the solution is filtered, 0.4 g. of methylcholanthrene is added, and the mixture is refluxed for a few minutes in order to bring the hydrocarbon into solution. On standing undisturbed overnight the solution deposits a few large clusters of long, fine, rather pale yellow needles of pure methylcholanthrene. This material is collected, and the filtrate is concentrated to a volume of about 125 cc. and allowed to stand overnight without disturbance. Methylcholanthrene-choleic acid separates at this point as small clusters of fine, colorless needles amounting to 0.7–2.1 g. The melting point usually is 196.5–197°, sometimes 197.5–198°. There is some drawing together of the particles a few degrees lower, and some darkening at the melting point. From 0.1 to 0.2 g. of methylcholanthrene, depending on the size of the first crop of the choleic acid, is dissolved in the mother liquor and on slow cooling a further crop of the choleic acid is obtained. This procedure can be repeated about four times, keeping the volume about 125 cc. If the solution darkens, it is clarified with Norite.

Summary

By a modification of the synthetic method previously described, methylcholanthrene can be prepared rapidly and on a large scale using *p*-chlorotoluene, β-chloropropionyl chloride, and α-bromonaphthalene as the starting materials. The over-all yield in the six-step process is 20%.

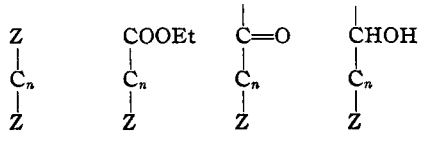
CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASS. RECEIVED OCTOBER 20, 1936

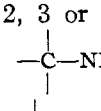
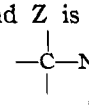
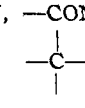
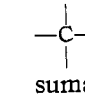
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Synthesis of Pyrrolidines, Piperidines and Hexahydroazepines[1,2]

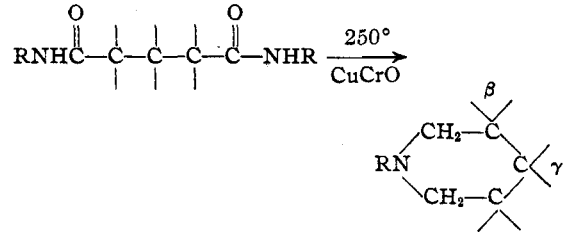
BY JOSEPH H. PADEN AND HOMER ADKINS

Compounds of the types



where n is 2, 3 or 4 and Z is —CN, —$CONH_2$, —CONHR,  ,  ,  ,  ,  ,  or  presumably may be converted into cyclic amines by catalytic hydrogenation. The present paper is concerned primarily with the synthesis of such amines from diamides of succinic, glutaric and adipic acids. Attention has been also given to the hydrogenation of imides to cyclic amides over nickel or to cyclic amines over copper–chromium oxide. In addition a new process for the preparation of cyclic amines by the alkylation of amines with glycols has been developed.

Piperidines from Glutaramides.—The eight substituted piperidines prepared by ring closure from glutaramides as indicated in Table I have substituents on the nitrogen and (or) in the gamma position.



Presumably piperidines bearing substituents in the beta position could be prepared similarly, while it is obviously impossible to prepare alpha substituted piperidines from glutaramides. Among the piperidines prepared, the group on the nitrogen was *n*-amyl, benzyl or phenethyl, while the substituents on the central carbon were methyl, dimethyl or phenyl. The yield of piperidines was not much modified by the character of the substituent, being approximately 70%, which was also the yield of piperidine obtained from glutaramide itself. The lowest yield (62%) of a piperidine was due to incomplete hydrogenation and becomes the highest (81%) if allowance is made for the recovered amide.

The other products of reaction, isolated in the yields given in Table I, can be accounted for by cleavage at the nitrogen to carbon bond in the amide or the piperidine. The effect of structure upon the extent of this type of reaction will be considered in a subsequent section.

Three dipentamethylene glutaramides of the type

(1) Azepine is the seven-membered ring containing one nitrogen atom and three double bonds. Hexahydroazepine was suggested by Dr. Austin M. Patterson in preference to the synonymous terms hexamethyleneimine or homopiperidine.

(2) The Wisconsin Alumni Research Foundation allotted funds for a research assistantship held by J. H. P.

TABLE I

HYDROGENATION OF AMIDES OVER COPPER–CHROMIUM OXIDE

The reactions were carried out at 250–260° under 200–400 atm. of hydrogen using 700–800 cc. of dioxane per mole of diamide.

