Catalytic Hydrogenation of Amides of α-Hydroxy-Acids.(1)

By Haruomi ÔEDA.

(Received February 13th, 1937.)

Several papers have been published on the reduction of acid amides. Reduction hitherto described are brought about by means of sodium, sodium amalgam or catalytic hydrogenation. The reaction goes along, according to the nature of amides in question and to the mode of reduction adopted, in two different directions as follows:

(I)(2) Amides are converted into alcohols, amino-groups being detached as ammonia:

$$R{\cdot}CO{\cdot}NH_2 \xrightarrow{4H} R{\cdot}CH_2{\cdot}OH + NH_3,$$

or (II)(3) converted into amines, with the formation of water:

$$R{\cdot}CO{\cdot}NH_2 \xrightarrow{4H} R{\cdot}CH_2{\cdot}NH_2 + H_2O.$$

Recently H. Adkins and B. Wojcik(4) have succeeded in preparing various amines by catalytic hydrogenation of amides with such a fair yield as had not been recorded in preceding reports. In unsubstituted amides, it is reported that the combined yields of primary and secondary amines amounted to 80–95%.

The present study was tried with the object of obtaining α-amino-alcohols from amides of α-hydroxy-acids in the same experimental conditions as in the works of Adkins. Hydrogenation was carried out in the presence of copper-chromium oxides at the temperature of 250°, initial pressure of hydrogen being 100–110 atmospheres at room temperature and dioxane was used as reaction medium. The present results carried out with two aliphatic amides (lactamide and leucic acid amide), however, are contrary to the expectation; and they never gave rise to α-amino-alcohols.

---

(1) Studies on Hydroxy-acids and their Derivatives. V.

(2) Guareschi, *Ber.*, **7** (1874), 1462; Bouveault and Blanc, *Compt. rend.*, **138** (1904), 148.

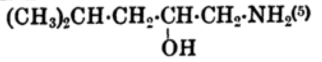
(3) Guerbet, *Chem. Zentr.*, **70** (1899), II, 623; Sabatier and Maihe, *Ann. chim.*, [8], **16** (1909), 70.

(4) *J. Am. Chem. Soc.*, **56** (1934), 2419. Adkins described one case of hydroxy-amide. γ-Hydroxy-valeramide, on hydrogenation, gave some 4-hydroxy-1-aminopentane, while for the most part, it was recovered as valerolactone.

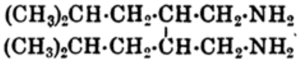
From both amides, neutral as well as basic substances were isolated by distillation of hydrogenated products. The former were found to be propylene glycol and isohexylene glycol, which were identified as such by preparing their phenylurethanes.

From leucic acid amide, an amine was obtained, whose boiling point is almost the same as that of the corresponding amino-alcohol. But the base easily solidifies (m.p. 62–64°) and the properties of its derivatives are not concordant with those of the amino-alcohol as shown in Table 1.

Table 1.

	HCl salt decomp. p.	Pt double choride decomp. p.	Benzoyl comp. m.p.	Picrate decomp. p.
Amine from C_6-amide	over 330°	over 330°	223–224° (corr.)	about 245°
 $\begin{array}{l}(CH_3)_2CH\cdot CH_2\cdot \underset{\mid}{C}H\cdot CH_2\cdot NH_2\\ \qquad\qquad\quad OH\end{array}$ (5)	175°	215°	128°	—

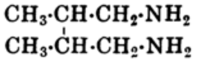
The analytical results of the free base and of every derivative tabulated closely resemble the value calculated for $C_6H_{13}\cdot NH_2$, but the base, viewed from its properties, can never be regarded as isohexylamine (e.g. discrepancy of boiling points: the difference attains to 100°). Molecular weight of the free base, determined by Rast's method, is equivalent nearly to the double that of hexylamine. From these facts, the base is concluded to be the following diprimary-diamine:



$$\begin{array}{l}(CH_3)_2CH\cdot CH_2\cdot CH\cdot CH_2\cdot NH_2\\ \qquad\qquad\qquad\quad \mid\\ (CH_3)_2CH\cdot CH_2\cdot CH\cdot CH_2\cdot NH_2\end{array}$$

2,3-Di-isobutyl-tetramethylene diamine.

