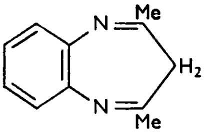
511. *Diazepines. Part I. Condensation of Acetylacetone with 1 : 2-Diamines.*

By Douglas Lloyd and Donald R. Marshall.

The study of the condensation of 1 : 2-diamines with acetylacetone, as briefly reported,[1] has been extended. The effect of pH and of temperature on the reactions between *trans*-1 : 2-diamino*cyclo*pentane and acetylacetone has been studied in detail.

Although much work has been carried out recently on carbocyclic compounds containing a seven-membered ring, comparatively little systematic investigation has been made of the heterocyclic analogues.

A readily available group of compounds of this type consists of the 1 : 4-diazepines (1 : 4-diaza*cyclo*heptatrienes) and their 2 : 3-dihydro-derivatives, which arise from condensation of 1 : 2-diamines and 1 : 3-diketones. Thiele and Stimming [2, 3] thus prepared 5 : 7-dimethyl-2 : 3-benzo-1 : 4-diazepine (I) from *o*-phenylenediamine and acetylacetone, and 2 : 3-dihydro-5 : 7-dimethyl-1 : 4-diazepine (II) has been prepared from ethylenediamine and acetylacetone.[4]



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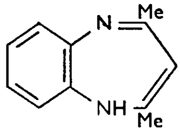

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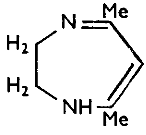

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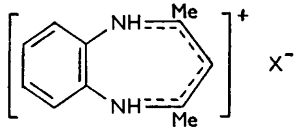

(III)

The double-bond structure in the seven-membered ring was not fully resolved; *e.g.*, the former compound may be represented as (I*A* or *B*), though the latter seems more likely, especially in the monoacid salts which may be represented as (III).[3] This matter will be discussed more fully in a later paper.

Haley and Maitland [5] found that the yield of diazepine from *o*-phenylenediamine and acetylacetone was dependent on the pH, being a maximum at pH ~4·8 and zero at pH >7·7. No mention is made of other products.

In the present work the reactions of ethylenediamine and *trans*-1 : 2-diamino*cyclo*pentane with acetylacetone have been investigated. In both cases the yield of diazepine is dependent on the pH of the reaction mixture, and different products can be obtained by variation of the pH, other conditions being constant : early workers [6] on the reaction between ethylenediamine and acetylacetone did not record the formation of any dihydrodiazepine derivative, but only an open-chain condensation product (IV) formed from two molecules of ketone and one of amine.* Schwarzenbach and Lütz [4] obtained both products by varying their reaction conditions.

In the present work, constant proportions of the two reactants were kept in aqueous solutions buffered to definite pH values for 48 hours at a constant temperature. Most attention was devoted to the reaction between the diamino*cyclo*pentane and acetylacetone,

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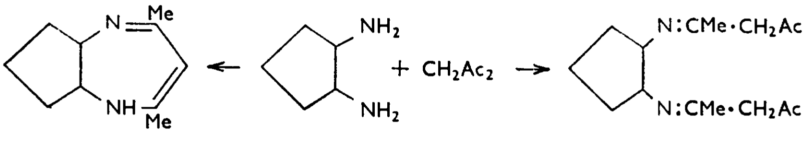
* Rosanova, although giving analytical results corresponding to the dihydrodiazepine, quotes physical constants which are those of the open-chain compound (IV).

[1] XIVth Int. Congr. Pure Appl. Chem., Zürich, 1955.
[2] Thiele and Stimming, *Ber.*, 1907, **40**, 955.
[3] See also Vaysman, *Trudy Inst. Khim. Khar'kov Gosudarst. Univ.*, 1938, **4**, 157; 1940, **5**, 57.
[4] Schwarzenbach and Lütz, *Helv. Chim. Acta*, 1940, **23**, 1139.
[5] Haley and Maitland, *J.*, 1951, 3155.
[6] Combes, *Compt. rend.*, 1889, **108**, 1252; *Bull. Soc. chim.*, 1892, **7**, 788; Rügheimer, *Ber.*, 1914, **47**, 2764; Rosanova, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 611.

as the products are not so highly soluble in water, and are thus more easily isolated and determined, than those arising with ethylenediamine.

