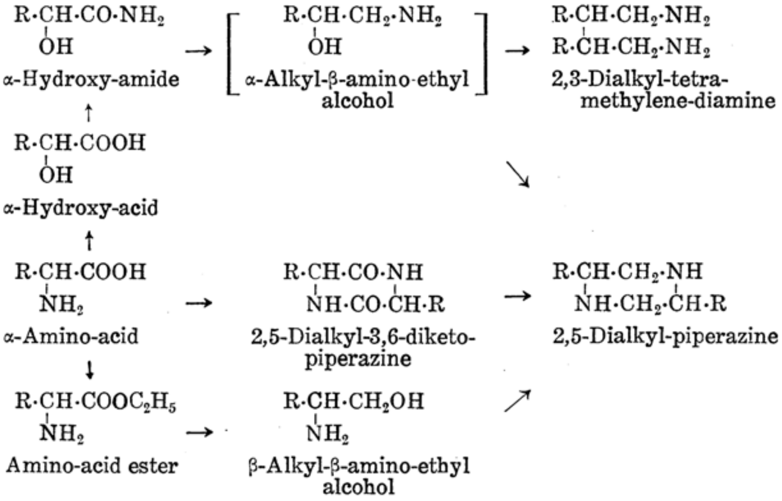
On Some 2,5-Dialkyl-piperazines.(1)

By Haruomi ÔEDA.

(Received June 3, 1938.)

In the previous papers it was described that solid bases were obtained by catalytic hydrogenation of some α-hydroxy-amides and the author concluded that the bases correspond to 2,3-dialkyl-tetramethylene-diamines (I) which would result from further reduction of supposed primary products, α-alkyl-β-amino-ethyl alcohols.



(I)

(II)

Formula I was given from the facts that the observed molecular weights of the bases were double those of desoxy-amines and that such a condensation of two molecules of amino-alcohols with elimination of two hydroxyls by reduction might probably occur, when deduced in comparison with the work of Rupe and Ackermann.(2) Three kinds of "dialkyl-tetramethylene-diamine" (dimethyl, di-isobutyl and dibenzyl compounds) were mentioned in the previous papers.

After the publication of these papers, the author noticed another possible formula for these bases: i.e. piperazine formula (II). The pipera-

---

(1) Studies on Hydroxy-acids and Their Derivatives. VII. Correction to V and VI, this Bulletin, **12** (1937), 121, 377.

(2) *Helv. Chim. Acta*, **2** (1919), 221.

zines may be assumed to be formed from two molecules of β-amino-alcohols by dehydration. Similar reactions of alcohols with amines have been observed by many investigators, though a ring formation from β-amino-alcohol leading to piperazine nucleus could not be found as yet described.(3)

The compounds I and II can hardly be distinguished from each other by their analytical results(4) when the radical R is large or the base is analysed in the form of its derivatives. As already described in the previous paper, the author's base is found to behave as a secondary amine in sulphamide reaction. This fact favours formula II for these bases.

Among the three dialkyl-piperazines, the dimethyl and di-isobutyl compounds are known. Dimethyl-piperazine,(5) and its various derivatives are fully described in the literature, while the author's base is isolated in pure state only in the form of its benzoyl compound. Melting points of the benzoyl derivatives of the two bases coincide with each other showing 227–228°. On the other hand, no sufficient data for di-isobutyl-piperazine(6) are given in the literature to discuss its identity with the author's base.

For direct comparison of the two bases in question, the author tried to prepare di-isobutyl-piperazine by reducing the corresponding diketo-piperazine according to the description of Cohn.

Di-isobutyl-piperazine prepared from leucine anhydride was isolated as its hydrochloride (decomp. p. over 330°), though its yield was very poor. Free base (m.p. 80–83°), benzoyl compound (m.p. 222–223°) and benzene-sulphonyl compound (m.p. 211–213°) were prepared. The melting points given above coincide with those of the base and its derivatives isolated from leucic acid amide described in the previous paper. Mixed melting points also prove their identity.

---

(3) In some α-amino-aldehydes or α-amino-ketones, similar condensations which result in the formation of dihydro-pyrazine or pyrazine itself, in the presence of some oxidant, are described.

