the filtrate, on standing at room temperature, well-shaped, pointed prisms commenced to form which, after recrystallization from methyl alcohol containing a little amyl alcohol, had m. p. 69° and $[\alpha]^{20}D$ 92.8° in water solution. The substance was, therefore, identical with Purves and Hudson's "crystalline gamma-methylfructoside." The ethyl acetate-insoluble substance (B) was again extracted with hot ethyl acetate and the aqueous solution of the insoluble portion was tested with invertase solution. The initial rotation (−35.2°) of the nonreducing solution then dropped rapidly to −64.4° and the solution became strongly reducing. The substance, therefore, must represent the "gamma-methylfructoside (a)" postulated by Purves and Hudson.

Acknowledgment is made to Dr. C. S. Hudson for the invertase samples used in this investigation. The author also wishes to thank Messrs. Walter J. Kauzmann and E. Justin Wilson, Jr., for their helpful assistance in the experimental work.

Summary

1. *d*-Fructosediethylmercaptal reacted at −80° with methyl alcoholic mercuric chloride to give crystalline *d*-fructosedimethylacetal in excellent yield.

2. The same reaction when carried out at 0° or higher temperature gave rise to a partly crystalline material, from which, beside the acetal, the "crystalline gamma-methylfructoside" of Purves and Hudson was isolated. Another constituent obtained from the mixture represented the "gamma-methylfructoside (a)," whose presence in the liquid gamma-methylfructoside mixtures was postulated by the same authors. This substance was hydrolyzed rapidly by invertase.

3. The apparent reaction of the acetal with invertase and yeast was found to be due to the hydrolyzing effect of the acidic media rather than to a genuine enzymotic effect. In solutions buffered to *p*H 7 the action of both invertase and yeast was found to be completely negative.

4. A new mechanism for the reaction of sugar mercaptals with alcoholic mercuric chloride was suggested.

5. Crystalline pentaacetyl *d*-fructosedimethylacetal was prepared.

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Hydrogenation of Hydroxyamides

BY JAMES D. D'IANNI[1] AND HOMER ADKINS

The multiplicity of reactions that may occur when a hydroxyamide reacts with hydrogen under the influence of copper chromite[2] made it seem desirable to investigate rather carefully the nature of the products in the hydrogenation of representative compounds of this type.[3] Oeda failed to obtain amino alcohols by the hydrogenation of α-hydroxyamides.[4]

Monohydroxy Amides.—Five hydroxyamides, in which hydroxyl was in the α, β, γ, δ or ε position with respect to the N-pentamethylenecarbonamido or —C(O)NC_5H_{10} group, were submitted to hydrogenation over copper chromite. The detailed results are given in Table I. A typical reaction was

$$CH_3CHOH(CH_2)_2C(O)NC_5H_{10} \longrightarrow CH_3CHOH(CH_2)_2CH_2NC_5H_{10} + H_2O$$

The yields of the corresponding hydroxyamines were as follows: α, 51%, β, 0%, γ, 79%, δ, 76%, ε, 60%.

In the case of the β-hydroxybutyramide the chief product was N-*n*-butylpiperidine in 78% yield, formed according to the reaction

$$CH_3CHOHCH_2C(O)NC_5H_{10} \longrightarrow CH_3(CH_2)_2CH_2NC_5H_{10} + 2H_2O$$

This reaction is in accord with the well-established labilizing effect toward hydrogenolysis of nitrogen or oxygen substituents in the β-position with respect to each other.[5] A 4% yield of propylpiperidine from a lactamide was also isolated and presumably was formed by the same type of reaction.

Evidence for another type of hydrogenolysis

(1) This investigation was carried out in part while Dr. D'Ianni was a teaching assistant of the University and in part while he was a Procter and Gamble Fellow in 1937–1938.

(2) Groger first prepared the compound $CuCr_2O_4$ which he called copper chromite [Groger, *Z. anorg. Chem.*, **58**, 412 (1908); **76**, 30 (1912). When this compound was first reported by Connor, Folkers and Adkins as a catalyst for hydrogenation (for references on its early use see Adkins, *Ind. Eng. Chem., News Ed.*, **15**, 548 (1937)], it was referred to by the same name. In later papers from this Laboratory the catalyst has been called "copper–chromium oxide," since in some cases, a change in composition occurred during the course of a hydrogenation. However, W. A. Lazier and others prefer the use of the more convenient term, copper chromite (Lazier, U. S. Patents 1,746,782, 1,746,783 (1930), 1,964,000 (1934)).

(3) For references to earlier work by Wojcik, Paden, Sauer and Adkins see THIS JOURNAL, **60**, 402 (1938).

(4) Oeda, *Bull. Chem. Soc. Japan*, **12**, 121–127, 377–381 (1937).

(5) Adkins, "Reactions of Hydrogen, etc.," University of Wisconsin Press, Madison, 1937, p. 88.

