Catalytic Hydrogenation of Amides of α-Hydroxy-Acids (Continued).⑴

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Experiments on the formation of 1,4-diamine and of 1,2-glycol from α-hydroxy-amide by catalytic hydrogenation in the presence of copper-chromium oxides, were extended to phenyl-lactamide.

From this amide benzyl-ethylene glycol and a solid base were obtained. The solid base, when fractionally recrystallized from alcohol, can be separated into two fractions, one of which melts at 142–144° (A) and the other at 166–167° (B). Results of analysis of both bases show that they correspond to the same diprimary diamine shown below, i.e. they are isomeric with each other.

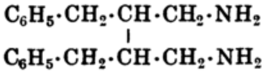
On benzoylation, the latter base (B) gives a derivative melting at 280–282° (*Bz*.B) in pure state, whereas the former (A) gives the same derivative (*Bz*.B) admixed with an isomeride which melts at 199–201° (*Bz*.A), and this mixture is easily separated into the components by the difference of their solubilities in alcohol. These results seem to indicate that base A⑵ contains some component besides one which is common in both bases (A and B).

By hydrolysis of the benzoyl derivative melting at 199–201° (*Bz*.A) with concentrated hydrochloric acid at 150–160°, a base was regenerated which melted at 153–155°. A component of base A is thus isolated. On the other hand, the benzoyl derivative (*Bz*.B) which is common in both bases and the corresponding benzenesulphonyl derivative (m.p. 226–227°) are very resistent to hydrochloric acid and can not be hydrolyzed by the same treatment. Thus the second component which is common in both bases (A and B) can not be isolated in the form of free base, but the fact that base B gives only one benzoyl (*Bz*.B) or benzenesulphonyl derivative, leads to the conclusion that base B represents the second component in its pure state.

⑴ Studies on Hydroxy-Acids and Their Derivatives. VI. Continued from this Bulletin, **12** (1937), 121.

⑵ Attempts to separate the base-mixture in the form of hydrochloride, picrate or oxalate were tried but they were found to be unfavourable on account of their small solubilities in ordinary solvents.

To summarize, the existence of two bases having the same composition (m.p. 153–155° and 166–167°) is ascertained which correspond to some two optical isomerides(3) among three possible forms (active, meso and racemic) of this base.



$$\begin{array}{l} C_6H_5\cdot CH_2\cdot CH\cdot CH_2\cdot NH_2 \\ | \\ C_6H_5\cdot CH_2\cdot CH\cdot CH_2\cdot NH_2 \end{array}$$

2,3-Dibenzyl-tetramethylene-diamine

Free base	Benzoyl derivative	Benzenesulphonyl derivative
M.p. 153–155°	M.p. 199-201°	—
M.p. 166–167°	M.p. 280-282°	M.p. 226-227°

Uniting the present results with previous ones(1) it is established that the scheme giving 1,4-diamine and 1,2-glycol from α-hydroxy-amides is similar for the three amides, namely, amides of lactic, leucic(4) and phenyl-lactic acids.

Experimental.

The experimental procedures of the hydrogenation and the separation of reaction products are the same as described in the previous paper.(1)

Phenyl-lactamide (m.p. 113–114°), 23 g. (0.14 mol); dioxane, 60 c.c.; catalyzer, 5.0 g.; time of hydrogenation, 2 hours at 245–255°; fractionation through Widmer column after expelling off the dioxane:

I	130 - 140°	under 5 mm.	3.9 g.
II	160 - 190°	,,	4.9 g.
III	over 190°	,,	

Fraction II tends to solidify in the receiver, while fraction III remains as viscous fluid even after long standing. Considerable amount of residue was found undistilled in the flask.

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(3) Meso and racemic forms may be assigned to the above bases from the follwing reason : Measurement of optical rotation can not be carried out with both forms separately due to scarcity of the sample, but the measurement with their mixture (base A) showed no activity.

(4) As to dimethyl- and di-isobutyl-tetramethylene-diamines(1), derived from amides of lactic acid and leucic acid respectively, three isomerides are also possible and in fact, in the latter diamine, the author obtained two isomeric forms by the recrystallization of the crude base from alcohol, one melting at 60–62°, and the other at about 80°, but the latter was not reported in the previous paper because the higher melting fraction was not isolated in its pure state even in the form of its derivatives.

(A) Fraction I. (a) Neutral Part. Fraction I was separated into neutral and basic parts by extracting the acidified mixture with ether. The neutral part, after boiling with sodium hydroxide solution, was twice refractionated through Widmer column, when the main part distilled at 147–149° (uncorr.) under 6 mm. Yield, 7.2 g. from 0.42 mol of amide. It was identified as benzyl-ethylene glycol by preparing its bis-phenylurethane.

