water per molecule even over sulphuric acid and dehydrate exceedingly slowly over phosphoric oxide; the other two acids cannot be made to crystallise from water and are precipitated by alcohol in anhydrous forms. Piperazinoacetic acid thus resembles piperidinoacetic acid, which retains one molecule of water with great tenacity (Bischoff, *Ber.*, 1898, **31**, 2841; Wedekind, *Ber.*, 1899, **32**, 723), rather than glycine, which is anhydrous. But if the combination with water is to be attributed to the grouping common to these two acids, $R<\begin{matrix}CH_2\cdot CH_2\\CH_2\cdot CH_2\end{matrix}>\overset{+}{N}H\cdot CH_2\cdot C\bar{O}_2$, where R is NH in piperazinoacetic acid and CH_2 in piperidinoacetic acid, it is difficult to see why the two higher acids do not share this property.

The salts of these acids are in some cases complex. For instance, the very dark blue copper salt of piperazinoacetic acid gives on dehydration a green salt which does not revert to the blue under any conditions tried, and in both the blue and the green solution some of the normal reactions for copper are absent. A detailed investigation of these salts is being undertaken.

The monosubstituted piperazines form with carbon dioxide unstable, and with carbon disulphide stable, *addition compounds*, of which the latter are formed with considerable heat evolution, sublime almost without decomposition, and are not desulphurised by metallic oxides. The molecular proportion of carbon disulphide to base in these compounds is 1 : 1 with ethylpiperazine, as it is in the case of piperazine itself (Herz, *Ber.*, 1897, **30**, 1585), and 1 : 2 with monoacylpiperazines. Two basic groups, one containing a mobile hydrogen atom, thus appear to be necessary for the formation of these compounds, and in view of the similarity of their behaviour to that of the dithiocarbamates formed from secondary amines (Grodzki, *Ber.*, 1881, **14**, 2756) they may be formulated as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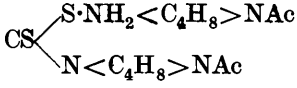
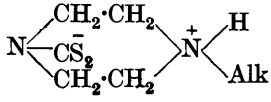


or more probably,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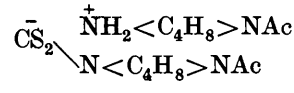

A few compounds $R\cdot NH\cdot C_2H_4\cdot NH\cdot CO_2Et$ and $R\cdot NH\cdot C_2H_4\cdot NH_2$ were prepared from carbethoxyethylenediamine by the same methods as were used for the piperazine derivatives, which they resembled in

general properties. Lower yields and the occurrence of residues during purification indicated that side reactions took place, as indeed would be expected since both ring-formation and condensation are obviously possible with most of the substances involved. The acid $H_2N{\cdot}C_2H_4{\cdot}NH{\cdot}OO_2H$ (which was prepared so that its salts might be compared with those of the acids derived from piperazine) is readily obtained anhydrous, differing thus from piperazinoacetic acid.

EXPERIMENTAL.

Derivatives of Piperazine.