From lactamide a liquid base was obtained. As it could not be isolated as hydrochloride in crystalline state, the base was converted into picrate. But the picrate was found to be a mixture and an attempt was made to separate them by recrystallisation from hot glacial acetic acid. The base (A in Table 2) of the picrate less soluble in the hot solvent was identified as the following diprimary-diamine by converting it into benzoyl compound:



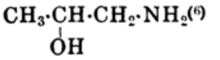
$$\begin{array}{l}CH_3\cdot CH\cdot CH_2\cdot NH_2\\ \qquad\quad \mid\\ CH_3\cdot CH\cdot CH_2\cdot NH_2\end{array}$$

2,3-Dimethyl-tetramethylene diamine.

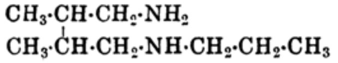
---

(5) Mousset, *J. Chem. Soc.*, **82** (1902), I, 254; Kanao, *J. Pharm. Soc. Japan*, **49** (1929), 173.

Table 2.

		Picrate decomp. p.	Benzoyl comp. m.p.	Pt double chloride decomp. p.
Amine for C_3-amide	A	over 260°	227–228° (corr.)	—
	B	about 238°	—	265–270°
 $CH_3\cdot\underset{OH}{CH}\cdot CH_2\cdot NH_2$(6)		142°	87°	195°

The other base B, whose picrate is more soluble, could not be definitely determined, as it does not give solid benzoyl compound, but the analytical data of the picrate as well as of the platinum double chloride coincide with those of the following primary-secondary-diamine:



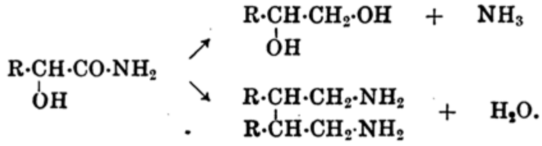
$$\begin{array}{l} CH_3\cdot CH\cdot CH_2\cdot NH_2 \\ CH_3\cdot CH\cdot CH_2\cdot NH\cdot CH_2\cdot CH_2\cdot CH_3 \end{array}$$

N-Propyl-2,3-dimethyl-tetramethylene diamine.

No information of these diamines was found in literature. They are the first substances obtained, which belong to 2,3-dialkyl derivatives of tetramethylene diamine.

From both amides, besides glycol and diamine, the higher boiling fractions were obtained in considerable quantity. All attempts to prepare crystalline derivatives from these fractions were unsuccessful.

The above hydrogenation can be regarded as the two known types of reduction of amides occurring side by side:



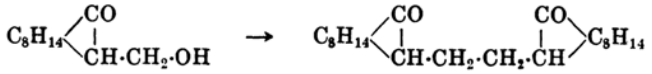
$$R\cdot\underset{OH}{CH}\cdot CO\cdot NH_2 \begin{array}{l} \nearrow\ R\cdot\underset{OH}{CH}\cdot CH_2\cdot OH \quad + \quad NH_3 \\ \searrow\ \begin{array}{l} R\cdot CH\cdot CH_2\cdot NH_2 \\ R\cdot CH\cdot CH_2\cdot NH_2 \end{array} \quad + \quad H_2O. \end{array}$$

In reduction to amines, these amides do not give amino-alcohols, but they are transformed into diamines by the elimination of two hydroxyls by further reduction.(7)

---

(6) Peeters, *Rec. trav. chim.*, **20** (1901), 264; Gabriel and Ohle, *Ber.*, **50** (1917), 808.

(7) An example of the similar condensation, taking place in hydroxy-groups, is described in the formation of bis-camphorylethane by the reduction (with sodium) of camphoryl carbinol. Rupe and Ackermann, *Helv. Chim. Acta*, **2** (1919), 221.



Experimental.

Copper-chromium oxide catalyser (containing a little barium) was prepared according to Adkins.(8) Acid amides(9) were mixed with 1/4–1/5 parts of the above catalyser and diluted with four times of its weight of distilled (over sodium) dioxane. The hydrogenation was carried out in the same conditions as described in the previous paper.(10)

Hydrogenated products were separated from catalyser with glass filter and dioxane was removed by distillation through Widmer column. The residue was fractionated in vacuum into several fractions again with the aid of Widmer column.

Hydrogenation of Amide of *l*-Leucic acid.

Amide (m.p. 82–83°) 24 g. (0.18 mol); dioxane 75 c.c.; catalyser 5.0 g.; time of hydrogenation 2.5 hrs. at 245–255°; fractionation:

I	110 – 120° under 14 mm.	4.4 g.
II	120 – 130° ,,	3.2 g.
III	over 140° ,,	7.5 g.

Fraction II has the tendency to solidify instantly in the delivery tube, and to prevent the blockade, hot water must be circulated through the jacket. Fraction III, on the contrary, does not solidify and remains as yellowish viscous fluid even after long standing.