TABLE I

HYDROGENATION OF AMIDES[a]

Amide	G. catalyst (moles amide)	% yield of products	
N-Pentamethylene-lactamide	6 $CuCr_2O_4$ (0.2)	51	1-Piperidinopropanol-2
		10	1,2-Di-piperidinopropane
		10	Propanediol-1,2
		10	Piperidine
		4	N-*n*-Propylpiperidine
	3 Ni(R) (0.1)	27	1-Piperidinopropanol-2
		18	Propanediol-1,2
		38	Piperidine
		23	Unchanged amide
N-Pentamethylene-β-hydroxy butyramide	3 $CuCr_2O_4$ (0.1)	78	N-*n*-Butylpiperidine
		12	Piperidine
	3 Ni(R) (0.1)	86	N-Pentamethylenebutyramide
		12	Piperidine
N-Pentamethylene-γ-hydroxy valeramide	4 $CuCr_2O_4$ (0.1)	79	5-Piperidinopentanol-2
		6	1,4-Dipiperidinopentane
		7	Piperidine
	5 Ni(R) (0.15)	15	5-Piperidinopentanol-2
		58	γ-Valerolactone
		44	Piperidine
		18	Unchanged amide
N-Pentamethylene-Δ-hydroxy caproamide	4 $CuCr_2O_4$ (0.1)	76	6-Piperidinohexanol-2
		14	1,4-Dipiperidinohexane
		4	Piperidine
	3 Ni(R) (0.1)	34	6-Piperidinohexanol-2
		29	Piperidine
		15	Δ-Caprolactone
		14	Unchanged amide
N-Pentamethylene-ε-hydroxy heptanoamide	2 $CuCr_2O_4$ (0.05)	60	7-Piperidinoheptanol-2
		26	Heptanediol-1,6
		14	1,6-Dipiperidinoheptane
		9	Piperidine
N-Pentamethylene caproamide	3 Ni(R) (0.1)	83	Unchanged amide
		7	Piperidine
		5	Hexanol-1
		6	N-*n*-Hexylpiperidine
Di-N-*n*-amyl-malamide	16 $CuCr_2O_4$ (0.4)	32	N-*n*-Amylpyrrolidone
		30	Di-*n*-amylamine
		14	N-*n*-Amylsuccinimide
		12	Di-N-*n*-amylsuccinamide
		9	N-*n*-Amylpyrrolidine
		7	*n*-Amylamine
Di-N-*n*-amyl-tartaramide	15 $CuCr_2O_4$ (0.25)	20	Di-*n*-amylamine
		11	N-*n*-Amylpyrrolidine
		8	*n*-Amylamine
2,2-Dimethyl-5-phenyl-4-oxazolidone	5 $CuCr_2O_4$ (0.15)	35	Mandelamide
		29	Phenylethylene glycol
		3	Phenethyl alcohol
		47	Diisopropylamine (as hydrochloride)

[a] The hydrogenations were made at 225° with the nickel catalyst and at 250–260° for copper chromite, except for the oxazolidone, for which 210–215° was used. The hydrogenations were made in dioxane solution (0.1 mole of amide, 40 ml. of dioxane), the time of reaction for nickel being five to eight hours and with copper chromite one to four hours.

was found in the glycols from each of the five amides, *i. e.*

$$CH_3CHOHC(O)NC_5H_{10} \longrightarrow CH_3CHOHCH_2OH + C_5H_{10}NH$$

Piperidine was isolated from each of the reaction mixtures and the glycol was isolated from the products of two of the amides. It is possible that this type of hydrogenolysis is the primary reaction with all the amides and that the hydroxyamine is actually formed by the interaction of the amine and the glycol, *i. e.*

$$CH_3CHOHCH_2OH + C_5H_{10}NH \longrightarrow CH_3CHOHCH_2NC_5H_{10} + H_2O$$

There exist no data, so far as we know, which show conclusively the course of the reaction or reactions by which an amine is formed from an amide.

Diamines were isolated in yields of 6 to 14% from the products of three amides. These presumably were formed by a reaction similar to that given just above.

$$CH_3CHOHCH_2NC_5H_{10} + C_5H_{20}NH \longrightarrow CH_3CH(NC_5H_{10})CH_2NC_5H_{10} + H_2O$$

Raney nickel, as compared to copper chromite, is relatively inactive for the hydrogenation of amides to amines. A fair comparison between the catalysts has not been made, as copper chromite has been used at 250 to 260° while Raney nickel has been used at 225°. Raney nickel in one case brought about a rather violent reaction between dioxane and hydrogen at 250° so that we have since hesitated to run hydrogenations with Raney nickel in dioxane above 225°. However, even at 225° Raney nickel has induced a considerable hydrogenation of the hydroxyamides. The yields of amino alcohols were in three cases 15, 27 and 34%, as compared with 79, 51 and 76% when copper chromite was used with the same amides at 250°. In each of the cases with Raney nickel, considerable amounts of unchanged amide remained in the reaction mixture, even after periods of reaction two or three times as long as required for complete hydrogenation with copper chromite.

The greater ease of hydrogenation over nickel of hydroxyamides, as compared with amides containing no hydroxyl group, is shown by the fact that 83% of the caproamide and only 14% of the Δ-hydroxycaproamide were recovered after each was hydrogenated for eight hours. A similar difference in the rate of reaction of the amides over copper chromite does not exist.

