217. *The Structure of Some Diamines Prepared by the Mannich Reaction.*

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The diamines, prepared by the Mannich reaction from acetone and two molecules of formaldehyde and dimethylamine or diethylamine, are shown, by their difference from authentic specimens of the diamines (I; R = Me or Et), to have the unsymmetrical structure (II; R = Me or Et). On treatment with oxalic acid they lose one molecule of secondary amine to give the butenones (III; R = Me or Et) which on reduction give the corresponding butanones (IV; R = Me or Et). These were identical with the Mannich bases prepared from methyl ethyl ketone, formaldehyde, and appropriate secondary amines.

The preparation of the diamine (I; R = Me) by an unambiguous method (Cardwell and McQuillin, *J.*, 1949, 708) prompted a comparison of this compound with the diamine prepared from acetone by the Mannich reaction, which Mannich and Salzmann (*Ber.*, 1939, **72**, 506) concluded to have the unsymmetrical structure (II; R = Me) on the basis of its degradation reactions but rigorous proof of structure was not given. Wilds and Shunk (*J. Amer. Chem. Soc.*, 1943, **65**, 469) have provided an elaborate, rigorous proof of structure for the diethyl compound (II; R = Et), prepared by the Mannich reaction.

A simple preparation of bis-2-dimethylaminoethyl ketone (I; R = Me) from 4-keto-1 : 1-dimethylpiperidinium iodide and aqueous dimethylamine is described in the experimental section. *Bis-2-diethylaminoethyl ketone* (I; R = Et) has been prepared similarly, and also from di-2-chloroethyl ketone and diethylamine. Further, 4-keto-1 : 1-dimethylpiperidinium iodide and sodium thiomethoxide have given 5-dimethylamino-1-methylthiopentan-3-one (*hydrogen oxalate*, m. p. 121—123°).

$$NR_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}NR_2$$

(I.)

$$Me{\cdot}CO{\cdot}CH(CH_2{\cdot}NR_2)_2$$

(II.)

$$Me{\cdot}CO{\cdot}C(\dot{:}CH_2){\cdot}CH_2{\cdot}NR_2$$

(III.)

$$Me{\cdot}CO{\cdot}CHMe{\cdot}CH_2{\cdot}NR_2$$

(IV.)

The diamines (I; R = Me or Et) form normal dihydrochlorides and di(acid oxalates); the unsymmetrical diamine (II; R = Me) forms a normal dihydrobromide (Mannich and Salzmann, *loc. cit.*), but it has now been shown that the unsymmetrical methyl- and ethyl-amine, on treatment with excess of oxalic acid in ethanol, give a molecule of dialkylamine oxalate. The mother liquor from the diethylamino-compound gave 3-*diethylaminomethylbut*-3-*en*-2-*one* (III; R = Et) (2 : 4-dinitrophenylhydrazone, m. p. 88·5—89·5°) on basification. This compound was hydrogenated to 3-diethylaminomethylbutan-2-one (IV; R = Et), the 2 : 4-*dinitrophenylhydrazone*, m. p. 82—83·5°, of which did not depress the melting point of the 2 : 4-dinitrophenylhydrazone of the monoamine prepared from methyl ethyl ketone and diethylamine by the Mannich reaction). The butenone (III; R = Me) was not isolated, but was reduced, as the hydrogen oxalate, to 3-*dimethylaminomethylbutan*-2-*one hydrogen oxalate* (m. p. 113—114°). This was identical with the hydrogen oxalate of the Mannich base prepared from methyl ethyl ketone, paraformaldehyde, and dimethylamine hydrochloride. This affords conclusive proof of structure of the Mannich base. Mannich and Hof (*Arch. Pharm.*, 1926, **264**, 749) had assigned the correct structure to this compound, but did not rigorously prove it. They described a second base, prepared by the same reaction (methyl ethyl ketone, formaldehyde, and dimethylamine) to which they ascribed the alternative linear formula $Et{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2$. Analysis of the di(hydrogen oxalate) (m. p. 144—145°) has now shown that this base is a diamine, and its independent preparation from the pure butanone (IV; R = Me), formaldehyde, and dimethylamine indicates that it must be (V) or (VI). Of these formulations (VI) is slightly preferred by analogy with the formation of 2-methyl-6-dimethylaminomethyl*cyclo*hexanone from 2-methyl*cyclo*hexanone (du Feu, McQuillin and Robinson, *J.*, 1937, 53).

$$Me{\cdot}CO{\cdot}CMe(CH_2{\cdot}NMe_2)_2$$

(V.)

$$NMe_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CHMe{\cdot}CH_2{\cdot}NMe_2$$

(VI.)