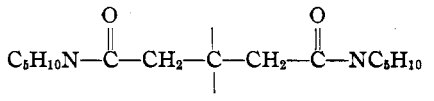
GLUTARAMIDES

Glutaramide (substituents)	Moles	Catalyst, g.	Time, hrs.	Yield of products, %
Unsubstituted[3]	0.068	4	2	70 Piperidine
Di-N-phenethyl	.18	11	1.5	77 1-Phenethylpiperidine[4] 19 Piperidine 25 Phenethylamine 15 Diphenethylamine 8 Ethylbenzene
Di-N-phenethyl-β-methyl	.10	6	3	70 1-Phenethyl-4-methylpiperidine 11 4-Methylpiperidine[5] 23 Phenethylamine 19 Diphenethylamine 5 Unchanged amide
Di-N-phenethyl-β-phenyl	.084	5	2.5	70 1-Phenethyl-4-phenylpiperidine 3 4-Phenylpiperidine[6] 8 Phenethylamine 7 Diphenethylamine
Di-N-*n*-amyl	.13	9	3	74 1-*n*-Amylpiperidine[7,8] 37 Di-*n*-amylamine 9 *n*-Amylamine Trace of piperidine
Di-N-*n*-amyl-β-methyl	.114	6	2	62 1-*n*-Amyl-4-methylpiperidine 18 Di-*n*-amylamine 24 Unchanged amide
Di-N-*n*-amyl-β-phenyl	.10	6	2.25	72 1-*n*-Amyl-4-phenylpiperidine 7 4-Phenylpiperidine[6] 32 Di-*n*-amylamine
Di-N-*n*-amyl-β,β-dimethyl	.115	6	4.6	69 1-*n*-Amyl-4,4-dimethylpiperidine 23 Di-*n*-amylamine 9 Unchanged amide
Di-N-benzyl-β-phenyl	.065	5	2	65 1-Benzyl-4-phenylpiperidine 16 4-Phenylpiperidine[6] 30 Benzylamine 20 Dibenzylamine
Di-N-pentamethylene	.18	9	1.5	46 1,5-Di-N-piperidinopentane[9] 30 5-(N-Piperidino)-pentanol-1[10] 20 Piperidine
Di-N-pentamethylene-β-methyl	.118	6	5	71 1,5-Di-N-piperidino-3-methylpentane
Di-N-pentamethylene-β,β-dimethyl	.11	6	5.5	45 1,5-Di-N-piperidino-3,3-dimethylpentane

MISCELLANEOUS AMIDES

Di-N-*n*-amyl adipamide	0.36	18	4	34 1-*n*-Amylhexahydroazepine 41 Di-*n*-amylamine
1-β-Cyclohexylethylpyrrolidone-2	.067	3	1	96 1-β-Cyclohexylethylpyrrolidine
1-*n*-Amylpyrrolidone-2	.04	3	1	87 1-*n*-Amylpyrrolidine[11]
1-β-Cyclohexylethyl-4-methylpiperidone-2	.057	3	1	89 1-β-Cyclohexylethyl-4-methylpiperidine

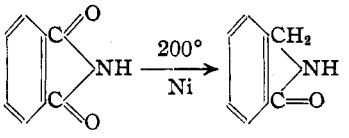
(3) Pinner, *Ber.*, **23**, 2943 (1890).
(4) Pollard and Robinson, *J. Chem. Soc.*, 2770 (1927).
(5) Ladenburg, *Ann.*, **247**, 69 (1888).
(6) Bally, *Ber.*, **20**, 2590 (1887); Schlinck, *ibid.*, **32**, 952 (1899).
(7) Robinson and Robinson, *J. Chem. Soc.*, **123**, 542 (1923).
(8) Coffman, THIS JOURNAL, **57**, 1978 (1935).
(9) Von Braun, Kühn and Goll, *Ber.*, **59**, 2337 (1926).
(10) Adkins, Kuick, Farlow and Wojcik, THIS JOURNAL, **56**, 2425 (1934).
(11) Wojcik and Adkins, *ibid.*, **56**, 2419 (1934).



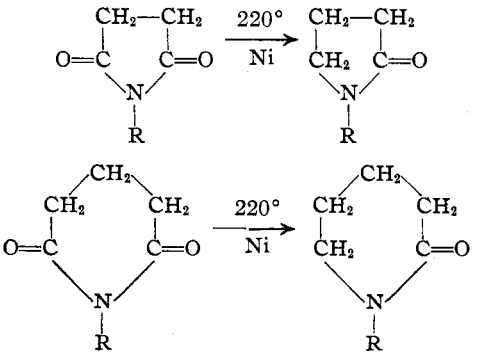
did not undergo ring closure but gave open chain diamines of the type $C_5H_{10}N(CH_2)_2(CCH_2)_2NC_5H_{10}$, *i. e.*, substituted cadaverines. Di-N-pentamethyleneglutaramide also gave a 30% yield of an amino alcohol, $C_5H_{10}N(CH_2)_4CH_2OH$.