The real value of Raney nickel in the hydrogenation of amides is indicated by the result of its use with the β-hydroxyamide. The hydroxyl group was removed and the amide group was unchanged, *i. e.*

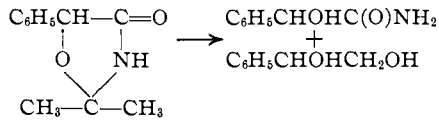
$$CH_3CHOHCH_2C(O)NC_5H_{10} \longrightarrow CH_3CH_2CH_2C(O)NC_5H_{10} + H_2O$$

The butyramide was obtained in 86% yield while with copper chromite, as noted above, the amide group was also hydrogenated and butylpiperidine obtained in 78% yield.

Another difference between the products isolated from a hydrogenation over nickel as compared with those over copper chromite, is the presence of lactones from the γ- and Δ-hydroxyamides. This may be due to the longer period of heating necessary with nickel or to the activity of copper chromite for the hydrogenation of lactones to glycols.

Hydroxy Diamides.—Hydrogenation of N-amylmalamides and N-amyltartaramides over copper chromite gave a mixture. Six products were isolated from the malamide while only three of the many formed were isolated from the tartaramide. The general course of the reactions is rather clearly indicated by the products from the malamide. The first step is apparently the loss of the hydroxy group to give a succinamide. The latter then goes to a succinimide, a pyrrolidone and a pyrrolidine, as reported by Paden,[6] with incidental formation of amyl- and diamylamines.

The hydrogenation of the cyclic amide, 2,2-dimethyl-5-phenyl-4-oxazolidone, over copper chromite gave interesting results, for the oxazolidone ring was cleaved at three different linkages, *i. e.*



Mandelamide and the glycol were formed in similar amounts, the latter was in part converted to phenethyl alcohol. Almost one-half of the isopropyl groups were recovered as diisopropylamine.

An amide derived from a tetrahydroxy acid such as mucic acid offers the possibility of many different reactions involving hydrogenation and hydrogenolysis. Twelve different products have actually been characterized, as listed in Table II. Attempts were made in early experiments to hydrogenate the compound with Raney nickel at 175–200° and with copper chromite at 225–235°. Acetylpiperidine, 1,4-dipiperidinobutane and piperidine were isolated from these experiments. The weight of these three products obtained from 34 g. of the amide was 7 g. after hydrogenation for ten hours over Raney nickel or 8 g. after four to five hours over copper chromite. Since the larger share of the products so obtained could not be separated or characterized, subsequent hydrogenations were made at 250° for five hours over copper chromite.

(6) Paden and Adkins, THIS JOURNAL, **58**, 2487 (1936).

TABLE II

PRODUCTS FROM DI-N-PENTAMETHYLENE MUCAMIDE

	Products	G.[a]	B. p. °C.	Mm.	$n^{25}D$
I	Piperidine	23	105–110	740	1.4368
II	N-Ethylpiperidine	10	125–135	740	1.4413
III	N-*n*-Butylpiperidine	7.5	165–175	740	1.4474
IV	2-Piperidinoethanol-1	7	70–80	8	1.4602
V	N-Acetylpiperidine	4.2	80–95	8	1.4682
VI	1,2-Di-piperidinoethane	12	110–120	8	1.4786
VII	6-Piperidinohexanol-1	11.5	125–135	8	1.4820
VIII	1,4-Di-piperidinobutane	44	140–150	8	1.4846
IX	1,6-Di-piperidinohexane	12.5	113–123	1	1.4859
X	1,6-Di-piperidinohexanol-2	22	127–137	1	1.4924
XI	1,6-Di-piperidinohexanediol-2,5	16	150–160	1	1.4990
XII	Di-N-pentamethyleneadipamide	11	160–170	1	1.5021

[a] These figures represent the weights of the various fractions obtained from the products of the hydrogenation of 1 mole of the amide (344 g.). As shown in the experimental part these figures do not represent pure compounds. Ninety-nine grams of water was formed. The intermediate fractions and mechanical losses during fractionation amounted to 77 g. The hydrogenations were made at 250–260° under 200–350 atm. during periods of five hours each using 40 g. of copper chromite with 0.5 mole of amide dissolved in 400 ml. of dioxane. One mole of amide took up 6.5 moles of hydrogen.

A reasonable scheme for the formation of the various products identified is given in Fig. 1. The formulas of two hypothetical intermediates not isolated are indicated in brackets.

The carbon chain of mucamide is broken between carbon atoms 2 and 3. In no case was a product isolated which contained an uneven number of carbon atoms from the acid radical. That is to say, rupture did not occur between carbons 1 and 2, or 3 and 4. This is a striking fact for in the hydrogenolysis of sugars the change occurs very largely between carbons 3 and 4, with small amounts of one and two carbon fragments.[7] The yield of products (0.24 mole) containing two carbon atoms was almost exactly equal to the yield of products containing four carbon atoms (0.25 mole). The yield of products (0.29 mole) containing the uncleaved chain of six carbon atoms was a little greater than the yield of cleavage products of either of the two types.