EXPERIMENTAL.

(M. p.s are uncorrected. Micro-analyses are by Mr. A. Bennett.)

Bis-2-dimethylaminoethyl Ketone.—4-Keto-1 : 1-dimethylpiperidinium iodide (12·7 g.) was dissolved in aqueous dimethylamine (25%; 150 c.c.) and kept at room temperature for 7 days. The solution was saturated with potassium carbonate and extracted with ether, the extract was dried (Na_2SO_4) and distilled, and the residue in ethanol was added to excess of anhydrous oxalic acid in hot ethanol. On cooling bis-2-dimethylaminoethyl ketone di(hydrogen oxalate) (13·6 g.), m. p. 155—156°, was collected (Cardwell and McQuillin, *loc. cit.*, give m. p. 155—156°). The *dihydrochloride* crystallised in colourless hygroscopic prisms, m. p. 191—192° (Found: N, 11·7. $C_9H_{20}ON_2,2HCl$ requires N, 11·4%).

Bis-2-diethylaminoethyl Ketone.—(*a*) This ketone was prepared from 4-keto-1 : 1-diethylpiperidinium iodide and aqueous diethylamine by the above method. *Bis-2-diethylaminoethyl ketone* distilled at 88—88·5°/0·05 mm., n_D^{15} 1·4570 (Found: N, 12·1. $C_{13}H_{28}ON_2$ requires N, 12·3%). The *di*(*hydrogen oxalate*) crystallised from aqueous ethanol in fronds of colourless, flattened needles, softening at 208° followed by progressive shrinking but not molten at 230° (Found: C, 50·0; H, 8·1; N, 6·8. $C_{13}H_{28}ON_2,2C_2H_2O_4$ requires C, 50·0; H, 7·8; N, 6·9%).

(*b*) Di-2-chloroethyl ketone (1·47 g.) in ethanol (2 c.c.) was added to diethylamine (5 c.c.) in ethanol (8 c.c.). After one hour at room temperature the mixture was evaporated to dryness under reduced pressure, and the residual solid was dissolved in a little water and treated with potassium carbonate. The base was isolated in the normal manner and precipitated from ether as the hydrogen oxalate (1·3 g.) which crystallised from aqueous ethanol in colourless needles. Alone or mixed with a specimen prepared as in method (*a*) it softened at 208° with progressive shrinking up to 300° (Found: C, 49·8; H, 7·7%).

5-*Dimethylamino*-1-*methylthiopentan*-3-*one*.—4-Keto-1 : 1-dimethylpiperidinium iodide (25·5 g.) was added to an ice-cold solution of sodium thiomethoxide (7·0 g.) in ethanol (50 c.c.). After one hour the mixture was acidified with dilute hydrochloric acid and extracted with ether. The aqueous layer was saturated with potassium carbonate and extracted with ether; examination of the ethereal extract indicated that it contained some bis-2-dimethylaminoethyl ketone (identified as the acid oxalate) as well as the desired dialkylamino-thioalkyl ketone.

It was therefore distilled and the fraction, b. p. 88—98°/3 mm. (6 g.), was precipitated as the acid oxalate and fractionally crystallised. 5-*Dimethylamino*-1-*methylthiopentan*-3-*one hydrogen oxalate* crystallised from ethanol in colourless flattened needles, m. p. 121—123° (Found : N, 5·1; S, 12·0. $C_8H_{17}ONS,C_2H_2O_4$ requires N, 5·3; S, 12·1%). The base had an odour of boiled lobsters.