A Hexahydroazepine from an Adipamide.—The yield of 1-*n*-amylhexahydroazepine from di-*n*-amyl adipamide was half as large as that of the piperidines from the glutaramides. The formation of a hexahydroazepine was overlooked in earlier experiments[11] since it has approximately the same boiling point as di-*n*-amylamine which is also produced in the hydrogenation.

Pyrrolidones and Piperidones from Imides.—Cramer[12] observed that phthalimide was converted to phthalimidine by treatment with a nickel catalyst in methylcyclohexane solution at 200° under 200–250 atm. of hydrogen.



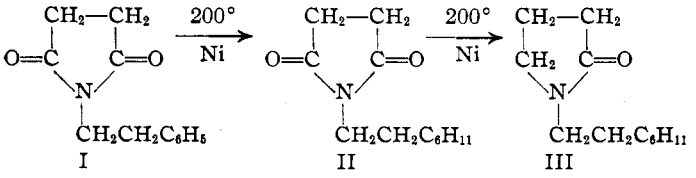
Attempts to obtain a similar reaction with succinimide or succinamide were not successful. It has now been found that succin- and glutaramides which bear an alkyl group on the nitrogen atom may be converted successfully at 200–220° over nickel to 2-pyrrolidones and 2-piperidones, respectively.



This behavior is similar to that observed in the pyrrole series where the presence of a group on the nitrogen atom greatly facilitates hydrogenation. The resulting pyrrolidones and piperidones are cyclic amides which do not react further under the conditions of the experiments.

As is indicated in Table II three imides were investigated and the yields of products were 46–79%. The reactions were rather slow at 200–220° and would probably have been much more rapid at a higher temperature, but dioxane is the only available solvent which is satisfactory for this type of reaction and it may not be used with Raney nickel above about 220°. The reaction with N-*n*-amylsuccinimide was incomplete after two applications of catalyst. The low yield reported is due to the difficulty of separating the pyrrolidone from the imide. The yields of products from N-phenethylimides were quite satisfactory and no difficulty was encountered in purifying them by fractionation since their boiling points differed much more from that of the starting material than was the case with 1-*n*-amylpyrrolidone-2.

The first reaction in the hydrogenation of the two N-phenethylimides was the saturation of the benzene ring which occurs very rapidly at 200°. It was found possible to isolate 1-β-cyclohexylethylsuccinimide (II) in a yield of 93% when the hydrogenation of N-phenethylsuccinimide (I) was interrupted after twenty minutes. Longer



treatment resulted in the removal of one carbonyl oxygen and in the formation of 1-β-cyclohexylethylpyrrolidone-2 (III).

These reactions are examples of two selective hydrogenations. First, the hydrogenation of a phenyl group in the presence of an imido carbonyl group which is labile to hydrogen under the conditions of the reaction. This is possible because of the difference in rate of reaction. Secondly, we have the hydrogenolysis of an imido carbonyl group while the amido carbonyl remains unchanged.

In the hydrogenation of N-phenethyl-β-methylglutarimide (IV) no attempt was made to isolate the N-cyclohexylethylimide. The reaction was allowed to proceed to completion and the product was 1-β-cyclohexylethyl-4-methylpiperidone-2 (V).

Piperidines from Glutarimides.—In a glutarimide (VI) the ring system of the piperidine

(12) Cramer and Adkins, THIS JOURNAL, **52**, 4354 (1930).

TABLE II

HYDROGENATION OF IMIDES OVER RANEY NICKEL

The reactions occurred at 200–220° under 200–400 atm. of hydrogen using 50–80 cc. of dioxane per tenth mole of imide.

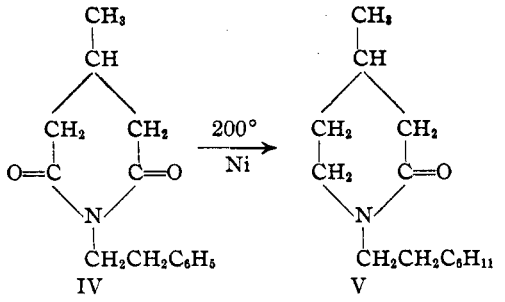
Imide	Moles	Catalyst, g.	Time, hrs.	Yield of products, %
N-Phenethylsuccinimide	0.1	4	0.3	93 N-β-Cyclohexylethylsuccinimide
N-β-Cyclohexylethylsuccinimide	.12	12	5	79 1-β-Cyclohexylethylpyrrolidone-2
N-*n*-Amylsuccinimide	.15	7	9	46 1-*n*-Amylpyrrolidone-2
N-Phenethyl-β-methylglutarimide	.11	7	10	74 1-β-Cyclohexylethyl-4-methylpiperidone-2

TABLE III

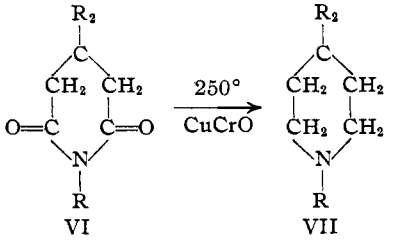
HYDROGENATION OF GLUTARAMIDES OVER COPPER–CHROMIUM OXIDE

The reactions were carried out at 250–260° under 200–400 atm. of hydrogen using 700–800 cc. of dioxane per mole of imide.