(A) **Neutral Part (Isohexylene glycol).** Fraction I was separated into neutral and basic parts by extracting the acidified mixture with ether as usual. The neutral part distilled at 109–111° under 13 mm. after refractionation. (The same neutral part was also obtained from fraction III by the same treatment.) It was found to be isohexylene glycol and the combined yield amounted to 10 mol%.(11)

Bis-phenylurethane. Prepared from the glycol and phenyl isocyanate by heating at 120–130° for one hour, the urethane being precipitated by adding ligroin. After recrystallisation from ligroin-alcohol, it melted at 116.5–117.5° (corr.), no depression of melting point was observed when mixed with the specimen described in the previous paper, m.p. 117.5° (corr.).(10)

---

(8) *J. Am. Chem. Soc.*, **54** (1932), 1139.

(9) Leucic acid amide: prepared from liquid ammonia and acetone-leucic acid at −33°. Lactamide: from liquid ammonia and ethyl lactate at room temperature. Ôeda, this Bulletin, **11** (1936), 385.

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

(11) The activity of this glycol was not examined owing to its minute quantity. The same glycol obtained in the previous experiment was found to be active. The two glycols show the same boiling range and give the phenylurethane of the same m.p. Rotation was determined in a 1-dm. tube (5 c.c.). $d^{13.5}_{13.5} = 0.9506$; $[\alpha]^{14}_{D} = -0.23°/0.95 = -0.24°$. The sample may be partially racemised during hydrogenation.

(B) **Basic Part.** Hydrochlorides obtained from fractions I and II were combined and evaporated to dryness on water bath and extracted with hot alcohol, when 2.3 g. of the sample remained unextracted.

(a) **Hydrochloride Insoluble in Alcohol (2,3-Di-isobutyl-tetramethylene diamine).** The insoluble hydrochloride was dissolved in a large bulk of hot water, filtered and was concentrated on water bath. During evaporation, a colourless hydrochloride began to crystallise out while still hot before the solution was completely dried up. After being purified by repeated crystallisation, it became, on heating, gradually coloured at 300° but did not decompose up to 330°. (Found: N, 10.46; Cl, 26.00. Calculated for $C_{12}H_{28}N_2 \cdot 2HCl$: N, 10.25; Cl, 25.98%.) Yield 9 mol%.

Platinum double chloride. Insoluble in alcohol. It turned black at 270° but did not decompose up to 330°. (Found: Pt, 32.07. Calculated for $C_{12}H_{28}N_2 \cdot H_2PtCl_6$: Pt, 32.00%.)

Free base. When the insoluble hydrochloride was warmed with an excess of dilute caustic potash, an oil separated out, which crystallised on cooling. The free base thus prepared was dissolved in alcohol, and decolourised with charcoal. By evaporation of the solvent colourless base (m.p. about 60°) was obtained as main product. It can also be recrystallised from ligroin, m.p. 62–64° after drying over caustic soda. (Found: C, 72.24; H, 13.66; N, 14.22. Calculated for $C_{12}H_{28}N_2$: C, 71.94; H, 14.09; N, 14.00%.) *Optical rotation.* Determined in a 1-dm. tube (5 c.c.) containing 0.250 g. of the free base and made up to 5.00 c.c. with alcohol. No rotation was observed. *Molecular weight* (camphor): 208. Calculated for $C_{12}H_{28}N_2$: 202.

Benzoyl compound. To a suspension of the powdered free base in 15% caustic potash, benzoyl chloride was gradually added with constant stirring. An oil formed first, then turned to a crystalline sticky mass, which was separated by suction and washed with hydrochloric acid, sodium bicarbonate solution and finally with water. It melted at 223–224° (corr.) after recrystallisation from alcohol. (Found: C, 76.58; H, 9.26; N, 7.12. Calculated for $C_{26}H_{36}O_2N_2$: C, 76.42; H, 8.88; N, 6.86%.)

Picrate. Obtained by mixing alcoholic solutions of the free base and of picric acid in excess. After recrystallisation from alcohol, it turned black at 240° and decomposed at about 248° with violent evolution of gas. (Found: C, 43.99; H, 5.05; N, 17.27. Calculated for $C_{12}H_{28}N_2 \cdot 2C_6H_3O_7N_3$: C, 43.74; H, 5.20; N, 17.03%.)