(4) In the previous papers, analytical results of the free bases, hydrochlorides, benzoyl derivatives, etc. are given. Difference of calculated values for the two formulæ in question becomes most notable in case of free bases. Calculated values for the two bases together with observed values are quoted from the previous paper as follows: Di-isobutyl base. Found: C, 72.24; H, 13.66; N, 14.22. Calculated for the piperazine, $C_{12}H_{26}N_2$: C, 72.73; H, 13.25; N, 14.15. Calculated for the tetramethylene-diamine, $C_{12}H_{28}N_2$: C, 71.94; H, 14.09; N, 14.00. Di-benzyl base. Found: C, 80.76; H, 8.54; N, 10.58. Calculated for the piperazine, $C_{18}H_{22}N_2$: C, 81.19; H, 8.35; N, 10.52. Calculated for the tetramethylene-diamine, $C_{18}H_{24}N_2$: C, 80.72; H, 9.02; N, 10.44.

(5) Hoyer, *Z. physiol. Chem.*, **34** (1901), 347.

(6) Cohn, *ibid.*, **29** (1900), 297. The base is isolated and analysed in the forms of its hydrochloride and platinum double chloride. No definite description is found of the free base and other derivatives.

Dibenzyl-piperazine is not found in the literature. Preparation of this base by reducing its diketo compound was unsuccessful, no trace of the piperazine being isolated when phenylalanine anhydride was reduced with sodium in ethyl or amyl alcoholic solution.

By reducing phenylalanine ester with sodium at 160°, Karrer⁽⁷⁾ obtained β-benzyl-β-amino-ethyl alcohol, $C_6H_5 \cdot CH_2 \cdot CHNH_2 \cdot CH_2OH$. The preparation⁽⁸⁾ was repeated by the present author and the expected amino-alcohol⁽⁹⁾ was isolated in two different forms: the one melted at 71–73° and was optically inactive (its monobenzoyl compound, m.p. 148–149°), while the other melted at 92–94° and was optically active, $[\alpha]_D^{23} = -24.4°$ (its monobenzoyl compound, m.p. 169–171°). Besides the amino-alcohol, another solid base which was not described by Karrer, was isolated in a small quantity from the reaction mixture. It showed the same melting point (166–167°) as one of the solid bases⁽¹⁰⁾ resulting from phenyl lactamide as described in the previous paper. Their identity was proved by the mixed melting point tests of the free bases as well as of their benzoyl compounds (m.p. 281–283°).

The amino-alcohol derived from phenylalanine is isomeric with the one which was assumed as an intermediate product in the previous paper, viz., α-benzyl-β-amino-ethyl alcohol, $C_6H_5 \cdot CH_2 \cdot CHOH \cdot CH_2NH_2$. If ring formation by dehydration occurs in these amino-alcohols, they give the same product, 2,5-dibenzyl-piperazine, and in fact, as shown above, the identical solid base was obtained by the reduction of either the hydroxy-amide or the amino-acid ester. This fact indicates that the compound is no doubt dibenzyl-piperazine.⁽¹¹⁾ The transformation of the amino-alcohols into the piperazine compound by dehydration might be favoured by the reaction temperature as high as 250° in the previous and 160° in the present experiments.

---

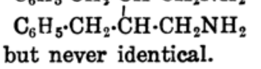
(7) *Helv. Chim. Acta,* **4** (1920), 97.

(8) Samples of natural leucine and phenylalanine which were the starting materials in the present preparations were the same as used in the preparation of amides of leucic acid and phenyl lactic acid in the previous work.

(9) Karrer isolated this amino-alcohol only in one form of its hydrochloride and no mention was given whether the starting material was active or racemic.

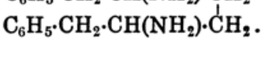
(10) In the previous paper another form of this base (m.p. 150–152°; its benzoyl compound, m.p. 198–200°) was isolated, but in the present experiment it could not be identified.

(11) If the bases resulting from the hydroxy-amide and the amino acid ester were products of further hydrogenation of the amino-alcohols (as considered in the previous paper), their formulæ would be



$$\begin{array}{l} C_6H_5 \cdot CH_2 \cdot CH \cdot CH_2NH_2 \\ \qquad\qquad\quad | \\ C_6H_5 \cdot CH_2 \cdot CH \cdot CH_2NH_2 \end{array}$$

and



$$\begin{array}{l} C_6H_5 \cdot CH_2 \cdot CH(NH_2) \cdot CH_2 \\ \qquad\qquad\qquad\qquad\quad | \\ C_6H_5 \cdot CH_2 \cdot CH(NH_2) \cdot CH_2 \end{array}.$$

They are isomeric with each other but never identical.

These considerations lead the author to conclude that 2,5-dialkyl-piperazine formulæ, instead of dialkyl-tetramethylene-diamine formulæ, are to be given to the solid bases described in the previous papers.

Experimental.