Glutarimide (substituents)	Moles	Catalyst, g.	Time, hrs.	Yield of products, %
β-Methyl[13]	0.118	6	1.5	46 4-Methylpiperidine[14]
β-Phenyl[15]	.118	6	1.5	55 4-Phenylpiperidine[16]
N-Benzyl-β-phenyl	.110	6	3	42 1-Benzyl-4-phenylpiperidine 32 4-Phenylpiperidine
N-*n*-Amyl-β,β-dimethyl	.148	8	3.5	67 1-*n*-Amyl-4,4-dimethylpiperidine 7 4,4-Dimethylpiperidine[17] 11 Unchanged imide
N-Phenethyl-β,β-dimethyl	.130	7	1.5	55 1-Phenethyl-4,4-dimethylpiperidine 16 4,4-Dimethylpiperidine 7 Unchanged imide
N-Benzyl-β,β-dimethyl	.081	4	7	32 1-Benzyl-4,4-dimethylpiperidine 31 4,4-Dimethylpiperidine



(VII) is already present, and it might be expected that the yields of piperidine would be somewhat greater than in the case of the amides, due to the lessening of any side reactions which might precede ring closure.



Inspection of Table III, however, shows that this is not the case. The yields of the corresponding piperidines from N-benzyl-β-phenyl-, N-*n*-amyl-β,β-dimethyl- and N-phenethyl-β,β-dimethylglutarimide were of the order of 70–75% of ring compounds. The cleavage of the phenethyl and benzyl groups from the nitrogen atom giving the piperidines free from substituents in the 1-position is quite noticeable in these compounds. An attempt to remove the benzyl group to a larger extent was made with N-benzyl-β,β-dimethylglutarimide by running the reaction for a longer time. That much of it was removed is shown by the low yield of 1-benzyl-4,4-dimethyl-piperidine.

The hydrogenation of β-methyl- and β-phenylglutarimides was not very satisfactory. Since the simple amides of glutaric acids are quite insoluble substances and so are difficult to purify by crystallization, it was hoped that the easily purified imides would furnish a convenient method for preparing the piperidines which are unsubstituted in the 1-position. The yields of 4-methyl- and 4-phenylpiperidines from these substances were rather low, however. In both cases the catalyst was found to be red after the reaction was over, indicating that it had been deactivated. This might be due to the hydrolysis of the imide by the

(13) Sircar, *J. Chem. Soc.*, 600 (1927).
(14) Ladenburg, *Ann.*, **247**, 69 (1888).
(15) Vorländer, *ibid.*, **320**, 86 (1902).
(16) Bally, *Ber.*, **20**, 2590 (1887).
(17) Komppa, *Ann. acad. sci. Fennicae*, A, 3 (1911); *cf. C. A.*, **7**, 1359 (1913).

water formed in the reaction, the resulting acid and ammonia deactivating the catalyst. Residues of high boiling material were left after the product had been distilled, amounting to 33% of the starting material in the case of β-methylglutarimide, and 24% with β-phenylglutarimide.

Since the amides of β,β-dimethylglutaric acid are difficult to obtain, and the imides may be prepared in satisfactory yields in most cases (see Table V), the hydrogenation of the imides seems to be the best method of preparing N-alkylated derivatives of 4,4-dimethylpiperidine.

Pyrrolidines and Piperidines from Pyrrolidones and Piperidones.—Three cyclic amides, 1-β-cyclohexylethyl-pyrrolidone-2, 1-*n*-amyl-pyrrolidone-2 and 1-β-cyclohexylethyl-4-methylpiperidine-2, were almost quantitatively converted over copper chromium oxide to pyrrolidines and a piperidine (Table I).

Pyrrolidines, Piperidines and a Hexahydroazepine from Glycols and Amines.—Speculation as to the course of the reaction involved in the formation of piperidines from glutaramides led to the development of another useful method for obtaining piperidines. As indicated in a later section, it seemed possible that the cyclic amines were formed from glycols and amines produced by the hydrogenolysis of the carbon to nitrogen bond in the amides

$$RHNC(=O)CH_2CH_2CH_2C(=O)NHR \longrightarrow 2RNH_2 +$$
$$HOCH_2(CH_2)_2CH_2OH \longrightarrow (CH_2)_5NR + RNH_2 + H_2O$$

Since 1,5-glycols may be prepared readily by the hydrogenation of glutaric esters, it was decided to ascertain whether glycols would react with amines to give piperidines. The reactions were carried out under the same conditions as were used for hydrogenation of amides. The results of four such reactions are summarized in Table IV. It is seen that pentanediol-1,5 and its 3-methyl and 3-phenyl derivatives react with *n*-amyl-, benzyl- or phenethylamine to give yields of 70–75% of piperidines. This is the same order of magnitude as the yields obtained from amides or imides (Tables I and II).