Ethyl Piperazine-1-carboxylate (*N-Carbethoxypiperazine*), $HN{<}C_4H_8{>}N{\cdot}CO_2Et$. —Ethyl chloroformate (25—32 c.c.) was allowed to react with piperazine (38·8 g. of hexahydrate) under the conditions described on p. 42, the additions of ester and sodium acetate being continued until the product of benzoylation of a few drops of the solution was completely soluble in ether. (Benzoylcarbethoxypiperazine is soluble, and dibenzoylpiperazine, which is formed on benzoylation so long as the solution still contains piperazine, is insoluble in ether. If unchanged piperazine remains, some of it will be extracted with the carbethoxy-compound and complicate the purification of the latter.) Sodium hydroxide (100 c.c. of 20% solution) was added, with ice-cooling to diminish saponification of the esters, and the dicarbethoxypiperazine extracted with ether (3 extractions). The solution was then saturated with potassium carbonate (ice-cooling), filtered from precipitated salts, and extracted exhaustively with ether. From the ethereal solution, dried over sodium sulphate, a colourless viscid liquid, b. p. 116—117°/12 mm. and 237°/760 mm., was obtained. The yield (average) was 22·2 g., and also 5·7 g. of dicarbethoxypiperazine (Found: C, 53·3; H, 9·0. $C_7H_{14}O_2N_2$ requires C, 53·2; H, 8·9%). The substance mixes in all proportions with water and the common organic solvents. When carbon dioxide is passed through its dry ethereal solution, it forms an addition product which deliquesces in air and loses carbon dioxide in a desiccator. An *addition compound*, $2HN{<}C_4H_8{>}N{\cdot}CO_2Et,CS_2$, precipitated with evolution of heat when carbon disulphide is added to an alcoholic solution of the substance, is a faintly yellow powder, insoluble in water, sparingly soluble in alcohol and benzene, which sublimes rapidly at 130—140° and melts (decomp.) at 148° (Found: N, 14·2. $C_{15}H_{28}O_4N_2S_2$ requires N, 14·3%).

Ethyl 4-benzoylpiperazine-1-carboxylate, $C_6H_5{\cdot}CO{\cdot}N{<}C_4H_8{>}N{\cdot}CO_2Et$, prepared by benzoylating carbethoxypiperazine in the cold in

presence of dilute alkali (*N*/10), is easily soluble in ether and benzene and is best recrystallised from light petroleum; m. p. 82° (Found : C, 64·4; H, 6·8. $C_{14}H_{18}O_3N_2$ requires C, 64·1; H, 6·9%).

N-*Benzoylpiperazine* can be obtained only in very small yield by shaking the preceding compound with cold *N*/10-sodium hydroxide, the main products being sodium benzoate and piperazine. It was prepared by direct benzoylation of piperazine under the conditions used in the preparation of carbethoxypiperazine (p. 42). At the end of the reaction the precipitate of dibenzoylpiperazine and benzoic acid was filtered off, the solution made alkaline, and the monobenzoylpiperazine extracted with chloroform. The substance is excessively hygroscopic, very soluble in the common organic solvents, but can be crystallised by evaporation of a dry ethereal solution in a desiccator; m. p. 64° (Found : C, 69·6; H, 7·6. $C_{11}H_{14}ON_2$ requires C, 69·5; H, 7·4%).

Ethyl 4-p-*toluenesulphonylpiperazine*-1-*carboxylate*,

$$C_7H_7\cdot SO_2\cdot N<C_4H_8>N\cdot CO_2Et,$$

was prepared by stirring an ethereal solution of *p*-toluenesulphonyl chloride with a weakly alkaline solution of carbethoxypiperazine After recrystallisation from benzene and ligroin it melted at 121° (Found : C, 53·9; H, 6·3. $C_{14}H_{20}O_4N_2S$ requires C, 53·9; H, 6·4%).

N-p-*Toluenesulphonylpiperazine* was obtained by boiling the preceding compound with 10% alcoholic potassium hydroxide for 2 hours. It is sparingly soluble in water (alkaline solution) and easily soluble in benzene. After recrystallisation from benzene and ligroin it melts, slowly heated, at 110°, but when heated rapidly it melts at 102°, resolidifies, and melts again at 110° (Found : C, 55·2; H, 6·6. $C_{11}H_{16}O_2N_2S$ requires C, 55·0; H, 6·7%). An *addition compound*, $2C_{11}H_{16}O_2N_2S,CO_2$, was precipitated when carbon dioxide was passed through its alcoholic solution. This decomposes on boiling with water and melts at 107° (decomp.) (Found : S, 12·1. $C_{23}H_{32}O_6N_4S_2$ requires S, 12·2%). On addition of carbon disulphide to an alcoholic solution of toluenesulphonylpiperazine a faintly yellow *addition product*, $2C_{11}H_{16}O_2N_2S,CS_2$, was precipitated. It is insoluble in water and the common solvents, melts at 171°, but sublimes at lower temperatures with very slight decomposition (Found : S, 23·5. $C_{23}H_{32}O_4N_4S_4$ requires S, 23·0%).