$AcCH_2{\cdot}CMe{:}N{\cdot}CH_2{\cdot}CH_2{\cdot}N{:}CMe{\cdot}CH_2Ac$
(IV)

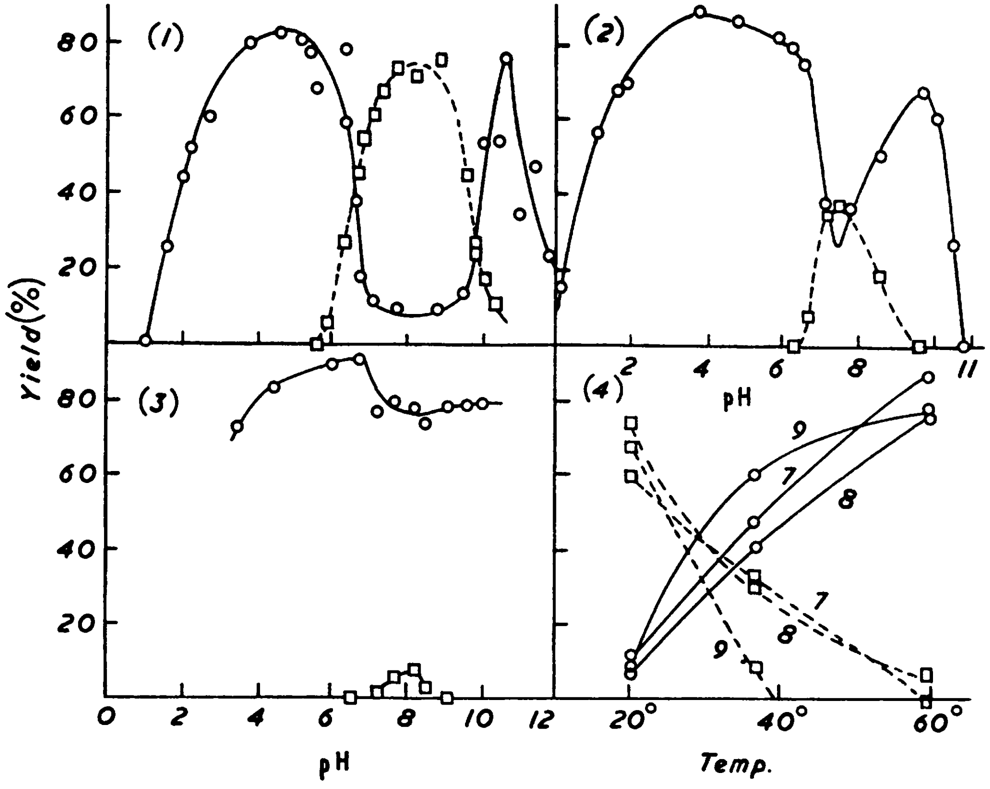


(V) (VI)

Two compounds (V) and (VI) were obtained, corresponding to the two compounds previously reported from ethylenediamine and acetylacetone.

The yields obtained at 20°, at various pH values, are shown in Fig. 1 : in mild alkali the dihydrodiazepine is the minor product, in more strongly alkaline solution and in acid solution it is the main product and, over a wide range of pH, the sole product.

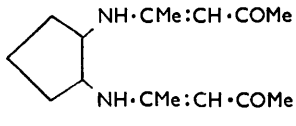
FIGS. 1, 2, *and* 3. *Variations of yield with* pH *at* 20°, 36·5°, *and* 59°, *respectively.*
FIG. 4. *Variations of yields with temperature, at given* pH *values.* (*Numerals on the curves denote* pH.)



—— Compound V. ---- Compound VI (the broken nature of the bottom curve in Fig. 3 is obscured by the points themselves).

In the reaction of ethylenediamine with acetylacetone a maximum yield of the open-chain compound (IV) is likewise obtained at 20° at pH ~8.

Several reactions are in competition, namely, the formation of compounds (V) and (VI) and their hydrolysis. 2 : 3-Dihydro-1 : 4-diazepines are very stable over a wide range of pH and thus their hydrolysis may be ignored save at high acidity and alkalinity. The product (VI) may, however, be regarded alternatively as an imine, or, in its tautomeric form (VI*A*), as an extended amide, and in either form would be easily hydrolysed; thus at all but moderately alkaline pH the hydrolysis equilibrium is such that this condensation is effectively suppressed, leaving formation of the dihydrodiazepine to proceed without competition and giving (V) as the sole product. At moderately alkaline pH, however, the product (VI) is stable and its formation predominates over that of the diazepine (V), presumably because of its precipitation.



(VI*A*)

The effect of temperature is shown in Figs. 2 and 3. Big differences in the proportions of the products (V) and (VI) may result : a difference of only 40° may, at some pH values, lead to a completely different ratio of the products (see Fig. 4). This may also be correlated with the different rates of hydrolysis.

At pH values other than those leading to its formation in the initial condensation, the product (VI) is largely converted into the diazepine derivative (V) and acetylacetone, but the reverse interconversion cannot be carried out, even at pH 8—9. These facts also accord with the suggestion that the nature of the main product is governed by the ease of hydrolysis under the conditions used.

Attempts to form the 2 : 4-dinitrophenylhydrazone of the product (VI) in acid solution gave only the derivative of acetylacetone, owing to hydrolysis.

EXPERIMENTAL

trans-1 : 2-Diamino*cyclo*pentane was prepared, with certain variations of detail, by the method of Cope *et al.*[7] from ethyl 2-oxo*cyclo*pentanecarboxylate by nitrosation.