Bis-phenylurethane. Prepared from the glycol (1.0 g.) and phenyl isocyanate (2.0 g.) by heating at 120–130° for half an hour, crude urethane (3.2 g.) being crystallized by adding ligroin. It melted at 133–134° (uncorr.) or 135–136° (corr.) after recrystallization from benzene (Found: C, 70.19; H, 6.11; N, 7.22. Calculated for $C_9H_{10}O_2(OC{\cdot}NH{\cdot}C_6H_5)_2$: C, 70.73; H, 5.68; N, 7.18%). $[\alpha]_D^{28} = -13°$ (1 dm. tube; 26.5 mg. in 1.00 c.c. of alcoholic solution). When the crude sample was recrystallized from alcohol, it showed the same m.p. as above and lower melting fraction was never isolated even when seeded with a crystal of sample A (see below). $[\alpha]_D^{28} = -11°$ (25.7 mg. in 1.00 c.c.)

Supplement to Previous Paper⁽⁵⁾: It was already described that this glycol is also obtainable from phenyl-lactic acid when hydrogenated in the form of its acetone-compound. The sample of hydroxy-acid was the same one as was used in the present experiment and is lævo-rotatory. In that paper two forms of urethane of this glycol were mentioned and their interconvertibility by crystallization and their monotropic change by heating were described. Preparation of those urethanes were tried again and it was proved that the previous descriptions are correct. Their analyses were repeated and their optical rotations were measured. Urethane recrystallized from alcohol (sample A), m.p. 109–110° (uncorr.) (Found: C, 70.06; H, 6.15; N, 7.15%). No rotation was observed (1 dm. tube; 26.9 mg. in 1.00 c.c. of alcoholic solution). Urethane recrystallized from benzene (sample B), m.p. 132–133° (uncorr.) (Found: C, 69.96; H, 6.16; N, 7.15. Calculated for $C_9H_{10}O_2(OC{\cdot}NH{\cdot}C_6H_5)_2$: C, 70.73; H, 5.68; N, 7.18%). No rotation was observed (26.4 mg. in 1.00 c.c.).

Now, it is shown that the present urethane is active, while both forms of the former are inactive. As to the nature of the two forms of inactive urethane, following facts were observed. Sample B shows nearly the same m.p. as the active urethane and moreover mixing of them caused no appreciable depression. Mixtures (once melted and left at 110° to solidify), on heating, slightly soften below 130° and melt clearly at 131–133° (uncorr.), in every case when ratio of mixing were varied as 3:1, 2:2 and 1:3. From these behaviours of sample B it is probable that B belongs to the type of mixed crystals. If the molten mixtures are kept at room temperature, they become hard glassy masses and never tend to crystallize. Thus the formation of sample A from the molten mixture can not be realized. Sample A must be racemic compound or *dl*-mixture, and as to the last point, because of the lack of data, no decision can be given. There exists a transition point⁽⁶⁾ between the two forms of inactive urethane. Sample A, on rapid heating, clearly melted at 110°, but when

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(5) this Bulletin, **10** (1935), 531.

(6) Existence of a transition point between two inactive forms was observed in several substances, such as camphoroxime, π-chlorocamphor and methyl-mannoside. But the formation of two forms by crystallization from different solvents was not mentioned on these substances (Freudenberg, "Stereochemie," 560, Leipzig (1932).).

maintained at this temperature, it gradually resolidified and the m.p. of the resolidified mass was just the same as that of sample B.

(b) **Basic Part.** A hydrochloride, easily soluble in hot water, was obtained in small quantity. It can be recrystallized from alcohol, m.p. 271–272° (corr.). No further study on this base was made.

(B) **Fractions II and III.** Combined fractions were diluted with five times its volume of alcohol and concentrated hydrochloric acid was added to it. A hydrochloride gradually precipitated, the yield was not good: 4.3 g. of crude hydrochloride was obtained from 0.42 mol of the amide. After extraction with hot alcohol, the residue was dissolved in a large bulk of hot water, filtered, and was concentrated on water bath. During evaporation, a hydrochloride began to crystallize out while still hot before the solution was completely dried up. Hydrochloride (2.5 g.) thus purified was colourless and on heating showed no change of appearance up to 300°.

When the above hydrochloride was warmed with a little excess of dilute caustic soda, it changed to a crystalline free base (1.8 g. from 2.5 g. of the hydrochloride). The free base was dissolved in hot alcohol and filtered. On cooling without evaporation of the solvent, a base melting between 145° and 160° was obtained. The base which was obtained from the above filtrate by evaporation of the solvent, melted below 150°. The former fraction, after repeated recrystallization from alcohol, melted sharply at 163–164° (uncorr.) or 166–167° (corr.) (base B) and weighed 249 mg., melting point remaining unchanged on further recrystallization. The melting range of latter fraction, after repeated recrystallization, became narrower and 584 mg. of the base which melted at 140–142° (uncorr.) or 142–144° (corr.) (base A) was obtained.