The preparation of piperidines from glycols and amines is a rather more convenient method than by the hydrogenation of amides: first, because glycols are in general more easily purified and handled than amides, and second, because only one mole of amine is necessary for this reaction, whereas four moles of amine are necessary to prepare a glutaramide from the corresponding ester.

Pyrrolidines may be prepared in a similar manner. The data in Table IV shows that butanediol-1,4 reacted with phenethyl- and benzylamine to give yields of 71 and 76% of the corresponding pyrrolidines. These yields are similar to those previously obtained by the hydrogenation of N-phenethylsuccinimide and N-*n*-amylsuccinimide.

It was thought that the reaction of glycols and amines might occur under milder conditions than were necessary for the hydrogenation of amides. Consequently, phenethylamine and butanediol-1,4

TABLE IV

REACTION OF GLYCOLS WITH AMINES

Equimolecular amounts of glycol and amine were heated at 250° for one hour under 200–400 atm. of hydrogen, using 600–800 cc. of dioxane and 30–60 g. of CuCrO per mole.

Amine	Glycol	Moles	Yield of products, %
Phenethyl	Pentanediol-1,5	0.25[a]	76 1-Phenethylpiperidine
			15 Phenethylamine
Benzyl	Pentanediol-1,5	.4	71 1-Benzylpiperidine
Benzyl	3-Methylpentanediol-1,5	.2	68 1-Benzyl-*d*-methylpiperidine
			5.5 4-Methylpiperidine
n-Amyl	3-Phenylpentanediol-1,5	.1	73 1-*n*-Amyl-4-phenylpiperidine
			3 4-Phenylpiperidine
			14 Di-*n*-amylamine
Benzyl	Butanediol-1,4	.2	76 1-Benzylpyrrolidine
			4 Benzylamine
Phenethyl	Butanediol-1,4	.15[b]	71 1-Phenethylpyrrolidine
Phenethyl	Butanediol-1,4	.15[c]	35 4-(N-Phenethylamino)-butanol-1
			19 1-Phenethylpyrrolidine
			43 Unchanged amine and glycol
Benzyl	Hexanediol-1,6	.22[d]	23 1-Benzylhexahydroazepine

[a] A 25% excess of amine was used, but this is disadvantageous. [b] Time of reaction was three and one-half hours. [c] 200° for half an hour. [d] One and one-half hours.

were heated at 200° for one-half hour, but the reaction was not complete. A yield of only 19% of 1-phenethylpyrrolidine was obtained, and 43% of the amine and glycol were recovered. A 35% yield of the amino alcohol formed by reaction at only one end of the glycol, was also obtained: $C_6H_5CH_2CH_2NHCH_2CH_2CH_2CH_2OH$. No more experiments along this line were carried out, but it is quite possible that by modifying the conditions, higher yields of amino alcohols of this type might be obtained.

It was of interest to determine whether or not hexanediol-1,6 would react with an amine to give a hexahydroazepine in the same manner as pentanediol-1,5 gives piperidines. It was found that benzylamine and hexanediol-1,6 reacted (Table IV) to give a 25% yield of 1-benzylhexahydroazepine. The structure of this substance was proved by removal of the benzyl group by treatment with copper–chromium oxide at 275°.

$$(CH_2)_6NCH_2C_6H_5 \xrightarrow[CuCrO]{H_2} (CH_2)_6NH + C_6H_5CH_3$$

The hexahydroazepine formed was characterized by the preparation of three derivatives which corresponded with those reported in the literature.

When a reaction should lead to a ring containing more than six atoms, rearrangements frequently occur resulting in the formation of five- or six-membered rings containing the extra atoms in a side chain. Thus Müller and Feld[18] found that on thermal decomposition 1,6-diaminohexane dihydrochloride gave 2-ethylpyrrolidine instead of hexahydroazepine.

$$(CH_2CH_2CH_2NH_3Cl)_2 \longrightarrow \begin{array}{l} CH_2{-}CH_2 \\ | \quad\quad | \\ CH_2 \quad CHC_2H_5 \\ \diagdown NH \diagup \end{array}$$

Also, a rearrangement to give a 2,3 or 4-methylpiperidine might be possible. All of these possibilities are ruled out by the derivatives of the hexahydroazepine mentioned above. The structure of the 1-amylhexahydroazepine might be assumed to be proved through analogy with the 1-benzyl derivative. It was found to differ in properties from 1-*n*-amyl-4-methylpiperidine which was formed from the corresponding glutaramide. A sample of 1-amyl-2-methylpiperidine was prepared by alkylating 2-methylpiperidine with *n*-amyl alcohol and this was different from the 1-amylhexahydroazepine.