Ethyl 4-*Ethylpiperazine*-1-*carboxylate*, $EtO_2C\cdot N<C_4H_8>NEt$.—When ethyl iodide reacts with carbethoxypiperazine in alcoholic solution a quaternary iodide is formed in addition to carbethoxyethylpiperazine, and it was not found possible to separate the latter compound from the carbethoxypiperazine left unchanged. A good yield (70—75%) of the *ethyl* derivative was obtained by heating

a solution of carbethoxypiperazine (12 g.) and excess of ethyl *p*-toluenesulphonate (20 g.) in dry alcohol (50 c.c.) with sodium carbonate (5·2 g.) at 100° until the evolution of carbon dioxide had ceased. After removal of the alcohol the residue was dissolved in 100 c.c. of *N*-sodium hydroxide and extracted with ether, a colourless viscid liquid, b. p. 136°/28 mm., being finally obtained (Found: C, 57·9; H, 9·7. $C_9H_{18}O_2N_2$ requires C, 58·1; H, 9·7%). The substance, which smells rather like triethylamine, mixes with water in all proportions at laboratory temperature, giving alkaline solutions which separate into two phases on warming.

N-*Ethylpiperazine dihydrochloride* was obtained as colourless, very deliquescent crystals by boiling the preceding compound with concentrated hydrochloric acid for 3 days, evaporating the solution, and precipitating the salt with alcohol (Found: Cl, 38·1. $C_6H_{14}N_2,2HCl$ requires Cl, 37·9%).

N-*Ethylpiperazine*.—By heating the hydrochloride with dry slaked lime, drying the distillate with solid potash and redistilling it, *ethylpiperazine* was prepared as a colourless mobile liquid, b. p. 155—158° (Found: C, 62·7; H, 12·3. $C_6H_{14}N_2$ requires C, 63·2; H, 12·3%). The base, which smells like triethylamine, mixes with water, ether, and chloroform in all proportions and is extracted only with difficulty from its aqueous solutions. It forms a normal *chloroplatinate* (Found: Pt, 37·1. $C_6H_{14}N_2,H_2PtCl_6$ requires Pt, 37·2%) and *chloroaurate* (Found: Au, 49·2. $C_6H_{14}N_2,2HAuCl_4$ requires Au, 49·6%). An *addition compound*, $C_6H_{14}N_2,CS_2$, is formed with heat evolution as a yellow precipitate when carbon disulphide is added to an alcoholic solution of the base. It is insoluble in the common solvents, and sublimes very rapidly above 160° (Found: N, 14·8. $C_7H_{14}N_2S_2$ requires N, 14·7%).

Ethyl 4-β-*hydroxyethylpiperazine*-1-*carboxylate*,

$$EtO_2C\cdot N<C_4H_8>N\cdot C_2H_4\cdot OH,$$

was prepared by heating carbethoxypiperazine (30 g.) with excess of ethylene chlorohydrin (20 g.) and anhydrous sodium carbonate (13·5 g.) at 110° under reflux for 6 hours, by which time the evolution of carbon dioxide had ceased. The temperature was raised to 140° for 1 hour, and the mixture then made alkaline with 10% sodium hydroxide solution and extracted with ether. From the ethereal solution, dried over sodium sulphate, a viscid colourless liquid, b. p. 184°/17 mm., was obtained. Yield, 70% (Found: C, 53·2; H, 8·9. $C_9H_{18}O_3N_2$ requires C, 53·5; H, 8·9%). The substance mixes in all proportions with water and the common solvents.