As a result of hydrogenolysis between carbon

(7) Zartman and Adkins, THIS JOURNAL, **55**, 4559 (1933). *Cf.* for example Horst and Balle, German Patent 624,443, January 21, 1936.

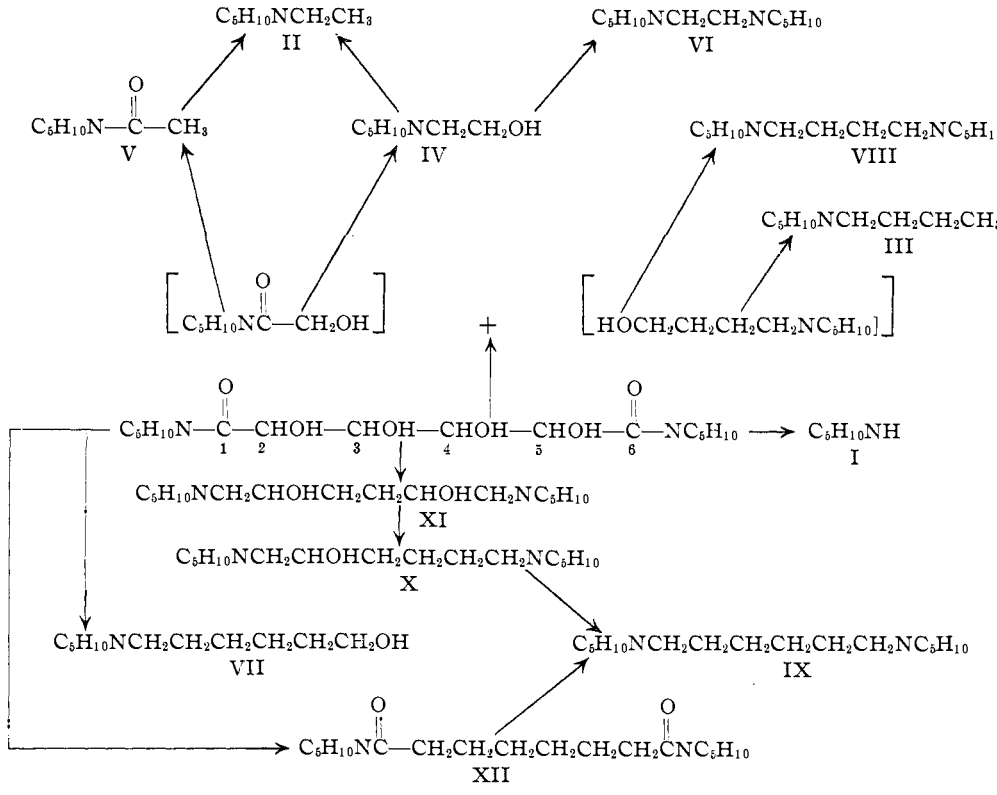


Fig. 1.—Hydrogenolysis of N-pentamethylenemucamide.

atoms 2 and 3 of the mucamide, acetylpiperidine, V, ethylpiperidine, II, and β-hydroxylethylpiperidine, IV, would be formed readily by hydrogenation. The reaction of IV with piperidine would give dipiperidinoethane, VI. Piperidine, I, as has been shown above, is a normal product of the hydrogenolysis of pentamethylene substituted amides. The fragment containing carbon atoms 3, 4, 5 and 6 would by similar transformations give butylpiperidine, III, and dipiperidinobutane, VIII. The compounds listed as VII to XII inclusive would result from the hydrogenolysis of oxygen or piperidino groups from the six carbon chain of the amide. There is no conclusive evidence for the position of the hydroxyl groups shown in XI and X. The hydroxyls are believed to be situated as shown for these are the positions in which hydroxyl groups are most stable toward hydrogenolysis.[5] Compounds would not be expected in which hydroxyl groups were beta to each other or to an amino group. Hydroxyls would therefore be found on carbon atoms 2 and (or) 5.

Experimental Part

The hydrogenations usually were made either in a vessel having a void of 270 ml. or one having a void of 1880 ml. The preparation of catalysts and procedure have been previously described.[5]

The separation of products was based upon fractional distillation of the products. In most cases a "modified Widmer" column having a spiral 15 cm. in length with 12 turns of the helix was used.[8] Spirals with greater or less pitch in the helix were occasionally advantageous. The usual rate of fractionation was 6 to 9 g. per hour, the conduct of the fractionation being as previously described.[8] In general it has been found advantageous to make a rough separation of the products into fractions boiling over 20 or 30° and then carefully fractionate the fractions so obtained. This was particularly important in separating the products from the mucamide.

Amines distilling over with dioxane were recovered as hydrochlorides and in most cases were then converted to the free amines and again fractionated. The same procedure was used for separating amines from glycols or amides having similar boiling points. Amines were characterized by boiling points, neutral equivalents and the formation of solid derivatives (see Table III). In a few cases it was not feasible to separate the components in the quantity of a mixture available. In these cases the proportion of the components of a mixture was estimated from the results of titration with acid, and the presence of each component established by the formation of solid derivatives.