2,5-Di-isobutyl-3,6-diketo-piperazine (Leucine Anhydride.) Prepared from natural leucine by heating at 170° in the presence of glycerine.(12) M.p. 263° (uncorr.) or 270° (corr.) after recrystallisation from alcohol.

Reduction of Leucine Anhydride. The anhydride (10 g.) was added to absolute alcohol (dehydrated with metallic sodium, 500 c.c.). It dissolved completely when the mixture was kept boiling. Large excess of sodium (30 g.) was added to the boiling solution in small pieces through reflux condenser in the course of half an hour. After cooling, an equal volume of water was added and the alcohol was removed in vacuum. When the volume of the residue diminished to nearly half of the initial, the distillation was stopped. After removing precipitated unreacted anhydride, the filtrate was extracted with a large bulk of ether. After drying over caustic soda, ether was expelled from the extract and a little anhydride again crystallised out. Total yield of recovered anhydride corresponded to more than 10%, even when large excess of sodium was used. The residue (2.5 g.), after separation of the crystals, was distilled under reduced pressure through Widmer column and was separated into two fractions:

(I)	up to 100°	under 6 mm.	0.5 g.
(II)	over 100°	,,	1.2 g.

Fraction II tended to solidify in the receiver, while fraction I remained as viscous fluid. Both of the fractions were dissolved in ether separately and were extracted with dilute hydrochloric acid. From fraction I a hydrochloride very soluble in water was isolated, while from fraction II another hydrochloride insoluble in water was obtained together with the above soluble one.

Hydrochloride, Soluble in Water (a Base Left Undetermined). Crude sample from fraction I weighed 0.25 g. After decolouration with charcoal it crystallised from alcohol in colourless leaflets. The combined yield of pure sample from both fractions was 125 mg. M.p. 160–162° (uncorr.). No study on this hydrochloride was made.

Hydrochloride, Insoluble in Water (2,5-Di-isobutyl-piperazine). Crude sample weighed 0.2 g. After washing with alcohol it was dissolved in a large volume of hydrochloric acid and, after decolouration with charcoal, the solution was evaporated on the water bath. Colourless hydrochloride crystallised out while still hot before the solution completely dried up. It weighed 168 mg. Decomp. p. over 330°.

Free base. When the pure hydrochloride (50 mg.) was warmed with dilute caustic soda, free base separated out as an oil and turned to crystals on cooling. The separated base was dissolved in alcohol and filtered. After evaporation to a small

---

(12) Maillard, *Ann. chim.*, [9], 3 (1915), 83.

bulk, the free base was crystallised by adding water. M.p. 80–83°(13) after drying over caustic soda.

Benzoyl compound. The pure hydrochloride (33 mg.) was added to dilute caustic soda (2 c.c.) and benzoyl chloride was added drop by drop. Benzoyl compound was formed as sticky mass and turned to crystals on shaking. M.p. 217–218° (uncorr.) or 222–223° (corr.) after one recrystallisation from alcohol. No depression of melting point was observed when mixed with the sample described in the previous paper. (Benzoyl compound of the solid base from leucic acid amide melted at 223–224° (corr.) and its analytical result was given in the previous paper.)

Benzene-sulphamide. To a suspension of the free base in dilute caustic soda (50 mg. of the hydrochloride in 1 c.c.) benzene-sulphonyl chloride (2 drops, nearly equivalent) was added. Crude sulphamide (70 mg.) separated out as crystals. After recrystallisation from alcohol, it (39 mg.) melted at 206–208° (uncorr.) or 211–213° (corr.), alone or mixed with the sample described below. (Found: N, 5.69. Calculated for $C_{12}H_{24}N_2(C_6H_5SO_2)_2$: N, 5.85%.)

Benzene-sulphamide of "solid base from leucic acid amide". From the free base melting at 62–64° (50 mg.) and benzene-sulphonyl chloride (3 drops), crude sulphamide (78 mg.) was obtained just in the same way as above. When recrystallised from alcohol, the purified sample (19 mg.) melted at 205–207° (uncorr.) or 210–212° (corr.) and it was used in the above mixed melting point test.

Ethyl Ester of Phenylalanine. Prepared from natural phenylalanine and alcohol by dehydration with gaseous hydrochloric acid.(14) B.p. 135–136° under 8 mm.