N-β-*Hydroxyethylpiperazine dihydrochloride* was prepared by hydrolysing the preceding compound with concentrated hydrochloric acid for 2 days, evaporating the solution, and precipitating

the salt with alcohol (Found: Cl, 34·9. $C_6H_{14}ON_2,2HCl$ requires Cl, 34·9%). It forms a normal *chloroplatinate* (Found: Pt, 36·5. $C_6H_{14}ON_2,H_2PtCl_6$ requires Pt, 36·5%) and *chloroaurate* (Found: Au, 48·6. $C_6H_{14}ON_2,2HAuCl_4$ requires Au, 48·7%).

Ethyl 4-*Carbethoxypiperazinoacetate*,

$$EtO_2C\cdot N<C_4H_8>N\cdot CH_2\cdot CO_2Et.$$

—Equivalent weights of carbethoxypiperazine (15·8 g.), ethyl chloroacetate (12·3 g.), and anhydrous sodium carbonate (5·4 g.) were heated together on the steam-bath until the evolution of carbon dioxide ceased (1—1½ hours). After the mixture had cooled, water just sufficient to dissolve the whole mass was added, and the solution extracted with ether. From the ethereal solution a viscid liquid, b. p. 183°/18 mm., was obtained (Found: C, 53·8; H, 8·3. $C_{11}H_{20}O_4N_2$ requires C, 54·1; H, 8·2%). The substance mixes in all proportions with water (alkaline reaction) and the common solvents, except ligroin. Complete hydrolysis with acid requires 2—3 days, but after a few hours' heating, evaporation and treatment with potassium carbonate gives an alcohol-soluble potassium salt; this is probably $KO_2C\cdot CH_2\cdot N<C_4H_8>N\cdot CO_2Et$, since in other compounds the carbethoxy-group is very resistant to acids. Hydrolysis by alkalis is rapid, but, on account of the difficulty in recovering piperazinoacetic acid from its metallic salts, not convenient in practice.

Piperazinoacetic acid hydrochloride,

$$HN<C_4H_8>N\cdot CH_2\cdot CO_2H,2HCl,$$

is very soluble in water, but the aqueous solution gives anhydrous crystals which with slow crystallisation may be ¼ inch long or more (Found: Cl, 32·6. $C_6H_{12}O_2N_2,2HCl$ requires Cl, 32·7%). The crystals were kindly examined by Dr. T. V. Barker, who reports that they belong to the orthorhombic system with the following forms about equally developed: *a* (100), *b* (010), *c* (001), *q* (011), *o* (111) and *x* (221). The axial ratios, $a:b:c = 0{\cdot}9562:1:0{\cdot}6408$, were computed from the following two-circle measurements:

	a (100).	*b* (010).	*x* (221).	*o* (111).	*q* (011).	*c* (001).
ϕ	polar	0° 0′	37° 52′	*57° 21′	57° 21′	90° 0′
ρ	face	90 0	50 24	*60 34	90 0	90 0

Piperazinoacetic acid, $HN<C_4H_8>N\cdot CH_2\cdot CO_2H$ or

$$HN<C_4H_8>\overset{+}{N}H\cdot CH_2\cdot \overset{-}{C}O_2,$$

was prepared by adding a suspension of silver carbonate to a boiling dilute solution of the hydrochloride, filtering the liquid hot, and removing the dissolved silver by means of hydrogen sulphide. (The solution, before treatment with the gas, is brown, and on standing deposits a few dark brown crystals of an explosive silver salt.) The acid was finally precipitated by alcohol from the concentrated

aqueous solution. It is very soluble in water (alkaline reaction), sparingly soluble in hot alcohol, and practically insoluble otherwise. From concentrated aqueous solutions it separates as transparent prisms which effloresce almost at once in air to a white powder; this loses no weight over sulphuric acid but still contains water which it loses at 100° or, very slowly, over phosphoric oxide (Found : C, 44·7; H, 8·7; N, 17·3; loss at 100°, 11·0. $C_6H_{12}O_2N_2,H_2O$ requires C, 44·5; H, 8·7; N, 17·3; H_2O, 11·1%). At 140—150°, the acid begins to darken and no melting takes place below 300°; when rapidly heated, it melts at 279°, decomposing into water and a mixture of solid products.