Many of the compounds referred to in this paper have not hitherto been described in the literature. The ana-

(8) Martha E. Smith and Adkins, THIS JOURNAL, **60**, 657 (1938).

lytical data and certain physical properties for thirty such compounds are given in Table III.

Certain derivatives have been described previously: 1-piperidinopropanol-2, b. p. 67–68° (7 mm.), $n^{25}D$ 1.4586, and its methiodide, m. p. 147° (from dry ethanol–ether);[9] 1,2-dipiperidinopropane, b. p. 120–123° (7 mm.);[10] picrate of N-*n*-butylpiperidine, m. p. 132–133°;[11] 3,5-dinitrobenzoate of hexanol-1, m. p. 59–60°;[12] picrate of N-*n*-hexylpiperidine, m. p. 108–109° (from ethanol);[13] N-*n*-amylpyrrolidine, b. p. 76–82° (25 mm.), and its picrate, m. p. 119–120° (from ethanol);[14] chloroplatinate of N-*n*-amylpyrrolidine, m. p. 150° (from ethanol);[15] hydrochloride of diisopropylamine, m. p. 209–211°;[16] phenylethylene glycol, b. p. 115–125° (1 mm.), m. p. 69–70° (from benzene), dibenzoate of phenylethylene glycol, m. p. 95–96° (from dilute alcohol);[17] α-naphthylurethan of phenethyl alcohol, m. p. 118–119° (from petroleum ether).[18]

N-*n*-Butylpiperidine (3 g., b. p. 165–175° at 740 mm.) was prepared by the hydrogenation of N-pentamethylenebutyramide (4.7 g.) in 15 ml. of dioxane, with copper chromite at 260° under 300 atm. within one hundred minutes. 7-Piperidinoheptanol-2 (1.2 g.) and 1,6-dipiperidinoheptane (1.1 g., b. p. 127–130°) were obtained by hydrogenating N-pentamethylene-ε-hydroxyheptanoamide (3 g.) with piperidine (2.6 g.) in 14 ml. of dioxane and 1 g. of copper chromite at 260° for 4.3 hours under 300 atm. The picrate of the diamine (m. p. 203–205° dec.) (from ethanol) was made. 1,4-Dipiperidinopentane (1.4 g., b. p. 118–119° at 1 mm., $n^{25}D$ 1.4806) was obtained by heating 5-piperidinopentanol-2 (2.0 g.) with piperidine (1.7 g.) in 10 ml. of dioxane and 1 g. of copper chromite for three and one-half hours at 250° under a pressure of 150 atm. of hydrogen. The picrate, m. p. 168–169° (from ethanol), as well as those given above were used for comparison and mixed melting points.

The fractions listed in Table II were characterized and estimated as follows: I. The neut. equiv. was 98 (calcd. 85). Piperidine was characterized by its addition product with carbon bisulfide, m. p. 170°. II. The neut. equiv. was 110 (calcd. 113) and the amine gave a picrate, m. p. 173–174°, which showed no lowering when the compound was mixed with an authentic sample.[19] III. The neut. equiv. was 156 (calcd. 141) with a picrate of m. p. 130–131°. IV. The neut. equiv. was 154 (calcd. 129) and the compound gave a hydrochloride of the benzoate, m. p. 173–174° (from absolute alcohol–ether), which was compared with an authentic sample.[20,21] The amine could not be separated by fractionation from the acetylpiperidine with which it formed a constant boiling mixture. The separation was made after acidifying the mixture with hydrochloric acid using congo red as an indicator. The amide, acid and water were then evaporated under 10 to 20 mm., the amine recovered from the salt showed a b. p. of 69–70° (9 mm.), $n^{25}D$ 1.4700. V. As indicated above acetylpiperidine could not be separated by fractionation from piperidinoethanol. Fraction V contained about 20% of the amine. The purest sample of the amide had a b. p. 90–91° (8 mm.), $n^{25}D$ 1.4775, and was characterized by hydrolysis to piperidine and acetic acid which were characterized in the usual way. VI. The neutral equivalent indicated that this fraction was quite impure, *i. e.*, 147 compared with 98. The dipiperidinoethane was converted into its methiodide, m. p. 246°, a hydrochloride of the correct analysis, m. p. over 323°,[22] and a picrate, m. p. 225–227° (dec.), were also obtained.[23] VII. The fraction showed the correct analysis for nitrogen and approximately the correct neutral equivalent (181 compared with 185). Solid derivatives could not be obtained. VIII. A sample purified from this fraction had a b. p. 98–99° (1 mm.) and $n^{25}D$ 1.4826, and neut. equiv. of 114 (calcd. 112). A hydrochloride, m. p. 309°, was compared with an authentic sample. The m. p. of picrate was 185–186° (from alcohol).[24] IX. A sample purified from this fraction had a b. p. 114–118° (1 mm.), $n^{25}D$ 1.4859 and a neut. equiv. of 131 (calcd. 126). The methiodide, m. p. 250–253°, showed the correct analysis.[25] X. A sample purified from this fraction, b. p. 125–130° (1 mm.), $n^{25}D$ 1.4949, showed a high neut. equiv. (150 as compared with 134), but gave 1.04 and 1.09 moles of methane in a Zerevitinoff analysis. A picrate, m. p. 138–139°, and a hydrochloride, m. p. 189–191°, were obtained. XI. The neutral equivalent of this fraction indicated the presence of a neutral compound to the extent of 30%. This impurity was presumably dipentamethyleneadipamide. The fraction was therefore hydrogenated in dioxane at 250° over copper chromite. The product, b. p. 150–160° (1 mm.), $n^{25}D$ 1.4943, showed a neut. equiv. of 148 (calcd. 142) and gave a dipicrate, m. p. 170–173° (from alcohol). There was also obtained 1,6-dipiperidinohexane, b. p. 110–120° (1 mm.), resulting from the hydrogenation of the dipentamethyleneadipamide. XII. This fraction was approximately equal parts amide and the glycol of XI, so that it was hydrogenated as above and the resulting 1,6-dipiperidinohexane characterized as the dimethiodide, m. p. 250–253° (from alcohol and ether).