(b) **Hydrochloride Soluble in Alcohol (A base left undetermined).** After recrystallisation from a little alcohol, powder of silky luster was obtained, it melted with decomposition at 220–230°. (Found: Cl, 18.94%. It corresponds to a free mono-amine, mol. wt. 151.(12) Owing to the minute quantity of purified sample, further study was given up.

(C) **Higher Fraction.** Fraction III was fractionated through Widmer column. It distilled between 135–180° under 13 mm. and showed no distinct boiling fraction. It was dissolved in hydrochloric acid, and insoluble resinous matter was filtered off. The hydrochloride of the base could not be brought into crystallisation. A ferrocyanate, insoluble in water, was obtained from the above solution, but no further study on this line has been made.

---

(12) Supposing the existence of a prim.-sec.-diamine, similar as in the case of lactamide, its molecular weight (calculated as mono-amine) will be: $\frac{1}{2} C_{18}H_{40}N_2 = 142$.

Hydrogenation of *dl*-Lactamide.

Amide (m.p. 77–78°) 14.5 g. (0.16 mol); dioxane 60 c.c.; catalyser 4.0 g.; time of hydrogenation, 3 hrs. at 240–255°; initial pressure of hydrogen 112 atms.; fractionation:

I	60 – 90°	under 20 mm.	0.9 g.
II	90 – 100°	,,	1.4 g.
III	over 100°	,,	2.2 g.

(A) **Picrates from Fractions I and II.** Obtained from the free base and a little excess of alcoholic picric acid. Yield, 1.9 g. from fraction I, 1.1 g. from II. The picrate is insoluble in water and alcohol, but partly soluble in hot glacial acetic acid. After washing completely with hot alcohol, it was extracted with hot glacial acetic acid, the residue being collected and again extracted with a new bulk of the solvent. The extraction was repeated until the amount of final residue decreased to one-tenth of the initial sample. The final residue so obtained is designated as picrate A. Each extract was cooled, the precipitated picrate being separately collected. The most soluble part (picrate B) was obtained by fractional crystallisation.

(a) **Picrate A.** Pale yellow amorphous powder. It showed no change in appearance up to 230–240°, and thereafter gradually coloured, but did not decompose up to 260°. The result of analysis is not actually identical with the value calculated for the diprimary-diamine. The discrepancy may be due to the incomplete separation of picrate B. (Found: C, 38.64, 38.78; H, 4.00, 3.42; N, 20.02. Calculated for $C_6H_{16}N_2 \cdot 2C_6H_3O_7N_3$: C, 37.61; H, 3.87; N, 19.50%.)

Benzoyl compound. The picrate was transformed into hydrochloride, from which benzoyl compound was prepared with benzoyl chloride in the presence of caustic potash. It separated as an oil, aqueous solution was removed by decantation, and the oil, on rubbing together with a little ether, yielded colourless crystals. Recrystallised from alcohol, it melted at 227–228° (corr.). (Found: C, 74.45; H, 7.46; N, 8.42. Calculated for $C_{20}H_{24}N_2$: C, 74.03; H, 7.47; N, 8.64%.)

(b) **Picrate B.** Yellow crystals. It decomposed at 237–240° with violent evolution of gas. (Found: C, 40.50, 40.34; H, 4.30, 3.70; N, 18.51. Calculated for prim.-sec.-diamine, $C_9H_{22}N_2 \cdot 2C_6H_3O_7N_3$: C, 40.88; H, 4.58; N, 18.17%.) The preparation of benzoyl compound was tried in similar way as above, but it could not be obtained in crystalline state.

Platinum double chloride. Obtained from the syrupy hydrochloride which was prepared from the above purified picrate. It decomposed at 265–270°. (Found: Pt, 34.50. Calculated for $C_9H_{22}N_2 \cdot H_2PtCl_6$: Pt, 34.33%.)

(B) **Glycol.** A little hydrochloric acid was added to another sample of fraction II and a neutral part was collected by extraction with a large bulk of ether. The extract distilled at 77–79° under 8 mm. It was found to be isohexylene glycol by converting it into bis-phenylurethane.

Bis-phenylurethane. Prepared from the glycol and phenyl isocyanate by heating at 120–130° for one hour. After recrystallisation from alcohol, it melted at 145–146° (corr.), alone or in admixture with the specimen (m.p. the same) described in the previous paper.(10)

The present study was carried out in the Chemical Institute, Faculty of Science, Imperial University of Tokyo. The author expresses his sincere thanks to Prof. K. Matsubara for kind inspection of this paper. His best thanks are also due to Dr. Y. Takayama for constant encouragement during this study.