As was mentioned above the same yields of piperidines were obtained whether the glutaramide or an amine and a glycol were used. In the formation of the seven-membered ring, however, a substantially higher yield was obtained from the amide than from the amine and glycol.

Mechanism of Conversion of Amides to Cyclic Amines.—The conversion of an amide to an amine of the same carbon content may proceed either through hydrogenolysis of the oxygen to carbon bond in the amide or through hydrogenolysis of the carbon to nitrogen bond followed by interaction of the alcohol and amine so formed.

$$RC(O)NHR^1 \begin{array}{l} \xrightarrow{2H_2} RCH_2NHR^1 + H_2O \\ \xrightarrow{2H_2} RCH_2OH + R^1NH_2 \end{array} \uparrow$$

There are no experimental observations available which definitely rule out one of these mechanisms as contrasted with the other. In support of the two-step process may be cited these facts. (1) Alcohols of the type RCH_2OH and amines of the type R^1NH_2 have been obtained as the result of the hydrogenation of amides. (2) Alcohols or glycols and amines react under the conditions used for the hydrogenation of amides to give amines in yields similar to those obtained directly from the amides. (3) Benzoylpiperidine is cleaved completely to toluene, piperidine and water far more rapidly than benzylpiperidine undergoes hydrogenolysis. This indicated that the primary cleavage in benzoylpiperidine is at the carbon to nitrogen rather than at the carbon to oxygen linkage. Against the two-step process may be cited the fact that ammonia does not react with glycols (at 250° over copper–chromium oxide in dioxane) to give good yields of the corresponding amines.

Since the hydrogenolysis of carbon to nitrogen bonds takes place under the same conditions as those effective for the breaking of carbon to oxygen bonds, it seems reasonable to assume that both types of reaction occur. Further studies in the reaction of alcohols and amines and of hydrogen with amides must be made before a definite conclusion can be drawn as to the relative importance of the two types of reactions.

Insofar as the formation of cyclic amines from open chain amides is concerned, it appears that hydrogenation precedes ring closure. There are two pieces of evidence which indicate that N-substituted glutaramides are not converted to imides. In the first place, di-N-*n*-amylglutar-

(18) Müller and Feld, *Monatsh.*, **58**, 12 (1931).

TABLE V

PREPARATION OF GLUTARAMIDES AND IMIDES FROM ESTERS

The ester (0.1 to 0.3 mole) was heated with amine (0.4 to 1.2 moles) under 100–150 atm. of hydrogen.

Diethyl glutarate (substituents)	Amine	Temp., °C.	Time, hrs.	Yield of products, % Amide	Imide
Unsubstituted	Ammonia	175	4	96[a]	..
Unsubstituted	Phenethyl	250	9	83[b]	..
Unsubstituted	*n*-Amyl	250	3	94[c]	..
Unsubstituted	Piperidine	250	10	81[f]	..
β-Methyl	Phenethyl	250	3	94[b]	..
β-Methyl	*n*-Amyl	200	3	93[d]	..
β-Methyl	Piperidine	200	4	93[f]	..
β-Methyl	Benzyl	200	5	42[b]	..
β-Phenyl	Phenethyl	180	4	93[b]	..
β-Phenyl	*n*-Amyl	200	3	87[e]	..
β-Phenyl	Piperidine	200	4	86[f]	..
β-Phenyl	Benzyl	200	5	85[b]	..
β,β-Dimethyl	Phenethyl	250	5	..	71[f,b]
β,β-Dimethyl	*n*-Amyl	250	7	35[f]	61[f]
β,β-Dimethyl	*n*-Amyl	250	1	36[f]	61[f]
β,β-Dimethyl	Piperidine	250	7	86[f]	..
β,β-Dimethyl	Benzyl	200	2.5	..	39[f,g]
β,β-Dimethyl	Benzyl	250	9	53[f]	44[f,g]

[a] This product was washed with ethyl acetate, acetone and ether. [b] Recrystallized from 95% ethyl alcohol. [c] Recrystallized from 95% ethyl alcohol to which two volumes of acetone was added. [d] Recrystallized from acetone. [e] Recrystallized from 95% ethyl alcohol to which two volumes of ether was added. [f] The product was fractionated. [g] Recrystallized from a small amount of methyl alcohol.

amide was recovered unchanged after heating at 200° for eight hours, so apparently heat does not cause the formation of imides from glutaramides. Secondly, when one mole of diethyl-β,β-dimethylglutarate was heated with four moles of *n*-amylamine in a bomb at 250° (Table V), the same yields of imide and amide were obtained after heating either for one or for seven hours. Similar results were obtained with the same ester and benzylamine. Evidently none of the amide cyclicized during the extra hours of heating, and it would seem that the two products were probably formed by different reactions.