Preparation of Esters.—Diethyl mucate,[26] m. p. 167–168° after one recrystallization from ethanol, was obtained in yields of 76 to 90% through the reaction of mucic acid (50 g.) and dry ethanol (800 ml.). Hydrogen chloride was passed in for three to four hours, the mixture refluxed with stirring, filtered hot and the ester allowed to crystallize out. The higher yields were obtained using four times the quantities selected above, and making allowance for the recovered acid.

Diethyl tartrate (b. p. 150–155° at 13 mm.)[27] in yields of 55 to 67% was made similarly except that the product was distilled.

(9) Laun, *Ber.*, **17**, 680 (1884).
(10) Aschan, *ibid.*, **32**, 991 (1899).
(11) Von Braun, *ibid.*, **40**, 3930 (1907).
(12) Malone and Reid, THIS JOURNAL, **51**, 3424 (1929).
(13) Von Braun and Buckman, *Ber.*, **64**, 2615 (1931).
(14) Von Braun, *ibid.*, **49**, 2641 (1916).
(15) Ochiai and Tsuda, *ibid.*, **67**, 1011 (1934).
(16) Skita and Keil, *ibid.*, **61**, 1457 (1928).
(17) Zincke, *Ann.*, **216**, 295 (1883).
(18) Bickel and French, THIS JOURNAL, **48**, 747 (1926).
(19) Evans, *J. Chem. Soc.*, **71**, 524 (1897).
(20) Von Braun, Braunsdorf and Rath, *Ber.*, **55**, 1674 (1922).
(21) Pyman, *J. Chem. Soc.*, **93**, 1801 (1908).
(22) Brühl, *Ber.*, **4**, 740 (1871).
(23) Knorr, Hörlein and Roth, *ibid.*, **38**, 3139 (1905).
(24) Bruno Wojcik, Ph.D. Thesis, Wisconsin, 1934.
(25) Von Braun, *Ber.*, **43**, 2862 (1910).
(26) Fischer and Speirer, *ibid.*, **28**, 3254 (1895).
(27) Anschütz, *ibid.*, **18**, 1399 (1885).