Di-(2-hydroxyimino*cyclo*pentylidene)hydrazine was prepared by adding to *cyclo*pentane-1 : 2-dione monoxime an equivalent of hydrazine hydrate in sodium acetate solution, being obtained as a *hemihydrate*, yellow needles, decomp. 192—194° (Found: C, 51·8; H, 6·4; N, 23·7. $C_{10}H_{14}O_2N_4,\frac{1}{2}H_2O$ requires C, 51·9; H, 6·5; N, 24·2%). Recrystallisation from hot methanol gives the *anhydrous form* as orange prisms, decomp. 188° (Found: C, 54·2; H, 6·3; N, 25·6. $C_{10}H_{14}O_2N_4$ requires C, 54·1; H, 6·3; N, 25·2%).

cyclo*Pentane*-1 : 2-*dione Dioxime*.—Instead of isolating the monoxime (see Cope[7]), the reaction mixture was treated directly with hydroxylamine hydrochloride at this stage. The solution containing the monoxime (0·5 mole) was acidified to remove carbon dioxide, then neutralised again and treated with a solution of hydroxylamine hydrochloride (0·5 mole) in ~3N-sodium hydroxide (0·5 mole). The dioxime was formed rapidly as fawn needles, decomp. 215° (68%).

trans-1 : 2-Diamino*cyclo*pentane was prepared from the dioxime as described by Cope, except that chloroform was used in the final extraction of the amine. Yields averaged 70%. The amine hydrochloride forms a *dihydrate* on exposure to air (Found: H_2O, 17·2. $C_5H_{12}N_2,2HCl,2H_2O$ requires H_2O, 17·2%).

*Condensations between Diamino*cyclo*pentane and Acetylacetone.*—Constant proportions of diamino*cyclo*pentane hydrochloride and acetylacetone (1 : 2·5 mols.) were mixed in phosphate- or acetate-buffered aqueous solutions and kept in a thermostat for 48 hr. The pH of the mixtures was determined potentiometrically at the beginning and end of each reaction. Excess of the ketone was used to enable either of the two competing reactions to go to completion.

In some cases a crystalline precipitate appeared which proved to be the product (VI). This was removed and the filtrate (or the unfiltered solution, where no precipitate had appeared) made alkaline. The dihydrodiazepine (V) was then precipitated. Complete separation of the products was obtained in this way.

trans-1 : 2-*Di*-(1-*methyl*-3-*oxobutylideneamino*)cyclo*pentane* (VI or VI*A*) formed needles, readily soluble in methanol and dilute aqueous acids, sparingly soluble in water and benzene, and having m. p. 157·5—158·5° (from benzene) (Found: C, 68·1; H, 8·9; N, 10·1. $C_{15}H_{24}O_2N_2$ requires C, 68·2; H, 9·1; N, 10·6%).

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[7] Cope, Estes, Emery, and Haven, *J. Amer. Chem. Soc.*, 1951, **73**, 1199.

2 : 3-*Dihydro*-5 : 7-*dimethyl*-2 ; 3-cyclo*pentano*-1 : 4-*diazepine* (V) is readily soluble in chloroform and ethanol, less soluble in carbon tetrachloride, sparingly soluble in benzene, and has m. p. 246—249° (decomp.) (from benzene) (Found: C, 73·1; H, 9·7; N, 16·9. $C_{10}H_{16}N_2$ requires C, 73·2; H, 9·8; N, 17·1%).

Conversion of Compound (VI) *into the Dihydrodiazepine* (V).—The compound (VI) was dissolved in hydrochloric acid, and the solution buffered to pH 4. Removal of the solvent by distillation (at room temperature) gave a distillate which gave a 2 : 4-dinitrophenylhydrazone and a colour with ferric chloride solution corresponding to those obtained from acetylacetone. When the residue from the distillation was made strongly alkaline the dihydrodiazepine (V) separated (m. p. 245—248°). On the other hand, at pH 9, little or no conversion occurred and at no pH could the reverse change be effected.

Condensations of Ethylenediamine with Acetylacetone.—A similar procedure was used to that in the condensations involving diamino*cyclo*pentane. Owing to the much greater solubility of the products it was difficult to isolate them quantitatively but a maximum yield of the open-chain compound (IV), m. p. 110—111°, was obtained at pH $\sim$ 8·5. 2 : 3-Dihydro-5 : 7-dimethyl-1 : 4-diazepine, obtained by the method of Schwarzenbach and Lütz,[4] had m. p. 85—91°. A sample obtained from the hydrochloride had m. p. 93—95°, b. p. 245—250°. An aqueous solution had pH $\geqslant$11; it is a strong enough base to decompose chloroform in which it is dissolved, resulting in the formation of the *hydrochloride*, m. p. 288—292° (from ethyl acetate–methanol) (Found: C, 52·2; H, 7·9; N, 17·8; Cl, 22·3. $C_7H_{13}N_2Cl$ requires C, 52·3; H, 8·1; N, 17·5; Cl, 22·1%). The perchlorate[4] has m. p. 138—141·5° (from water).

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