There appears to be no experimental observation that definitely answers the question as to whether the ring closure involves an aminoamide, an hydroxyamide, a diamine or a glycol and an amine. All of these reactions may occur under the conditions used for the conversion of amides to cyclic amines.

Hydrogenolysis of N-Substituted Piperidines.—The preparation of *pure* primary glutaramides is difficult. The N-monosubstituted glutaramides are readily prepared in high purity. Moreover, primary glutaramides are not as readily hydrogenated as are the substituted amides. Thus it is better to use N-substituted amides even though a piperidine is desired which contains no substituent on the nitrogen. This necessitates using an amine such as benzyl or phenethyl in which the carbon to nitrogen bond has been rendered liable toward hydrogenolysis by the presence of a phenyl group. The tendency of such amides and amines to undergo cleavage is shown in Table I by the formation of 19% piperidine along with 77% 1-phenethylpiperidine, 11% 4-methylpiperidine along with 70% 1-phenethyl-4-methylpiperidine and 16% 4-phenylpiperidine along with 65% 1-benzyl-4-phenylpiperidine.

Data are given in Table VII which indicate the conditions necessary for the cleavage of the amines. A comparison of these data with those in

TABLE VI

PREPARATION OF IMIDES FROM ACIDS

One mole of acid was heated with one mole of amine at 250° under 100–150 atm. of hydrogen using 350–400 cc. of dioxane per mole of acid.

Acid	Amine	Time, hrs.	Yield of products, % Amide	Imide
β-Phenylglutaric	Benzyl	7		62[a,b]
Glutaric	*n*-Amyl	6.5	14[c]	42[a]
β-Methylglutaric anhydride	Phenethyl	4	10[d]	58[d]
Succinic	Phenethyl	5.5		89[b]

[a] This product was fractionated. [b] Recrystallized from 95% ethyl alcohol. [c] Recrystallized from a mixture of equal volumes of 95% ethyl alcohol and acetone. [d] These products were partially separated by fractional crystallization from methyl alcohol. The yields given here are of the pure substances (see Experimental Part).

TABLE VII

HYDROGENOLYSIS OF 1-PHENETHYL- AND 1-BENZYLPIPERIDINES

Forty cc. of dioxane was used as the solvent in each experiment

Piperidine	Moles	Catalyst, g.	Time, hrs.	Temp., °C.	Yields, % Piperidine	Yields, % Unchanged material
1-Phenethyl	0.104	4CuCrO	4.3	250	18	68
1-Phenethyl	.104	4Ni	4	165	7	87
1-Benzyl	.118	4CuCrO	6	250	36	54
1-Benzyl	.149	7Ni	7	170	43	49

Table I would indicate that hydrogenolysis occurred more rapidly with the amides than with the piperidines.

Experimental Part

The reaction products from the hydrogenations were in general centrifuged and fractionated through a Widmer column. Low boiling basic compounds carried over in the dioxane fraction were recovered as hydrochlorides which were recrystallized from ethanol and ether. The various amines were characterized by their neutral equivalents and in most cases by the formation of solid derivatives. The hydrochlorides of all the piperidines and pyrrolidines except 4-phenylpiperidine were prepared. The properties and analyses of those substances which apparently have not been previously reported are given in Table VIII.

In a number of cases where separation could not be effected by fractionation, it was necessary to purify tertiary amines through the use of benzenesulfonyl chloride. In the case of 1-phenethyl-4-phenylpiperidine it was necessary to distil the amine away from the sulfonamide since the hydrochloride of the amine is insoluble in water. In a few cases the yield of secondary amine reported in the tables is based upon the yield of its benzenesulfonamide isolated. 4-Phenylpiperidine was separated from dibenzylamine by cooling the mixture in ice and salt.

The **1-benzyl-4-phenylpiperidine** from **di-N-benzyl-β-phenylglutaramide** gave the correct neutral equivalent of 251 and the hydrochloride gave the correct chlorine analysis, but it was contaminated with some substance apparently of the same molecular weight. The hydrochloride melted at 198–201° and the melting point was lowered by recrystallization. This substance when prepared by hydrogenating N-benzyl-β-phenylglutarimide gave a hydrochloride melting at 210–211°. The 1-benzyl-4-phenylpiperidine was purified by treatment of 8.8 g. with 3.0 g. of $C_6H_5SO_2Cl$ and 20 cc. of 10% sodium hydroxide solution. The benzenesulfonamide of the impurity was a red oil which was insoluble in ether, dilute hydrochloric acid and dilute sodium hydroxide. It was carried through the separation procedure (with appreciable mechanical loss, due to its insolubility) until the piperidine was in solution in dilute hydrochloric acid. At this point, it formed a lower insoluble layer which was separated. It did not crystallize. This treatment gave 7.6 g. of the pure piperidine which corresponded to a yield of 10.6 g. (0.042 mole) in the original fraction of 12.2 g. from 0.065 mole of amide. The yield was thus 65% of the theoretical. The hydrochloride now melted at 211–212°.