(a) **Free Base Melting at 142–144° (base A).** (Found: C, 80.74; H, 9.31; N, 10.24. Calculated for $C_{18}H_{24}N_2$: C, 80.72; H, 9.02; N, 10.44%.) No rotation was observed (1 dm. tube; 25.8 mg. in 1.00 c.c. of alcoholic solution).

Benzoyl derivative melting at 199–201° (*Bz.*A). To a suspension of the base in dilute caustic soda, benzoyl chloride was added drop by drop with constant stirring. A sticky mass first formed, turned to crystallize. Benzoyl compound thus separated (660 mg. from 465 mg. of the free base) was extracted with alcohol. Benzoyl compound which was obtained from the alcoholic extract after expelling off the alcohol, melted at 195–197° (uncorr.) or 199–201° (corr.) after recrystallizations from alcohol (Found: C, 80.48; H, 6.47; N, 6.06. Calculated for $C_{18}H_{20}(NH{\cdot}CO{\cdot}C_6H_5)_2$: C, 80.60; H, 6.80; N, 5.88%).

The residue of the above extraction (149 mg.), on purification, was found to be identical in m.p. with a benzoyl compound (*Bz.*B) obtainable from the other base (base B) and it was combined with that fraction described below.

Hydrolysis. Mixture of the benzoyl compound (*Bz.* A: 85 mg.) and concentrated hydrochloric acid (10 c.c.) was heated at 150–160° in a closed vessel for four hours. After cooling, a gelatinous precipitate of hydrochloride of the regenerated base (55 mg.) was separated and it was recrystallized from water after being washed with alcohol (Found: N, 7.97. Calculated for $C_{18}H_{24}N_2{\cdot}2HCl$: N, 8.21%).

Free Base Regenerated. The base (26 mg.) which was obtained from the above hydrochloride (36 mg.) was recrystallized from alcohol and dried on porous plate over solid caustic soda, m.p. 150–152° (uncorr.) or 153–155° (corr.) (Found: C, 80.76; H, 8.54; N, 10.58. Calculated for $C_{18}H_{24}N_2$: C, 80.72; H, 9.02; N, 10.44%).

(b) **Free Base Melting at 166-167° (Base B).** (Found: C, 80.53; H, 8.55; N, 10.47. Calculated for $C_{18}H_{24}N_2$: C, 80.72; H, 9.02; N, 10.44%).

Benzoyl compound melting at 280–282° (*Bz*.B). The base was benzoylated in the same way as above, 233 mg. being obtained from 150 mg. of the free base. After extraction with hot alcohol, the residue was recrystallized from glacial acetic acid, m.p. 273–275° (uncorr.) or 280–282° (corr.) (Found: C, 80.23; H, 6.94; N, 5.78. Calculated for $C_{18}H_{20}(NH{\cdot}CO{\cdot}C_6H_5)_2$: C, 80.60; H, 6.80; N, 5.88%).

Attempted Hydrolysis. The benzoyl compound is insoluble in hot concentrated hydrochloric acid and was not hydrolyzed by this reagent at 150–160°, 85% of the sample (77 mg. out of 91 mg.) being recovered unchanged after heating for four hours.

Sulphamide melting at 226–227°. The free base was added to dilute caustic soda and benzenesulphonyl chloride was added to it drop by drop. A sticky mass separated, which gradually turned to crystals on heating over water bath. After separation of the sulphamide by suction, hydrochloric acid was added to the filtrate but no precipitate was formed. The insoluble sulphamide(7) (133 mg. from 83 mg. of the free base), after acidifying with hydrochloric acid, was recrystallized from glacial acetic acid, m.p. 220–221° (uncorr.) or 226–227° (corr.) (Found: C, 65.47; H, 6.19; N, 5.12. Calculated for $C_{18}H_{20}(NH{\cdot}SO_2{\cdot}C_6H_5)_2$: C, 65.61; H, 5.91; N, 5.10%).

Attempted Hydrolysis. The sulphamide was added to a mixture of glacial acetic acid and hydrochloric acid (1:3) and was heated in sealed tube at 150–160° for four hours. The sample was not hydrolyzed: 21 mg. of sulphamide out of 25 mg. was recovered unchanged.

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(7) Yielding of sulphamide, insoluble in alkaline media, is a usual reaction of secondary amines, but the base in question, on analysis, was proved to be primary amine. It was known that some sulphamide of primary amine remained undissolved even in alkaline solution, i.e. the sodium compounds are insoluble in water, differing from the usual ones.