TABLE III

ANALYTICAL DATA ON PREVIOUSLY UNREPORTED COMPOUNDS

Compound	Formula	$n^{25}D$	B. p. or m. p. °C.	Mm.	Analyses, % Calcd.	Found
N-Pentamethylene lactamide	$C_8H_{15}NO_2$	1.4850	105–108	2	8.92 N	8.78
			128–129	7		
N-Pentamethylene-β-hydroxybutyramide	$C_9H_{17}NO_2$	1.5065	118–123	7	8.19 N	8.35
			84–88	1		
N-Pentamethyl-Δ-hydroxycaproamide	$C_{11}H_{21}NO_2$	1.4910	135–140	1	7.04 N	7.07
N-Pentamethylene-ε-hydroxyheptanoamide	$C_{12}H_{23}NO_2$	1.4857	145–148	0.5	6.57 N	6.53
Di-N-*n*-amyl malamide	$C_{14}H_{28}N_2O_3$		146		10.29 N	10.45
Di-N-*n*-amyl tartaramide	$C_{14}H_{28}N_2O_4$		194–195		9.72 N	9.84
Di-N-*n*-amyl succinamide	$C_{14}H_{28}N_2O_2$		180–181		10.94 N	11.16
N-Pentamethylene butyramide	$C_9H_{17}NO$	1.4750	105–109	7	9.03 N	8.92
Di-N-pentamethylene mucamide	$C_{16}H_{28}N_2O_6$		231 (dec.)		8.14 N	8.03
1,2-Di-piperidinopropane dipicrate	$C_{25}H_{32}N_8O_{14}$		171–172		16.77 N	16.72
5-Piperidino-pentanol-2	$C_{10}H_{21}NO$	1.4698	107	6	8.19 N	8.15
5-Piperidino-pentanol-2 picrate	$C_{16}H_{24}N_4O_8$		97–98		14.00 N	14.22
1,4-Di-piperidinopentane	$C_{15}H_{30}N_2$	1.4806	118–119	1	11.76 N	11.70
1,4-Di-piperidinopentane dipicrate	$C_{27}H_{36}N_8O_{14}$		168–169		16.09 N	16.13
6-Piperidino-hexanol-2	$C_{11}H_{23}NO$	1.4720	123–125	7	7.57 N	7.76
6-Piperidino-hexanol-2 picrate	$C_{17}H_{26}N_4O_8$		86–89		13.53 N	13.55
1,5-Di-piperidinohexane	$C_{16}H_{32}N_2$	1.4810	122–123	0.5	11.11 N	10.91
1,5-Di-piperidinohexane dipicrate	$C_{28}H_{38}N_8O_{14}$		166–167		15.78 N	15.89
7-Piperidino-heptanol-2	$C_{12}H_{25}NO$	1.4729	105–106	1	7.04 N	6.88
7-Piperidino-heptanol-2 picrate	$C_{18}H_{28}N_4O_8$		62–64		13.08 N	12.98
1,6-Di-piperidinoheptane	$C_{17}H_{34}N_2$	1.4808	127–130	1	10.53 N	10.37
1,6-Di-piperidinoheptane dipicrate	$C_{29}H_{40}N_8O_{14}$		203–205 (dec.)		15.47 N	15.62
1,4-Di-piperidinobutane dipicrate	$C_{26}H_{34}N_8O_{14}$		185–186		16.42 N	16.52
1,6-Di-piperidino-hexanol-2	$C_{16}H_{32}N_2O$	1.4949	125–130	1	10.45 N	10.38
1,6-Di-piperidino-hexanol-2 dipicrate	$C_{28}H_{38}N_8O_{15}$		138–139		15.43 N	15.65
1,6-Di-piperidino-hexanol-2 dihydrochloride	$C_{16}H_{34}N_2OCl_2$		189–191		20.82 Cl	20.6
1,6-Di-piperidino-hexanediol-2,5	$C_{16}H_{32}N_2O_2$	1.4943	150–160	1	9.86 N	9.81
N-Pentamethylene β-(β′-hydroxybutyryl)-hydroxybutyramide	$C_{13}H_{23}NO_4$	1.4896	105–110	1	5.45 N	5.97
N-Pentamethylene α-(α′-hydroxyisobutyryl)-hydroxy-isobutyramide	$C_{13}H_{23}NO_4$	1.4651	108–108.5	1	5.45 N	5.43
1,6-Di-piperidino-hexanediol-2,5 dipicrate	$C_{28}H_{38}N_8O_{16}$		170–173		15.09 N	15.24

Diethyl malate[28] (471 g., b. p. 120–130° at 13 mm. from 500 g. acid) was prepared similarly except that about 60% of the volume of the alcohol used was distilled off, replaced with dry ethanol and the esterification repeated.

Ethyl lactate (80 g., b. p. 83–84° at 50 mm.) was made through the reaction of dry ethanol (500 ml.), lactic acid (250 g. of 85% acid) in carbon tetrachloride (250 ml.) for twenty-four hours using an automatic separator which returned the heavier liquid to the flask. Additional ethanol was added and the refluxing continued as long as water was formed.

Ethyl β-hydroxybutyrate (b. p. 64–65° at 7 mm.), ethyl γ-hydroxyvalerate (b. p. 55–60° at 0.5 mm.), ethyl ε-hydroxyheptoate (b. p. 89–91.5° at 0.5 mm., $n^{25}D$ 1.4309) and Δ-caprolactone (b. p. 95–97° at 8 mm., $n^{25}D$ 1.4470) were made by the hydrogenation in ethanol of the corresponding keto esters.[29] Copper chromite at 150° was used for acetoacetic ester while Raney nickel at 125–130° was used in the other cases.

Ethyl ε-ketoheptoate (18 g., b. p. 110–113° at 7 mm., $n^{25}D$ 1.4385) was prepared by the hydrolysis of α-acetyl-Δ-cyanovaleric ester (33.5 g.) during eight hours of refluxing with 20% hydrochloric acid (175 ml.). The solution was cooled, saturated with ammonium sulfate, extracted nine times with ether, the solution dried over anhydrous sodium sulfate and the ether distilled. The residue was taken up in 200 ml. of dry ethanol and filtered. The crude acid was esterified in 100 ml. of carbon tetrachloride for twelve hours using an automatic separator, and the ester separated by fractionation.

The α-acetyl-Δ-cyanovaleric ester (b. p. 85–91° at 1 mm.) used in the above preparation was prepared as by Derick and Hess[30] but the yields were about one-fourth that reported by these investigators.

Ethyl Δ-ketocaproate[31] (161 g., b. p. 98–99° at 9 mm.) was made from α-acetylglutaric ester (274 g.) by refluxing with 500 ml. of 4 *N* hydrochloric acid for nine to ten hours. The Δ-ketocaproic acid (142 g., b. p. 103–107° at 1 mm.) obtained by fractionation was esterified in 250 ml. of ethanol and 125 ml. of carbon tetrachloride for six hours as in the preparation of the ethyl ε-ketoheptoate.