4-*Diethylamino*-3-*diethylaminomethylbutan*-2-*one* was prepared by Wilds and Shunk's method (*loc. cit.*) and, after 24 hours with anhydrous diethylamine (to convert any butenone into diamine), was carefully purified by fractional distillation. In our experience separation of the monoamine and diamine by distillation is easy provided butenone is not present. The sample used had b. p. 94°/0·5 mm., n_D^{22} 1·4490 (*idem, ibid.*, b. p. 92—92·5°/0·4 mm., n_D^{24} 1·4472).

3-*Diethylaminomethylbut*-3-*en*-2-*one*.—The above diamine (22·8 g.) in ethanol (25 c.c.) was added to anhydrous oxalic acid (25 g.) in ethanol (75 c.c.). The mixture was cooled to 0° and filtered, giving diethylamine hydrogen oxalate (15·1 g.; theory for 1 mol., 16·3 g.), m. p. 208—209° (decomp.) alone or mixed with an authentic specimen (Found : C, 44·5; H, 8·5; N, 8·5. Calc. for $C_4H_{11}N,C_2H_2O_4$: C, 44·2; H, 8·0; N, 8·6%). The mother liquor was evaporated to dryness under reduced pressure, and the residue was dissolved in a little water, treated with potassium carbonate, and extracted with ether. The ether was dried (Na_2SO_4) and distilled; the residual oil (13 g.; theory, 15·5 g.) was distilled and the fraction, b. p. 85—91°/27 mm., was collected. On redistillation 3-*diethylaminomethylbut*-3-*en*-2-*one* boiled at 82°/18 mm. and had n_D^{21} 1·4514 (Found : C, 69·3; H, 11·1; N, 9·2. $C_9H_{17}ON$ requires C, 69·7; H, 11·0; N, 9·0%). This colourless mobile liquid had a pronounced vinyl ketone odour, and gave an oily methiodide and oily hydrogen oxalate. The hydrochloride was extremely hygroscopic. The 2 : 4-*dinitrophenylhydrazone ethyl hydrogen sulphate* crystallised from ethanol in stout, red needles, m. p. 174—176° (Found : C, 45·0; H, 5·6; N, 15·2; S, 7·0. $C_{15}H_{21}O_4N_5,C_2H_6O_4S$ requires C, 44·3; H, 5·9; N, 15·2; S, 7·0%). The 2 : 4-*dinitrophenylhydrazone* crystallised from light petroleum (b. p. 60—80°) in red, elongated plates, m. p. 88·5—89·5° (Found : C, 54·1; H, 6·9; N, 20·8. $C_{15}H_{21}O_4N_5$ requires C, 53·8; H, 6·3; N, 20·9%).

3-*Diethylaminomethylbutan*-2-*one*.—(*a*) 3-Diethylaminoethylbut-3-en-2-one (1·8 g.) was precipitated from dry ether as the hydrochloride. The ether was decanted and the hydrochloride was dissolved in ethanol (20 c.c.). Hydrogenation at normal temperature and pressure in the presence of 3% palladised charcoal (0·3 g.) was complete in 30 minutes. After filtration from catalysts and removal of excess of solvent (on the steam-bath), the product was converted directly into the 2 : 4-dinitrophenylhydrazone. 3-*Diethylaminomethylbutan*-2-*one* 2 : 4-*dinitrophenylhydrazone* crystallised from *cyclo*hexane in yellow flattened needles, m. p. 82—83·5° (Found : C, 53·6; H, 6·8; N, 20·5. $C_{15}H_{23}O_4N_5$ requires C, 53·4; H, 6·8; N, 20·8%). A mixture with the 2 : 4-dinitrophenylhydrazone of the butenone melted at 69—73°.

(*b*) A sample of the base was prepared from methyl ethyl ketone, paraformaldehyde, and diethylamine hydrochloride by Lur'e's method (*J. Gen. Chem. Russia*, 1939, **9**, 287). It had b. p. 80—83°/18 mm. (Lur'e gives b. p. 78—80°/15 mm.). The 2 : 4-dinitrophenylhydrazone, prepared from this base, crystallised from light petroleum (b. p. 60—80°) in yellow flattened needles, m. p. 82·5—84° alone or mixed with a specimen prepared as in (*a*) above (Found : N, 20·8%).