The procedure described on p. 48 served also for the preparation of *ethyl 4-carbethoxypiperazino-β-propionate*,

$$EtO_2C{\cdot}N{<}C_4H_8{>}N{\cdot}[CH_2]_2{\cdot}CO_2Et,$$

b. p. 198°/22 mm. (Found : C, 55·8; H, 8·5. $C_{12}H_{22}O_4N_2$ requires C, 55·9; H, 8·6%), from ethyl β-iodopropionate, and of *ethyl 4-carbethoxypiperazino-γ-butyrate*, $EtO_2C{\cdot}N{<}C_4H_8{>}N{\cdot}[CH_2]_3{\cdot}CO_2Et$, b. p. 207°/21 mm. (Found : C, 57·1; H, 8·8. $C_{13}H_{24}O_4N_2$ requires C, 57·4; H, 8·9%), from ethyl γ-chlorobutyrate, except that a higher temperature was required in the latter case. The further treatment of these esters to produce the four following compounds was the same as for the similar derivatives of acetic acid.

Piperazino-β-propionic acid dihydrochloride is too soluble to be crystallised from water, but is precipitated as extremely deliquescent crystals by alcohol (Found : Cl, 30·8. $C_7H_{14}O_2N_2,2HCl$ requires Cl, 30·7%).

Piperazino-β-propionic acid, $HN{<}C_4H_8{>}N{\cdot}[CH_2]_2{\cdot}CO_2H$ or $HN{<}C_4H_8{>}\overset{+}{N}H{\cdot}[CH_2]_2{\cdot}C\bar{O}_2$, cannot be crystallised from water. It has an alkaline reaction. When heated quickly, it melts at 215°, but at 200° decomposition with subsequent melting is rapid (Found : C, 52·9; H, 8·8. $C_7H_{14}O_2N_2$ requires C, 53·2; H, 8·9%).

Piperazino-γ-butyric acid hydrochloride was too deliquescent for convenient handling, so the *chloroplatinate* was prepared for analysis (Found : Pt, 33·4. $C_8H_{16}O_2N_2,H_2PtCl_6$ requires Pt, 33·5%).

Piperazino-γ-butyric acid, $HN{<}C_4H_8{>}N{\cdot}[CH_2]_3{\cdot}CO_2H$ or $HN{<}C_4H_8{>}\overset{+}{N}H{\cdot}[CH_2]_3{\cdot}C\bar{O}_2$, resembles the preceding acid in its solubilities. It melts at 235° with rapid heating, but decomposes slowly at lower temperatures.

Derivatives of Ethylenediamine.

Carbethoxyethylenediamine, $EtO_2C{\cdot}NH{\cdot}C_2H_4{\cdot}NH_2$, was prepared by the method described for carbethoxypiperazine, except that bromocresol-green was used as indicator. The substance is extracted

only slowly by ether from its aqueous solutions even after saturation with potassium carbonate. The smaller yield when sodium acetate is used (p. 43) is due to incomplete saturation with potassium carbonate, for there is a slow separation of potassium acetate from the solution during extraction. The substance is a colourless viscid liquid, b. p. 135°/20 mm. (Found: C, 45·2; H, 9·2. $C_5H_{12}O_2N_2$ requires C, 45·5; H, 9·1%). Heated under atmospheric pressure, it decomposed before boiling and a mixture of products was left from which on distillation (314—320°) a fraction was obtained having the m. p. and solubilities of ethylenecarbamide (E. Fischer and Koch, *Annalen*, 1886, **232**, 227); the same substance is formed when a solution of carbethoxyethylenediamine in dilute aqueous soda is kept for a few days. But the pure compound may be kept for weeks, or repeatedly distilled under a low pressure, without ring closure occurring. On exposure to air the substance absorbs carbon dioxide and water and ultimately gives crystals of an *addition compound*, $2C_5H_{12}O_2N_2,CO_2$, which is best prepared by passing carbon dioxide into an ethereal solution. The addition compound is soluble in water and alcohol, melts, when heated rapidly, at 102—103°, but decomposes slowly at lower temperatures (Found: C, 43·0; H, 7·8. $C_{11}H_{24}O_6N_4$ requires C, 42·9; H, 7·8%). With carbon disulphide in ethereal solution the carbethoxy-compound reacts, but without heat evolution, to produce a compound quite unlike that given by carbethoxypiperazine in being very hygroscopic and soluble in alcohol. It has not yet been obtained pure enough for analysis.