Reduction of Phenylalanine Ester. Metallic sodium (45 g.) cut in small pieces was placed in a litre-flask which was immersed in an oil bath (160°). Mixture of the ethyl ester of phenylalanine (38 g.) and absolute alcohol (120 c.c.) was added drop by drop to the sodium through reflux condenser in the course of one hour. After interval of half an hour, a new bulk of alcohol (150 c.c.) was added and then the oil bath was detached. Alcohol was again poured until the metallic sodium completely disappeared. After cooling, water was added to dissolve separated alcoholate. The alcohol was removed in vacuum at 50–70° and the residue was concentrated also in vacuum until a light coloured oil separated in the flask.

The oil (not miscible with ether) and the water layer were separately extracted with a large bulk of ether. From the combined extract, after dehydration with sodium sulphate, ether was removed and the residue was concentrated to a small bulk on boiling water bath. Small amount of crystals gradually deposited on standing.

Dibenzyl-piperazine. The crystals were separated and washed with a little ether. After recrystallisation from alcohol, it melted at 163–164° (uncorr.) or 166–167° (corr.) and the sample amounted to 0.45 g. No depression of melting point was observed when the base was mixed with the base resulting from phenyl lactamide (m.p., the same; its analytical result was given in the previous paper).

---

(13) Solid base isolated from leucic acid amide, as already mentioned, shows different melting points 62–64° and over 80°). They are identical in analytical result and may be presumed to be mixtures of isomers. But their differentiation in the form of derivatives was unsuccessful.

(14) Fischer and Schöller, *Ann.*, **357** (1907), 1.

Benzoyl compound. Prepared from the above base (50 mg.) and benzoyl chloride (180 mg.) in alkaline medium (1.5 c.c. of 2N caustic soda). Crude benzoyl compound (79 mg.) separated, after washing with hot alcohol, was once recrystallised from glacial acetic acid. M.p. 274–276° (uncorr.) or 281–283° (corr.), alone or mixed with the benzoyl compound of the base resulting from phenyl lactamide (m.p., 280–282°; its analytical result was given in the previous paper).

β-Benzyl-β-amino-ethyl alcohol. After removal of dibenzyl-piperazine, the remaining syrup was subjected to vacuum distillation. The part distilling at 147–151° under 10 mm. was collected. It amounted to 4.4 g. and was colourless viscous fluid tending to crystallise after long standing. The crystals, after washing with a little benzene, on heating, softened at 65–70° and melted below 75°. By fractional recrystallisation from benzene it could be separated into two fractions. The part less soluble in benzene (1.27 g.) melted at 91–93° (uncorr.) or 92–94° (corr.) (Found: C, 71.63; H, 9.31;(15) N, 9.10%), $[\alpha]^{23}_{D} = -24.4°$ (28.25 mg. in 1.00 c.c. alcoholic solution; $l = 1$ dm.; $\alpha^{23}_{D} = -0.69°$). The part more soluble in benzene (0.94 g.) melted at 70–72° (uncorr.) or 71–73° (corr.) (Found: C, 71.78; H, 9.04; N, 9.29. Calculated for $C_9H_{13}ON$: C, 71.45; H, 8.67; N, 9.26%), $[\alpha]^{23}_{D}$ = almost null ($-0.35°$) (28.55 mg. in 1 c.c. alcoholic solution; $l = 1$ dm.; $\alpha^{23}_{D} = -0.01°$).

Benzoyl compound. The unfractionated mixture of the base (200 mg.) was dissolved in 2N caustic soda (6 c.c.) and benzoyl chloride (500 mg.) was added drop by drop with constant shaking. Crude benzoyl compound (250 mg.) separated could be differentiated into two fractions by fractional recrystallisation from benzene-alcohol (1:1). They were found, on analysis, to be mono-benzoyl derivatives. The part less soluble in the solvent (40 mg.) melted at 166–168° (uncorr.) or 169–171° (corr.) (Found: C, 75.34; H, 7.29; N, 5.45%). The more soluble part (51 mg.) melted at 146–147° (uncorr.) or 148–149° (corr.) (Found: C, 75.25; H, 7.14; N, 5.42. Calculated for $C_9H_{12}ON(C_6H_5CO)$: C, 75.25; H, 6.72; N, 5.49%).

The two forms of the benzoyl compound could be prepared from the fractionated free bases; the base with higher melting point giving the derivative with higher melting point and the lower one giving that with lower melting point.

In conclusion, the author expresses his sincere thanks to Mr. R. Suzuki, Director of the factory, for every facility given to the author and also to Dr. Y. Takayama for constant encouragements.

Chemical Laboratory, S. Suzuki (Ajinomoto) & Co., Ltd.
Kawasaki, near Tokyo.

---

(15) Determinations of carbon and hydrogen and measurements of optical rotation in this paper were done by Mr. Toshio Ando, to whom the author is very grateful.