Preparation of Amides.—The N-pentamethylene amides of β-hydroxybutyric and ε-hydroxyheptanoic acids were made in 60% yields by heating the corresponding

(28) Wislicenus, *Ber.*, **25**, 2448 (1892).

(29) Connor, Cramer and Adkins, THIS JOURNAL, **52**, 5192 (1930

(30) Derick and Hess, *ibid.*, **40**, 547 (1918).

(31) Isbell, Wojcik and Adkins, *ibid.*, **54**, 3685 (1932).

ethyl esters (0.5 mole) with piperidine (1.0 mole) for four hours at 200° under hydrogen. N-Pentamethylene-Δ-hydroxycaproamide was made in the same way in 86% yield except that caprolactone was used instead of an ethyl ester. The b. p. and refractive index of the pentamethylene β-hydroxybutyramide are b. p. 118–123° (7 mm.), and $n^{25}D$ 1.5065, and not as previously given.[32]

N-Pentamethylene lactamide, di-N-*n*-amyl malamide, and di-N-*n*-amyl tartaramide were made by refluxing the ethyl ester of the acid (0.5 mole) with a 10% excess of piperidine or amylamine. The yields of the lactamide were 70 to 80% after twenty hours, 87% after three hours for the malamide and 98% after five hours for the tartaramide. The amides were recrystallized from dilute alcohol.

Di-N-pentamethylene mucamide (m. p. 231 dec.) was obtained in quantitative yield by gently heating and stirring a mixture of diethyl mucate (57 g.) with piperidine (40 g.) for a few minutes. The product was washed with ether and alcohol but was not recrystallized.

N-Pentamethylene caproamide (b. p. 95–99° at 1 mm., $n^{25}D$ 1.4725) was made in 81% yield by heating caproic acid (29 g.) and piperidine (21 g.) in dioxane (48 ml.) for three hours at 250° under hydrogen.

Attempts to distil N-pentamethylene-γ-hydroxy-valeramide (prepared by the reaction for four hours of 72 g. of the ester and 85 g. of piperidine at 200° under hydrogen) gave caprolactone. Therefore the crude amide was subjected to hydrogenation without purification.

2,2-Dimethyl-5-phenyl-4-oxazolidone (80 g., m. p. 127°) was obtained by the reaction of mandelamide (160 g.) with acetone (600 ml.).[33] The product was refluxed with Raney nickel in ethanol for thirty minutes and then crystallized from ethanol.

Refluxing ethyl β-hydroxybutyrate (100 g.) for four hours with piperidine (77 g.) gave only 19 g. of the desired amide. There was also obtained 46 g. of a compound, b. p. 105–110° at 1 mm., $n^{25}D$ 1.4896, which gave the correct analysis for N-pentamethylene-β-(β′-hydroxybutyryl)-hydroxybutyramide. Similarly when ethyl α-hydroxyisobutyrate (132 g.) was heated, for four hours at 200° under hydrogen, with piperidine (170 g.) the desired amide was not obtained. Instead a compound (56 g.), b. p. 108° at 1 mm., $n^{25}D$ 1.4651, was obtained which showed the correct analysis for N-pentamethylene-α-(α′-hydroxyisobutyryl)-hydroxyisobutyramide. The formation of these products is analogous to those formed in the hydrogenation of β-keto esters in the absence of a solvent.[29]

(32) Wojcik and Adkins, THIS JOURNAL, **56**, 2423 (1934).

(33) Fischer, *et al.*, *Ber.*, **65B**, 1032 (1932).

Summary

Various N-pentamethylene amides having a hydroxyl group in the α, β, γ, δ or ε position have been submitted to hydrogenation over copper chromite. The corresponding amino alcohols have been obtained in yields of 51 to 79%, except from the amide having the hydroxyl group in the β-position, in which case the hydroxyl group was eliminated and the chief product was the alkylpiperidine. Glycols and diamines were also obtained in low yields from certain of the hydroxy amides.

Raney nickel catalyzed the same types of reaction with hydroxyamides as did copper chromite. However, reaction was not so rapid and the yields of piperidino alcohols were much lower than with copper chromite.

Raney nickel with $CH_3CHOHCH_2C(O)NC_5H_{10}$ gave the amide $CH_3CH_2CH_2C(O)NC_5H_{10}$ while copper chromite also catalyzed the hydrogenation of the carbonyl group giving the amine $CH_3CH_2CH_2CH_2CH_2NC_5H_{10}$.

The action of hydrogen over copper chromite upon di-N-pentamethylene mucamide gave twelve products as listed in Table II. It is a striking fact that cleavage of the six carbon chain occurred exclusively between carbon atoms 2 and 3 and never between carbon atoms 3 and 4, as in the hydrogenolysis of the six carbon sugars and the corresponding alcohols.

The hydrogenolysis of amides derived from malic, tartaric and mandelic acids has also been studied.

MADISON, WISCONSIN RECEIVED MARCH 9, 1939