N-*Benzoyl*-N′-*carbethoxyethylenediamine*,

$$C_6H_5{\cdot}CO{\cdot}NH{\cdot}C_2H_4{\cdot}NH{\cdot}CO_2Et,$$

is sparingly soluble in water and readily soluble in the common solvents and crystallises from dilute alcohol in clusters of small needles, m. p. 130° (Found: C, 60·8; H, 6·8. $C_{12}H_{16}O_3N_2$ requires C, 61·1; H, 6·8%).

N-*Toluenesulphonyl*-N′-*carbethoxyethylenediamine*,

$$C_7H_7{\cdot}SO_2{\cdot}NH{\cdot}C_2H_4{\cdot}NH{\cdot}CO_2Et,$$

is almost insoluble in water, soluble in the common solvents, and is best recrystallised from ether; m. p. 66° (Found: C, 50·3; H, 6·3. $C_{12}H_{18}O_4N_2S$ requires C, 50·4; H, 6·3%).

N-*Toluenesulphonylethylenediamine* was prepared by boiling the preceding compound for 2 hours with 10% alcoholic potassium hydroxide. After removal of the alcohol and neutralisation the substance separates slowly in fine needles, or can be extracted by chloroform. It is sparingly soluble in water and ether, and easily soluble in chloroform and benzene. Recrystallised from benzene, it melts at 121° (Found: C, 50·3; H, 6·4. $C_9H_{14}O_2N_2S$ requires C, 50·5; H, 6·6%).

Ethyl N′-*carbethoxyethylenediamino*-N-*acetate*,

$$EtO_2C{\cdot}NH{\cdot}C_2H_4{\cdot}NH{\cdot}CH_2{\cdot}CO_2Et,$$

was prepared from carbethoxyethylenediamine under the conditions given (p. 48) for the preparation of the corresponding piperazine derivative. But on attempting to distil the ester, decomposition occurred and distillation did not commence until 217°/21 mm. was reached; the product then obtained had properties different from those of the original ester. This was therefore hydrolysed, without previous distillation, to the *hydrochloride* of β-aminoethylglycine, $H_2N{\cdot}C_2H_4{\cdot}NH{\cdot}CH_2{\cdot}CO_2H,2HCl,2H_2O$ (Found: Cl, 31·2; loss over P_2O_5, 15·8. $C_4H_{10}O_2N_2,2HCl,2H_2O$ requires Cl, 31·2; H_2O, 15·9%). The salt loses both hydrogen chloride and water at 105° and dehydrates only slowly over sulphuric acid.

β-*Aminoethylglycine* was prepared from the hydrochloride under the conditions described on p. 48, and was obtained by precipitation with alcohol as an excessively hygroscopic substance. m. p. 144°, sparingly soluble in hot alcohol, insoluble in other organic solvents (Found: C, 40·8; H, 8·6. $C_4H_{10}O_2N_2$ requires C. 40·7; H, 8·5%). At the same time an alcohol-soluble substance was produced, of which sufficient for identification has not yet been obtained.

The authors wish to express their gratitude to Professor W. P. Wynne for providing one of them (V. M. T.) with facilities for carrying out part of this work in the Chemical Laboratory of the University of Sheffield, and to the Research Fund Committee of the Chemical Society for a grant which has defrayed part of the cost of the investigation.

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