Dimethylamine hydrogen oxalate. This separated as an oil, which rapidly crystallised, on addition of an ethereal solution of dimethylamine to an ethereal solution of anhydrous oxalic acid. *Dimethylamine hydrogen oxalate* crystallised from ethanol in fern-like prisms or rods, m. p. 149—150° (Found : N, 10·4. $C_2H_7N,C_2H_2O_4$ requires N, 10·4%) When a methanolic solution of dimethylamine was added to an excess of oxalic acid in methanol a *sesqui* (*hydrogen oxalate*) was formed, this crystallised from ethanol in colourless thick plates, m. p. 146·5—147·5° (Found : C, 33·5; H, 5·6; N, 7·7. $C_2H_7N,1\frac{1}{2}C_2H_2O_4$ requires C, 33·3; H, 5·6; N, 7·8%). A mixture with dimethylamine hydrogen oxalate melted at 135—138°.

3-*Dimethylaminomethylbutan*-2-*one*.—(*a*) 4-Dimethylamino-3-dimethylaminomethylbutan-2-one (Mannich and Salzman, *loc. cit.*) (17·2 g.) (b. p. 57—58°/1·5 mm., n_D^{19} 1·4450) in ethanol (20 c.c.) was added to anhydrous oxalic acid (25 g.) in ethanol (60 c.c.) After the solution had cooled to 0° dimethylamine hydrogen oxalate (12 g.; theory, 13·5 g.), m. p. 148—150°, was collected (Found : C, 35·7; H, 7·0; N, 10·7. Calc. for $C_2H_7N,C_2H_2O_4$: C, 35·6; H, 6·7; N, 10·4%); it did not depress the m. p. of an authentic specimen. The ethanolic mother liquors were scratched; impure 3-dimethylaminomethylbut-3-en-2-one hydrogen oxalate (m. p. 81—86°; from ethanol) was deposited. This compound could not be purified satisfactorily by recrystallisation. An ethanolic solution was therefore hydrogenated at N.T.P. in the presence of 3% palladised charcoal (1·0 g.). After one hour the hydrogen absorption was 110% of theory. The solution was filtered from the catalyst, which was extracted with a further quantity of ethanol. Careful addition of ether to the warm ethanolic filtrate led to crystallisation; after two recrystallisations from ethyl acetate–ethanol 3-*dimethylaminomethylbutan*-2-*one hydrogen oxalate* formed colourless needles, m. p. 113—114°, alone or mixed with a sample (see below) prepared from methyl ethyl ketone by the Mannich reaction (Found : C, 49·2; H, 7·8; N, 6·5. $C_7H_{15}ON,C_2H_2O_4$ requires C, 49·3; H, 7·8; N, 6·4%).

(*b*) The major fraction from the Mannich reaction of methyl ethyl ketone, paraformaldehyde, and dimethylamine hydrochloride (b. p. 60—65°/19 mm., n_D^{19} 1·4265; Mannich and Hof, *Arch. Pharm.*, 1926, **265**, 589, give b. p. 53—55°/13 mm.) was precipitated from ether as the hydrogen oxalate and was crystallised from ethyl acetate–ethanol to constant m. p. 113—114°. The higher-boiling fraction (b. p. 98—102°/18 mm; Mannich and Hof give b. p. 103—104°/12 mm.) from this preparation was precipitated as the oxalate and crystallised from aqueous ethanol.

1 : 5-*Bis*(*dimethylamino*)-2-*methylpentan*-3-*one Di*(*hydrogen Oxalate*) formed colourless micro-needles, m. p. 144—145° (Found : C, 45·8; H, 7·0; N, 7·6. $C_{10}H_{22}ON_2,2C_2H_2O_4$ requires C, 45·9; H, 7·1;

N, 7·7%). This oxalate was also isolated in small yield after 3-dimethylaminomethylbutan-2-one had been heated under reflux in ethanol with paraformaldehyde and dimethylamine hydrochloride. It then formed colourless micro-needles, m. p. 145—146° alone or mixed with the previous specimen (Found : C, 45·8; H, 6·8; N, 7·7%).

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