The principal fraction from the hydrogenation of **di-N-*n*-amyladipamide** distilled at 80–88° (9 mm.) and weighed 53.5 g. This was divided for purposes of preliminary investigation into two fractions: (1) 37.3 g., b. p. 80–88° (9 mm.), and (2) 16.2 g., b. p. 88° (9 mm.). Both fractions gave the pure phenyl isocyanate derivative of diamylamine, m. p. and mixed m. p. 78–79°. By titration, it was found that fraction (1) was 36% **1-*n*-amylhexahydroazepine** and 64% diamylamine. Fraction (2) was found to contain 89% of the hexahydroazepine and 11% of diamylamine. These figures indicated that 28.0 g., or 46%, of the hexahydroazepine, and 25.5 g., 45%, of diamylamine were formed in the reaction.

To separate these two substances 50.4 g. of fractions (1) and (2) were combined and treated gradually with 55.0 of benzenesulfonyl chloride and 185 cc. of 10% sodium hydroxide solution. On working up the reaction mixture in the usual manner, there was obtained 19.0 g. of 1-*n*-amylhexahydroazepine b. p. 94–95° (13 mm.). This corresponded to 21.0 g. in the original fraction or 34% of the theoretical. Forty-three and nine-tenths grams of the benzenesulfonamide of diamylamine was obtained which is 41% of the theoretical. That the 1-*n*-amylhexahydroazepine is not identical with either 1-amyl-2- or -4-methylpiperidine is shown by the difference in the refractive indices and the wide divergence in the melting points of the hydrochlorides (see Table VIII). The picrate of 1-*n*-amylhexahydroazepine melts at 109–110° (corr.).

The 25% excess of phenethylamine used in the preparation of 1-phenethylpiperidine[19] from amine and glycol was detrimental since the yield was not increased, and the excess amine contaminated the product.

The fraction from the reaction of **3-phenylpentanediol-1,5** and *n*-amylamine boiling at 133–137° at 2 mm. was found to contain 3% of **4-phenylpiperidine** and 73% of **1-*n*-amyl-4-phenylpiperidine.** Two grams of this fraction was treated with enough benzenesulfonyl chloride to react completely if all the fraction was 4-phenylpiperidine. After reaction was complete, the material was dissolved in ether and the unreacted tertiary amine extracted with dilute hydrochloric acid. The ether solution was dried and the ether evaporated, leaving 0.12 g. of the benzenesulfonamide of 4-phenylpiperidine, m. p. and mixed m. p. 108–109°, after one recrystallization. This amount corre-

(19) Pollard and Robinson, *J. Chem. Soc.*, 2770 (1927).

TABLE VIII

ANALYTICAL DATA

Glutaramides

Glutaramide (substituents)	Formula	B. p. or m. p.,[a] °C.	$n^{25}D$	Nitrogen, % Calcd.	Nitrogen, % Found	M. p., °C.	Hydrochloride Analysis for chlorine Calcd.	Hydrochloride Analysis for chlorine Found
Di-N-phenethyl	$C_{21}H_{26}O_2N_2$	M 158.5–159.5		8.28	8.29			
Di-N-*n*-amyl	$C_{15}H_{30}O_2N_2$	M 147–148		10.37	10.43			
Di-N-pentamethylene	$C_{15}H_{26}O_2N_2$	B 193–197 (1 mm.) M 53–54		10.53	10.69			
Di-N-phenethyl-β-methyl	$C_{22}H_{28}O_2N_2$	M 190–191.5		7.95	7.82			
Di-N-*n*-amyl-β-methyl	$C_{16}H_{32}O_2N_2$	M 149–150		9.85	9.70			
Di-N-benzyl-β-methyl	$C_{20}H_{24}O_2N_2$	M 194–195		8.64	8.52			
Di-N-pentamethylone-β-methyl	$C_{16}H_{28}O_2N_2$	B 188–190 (1 mm.)	1.5122	9.99	10.00			
Di-N-phenethyl-β-phenyl	$C_{27}H_{30}O_2N_2$	M 177.5–178		6.76	6.63			
Di-N-*n*-amyl-β-phenyl	$C_{21}H_{34}O_2N_2$	M 166–167		8.09	8.07			
Di-N-benzyl-β-phenyl	$C_{26}H_{26}O_2N_2$	M 159.5–160.5		7.25	7.10			
Di-N-pentamethylene-β-phenyl	$C_{21}H_{30}O_2N_2$	B 240–248 (1 mm.)		8.18	8.02			
Di-N-*n*-amyl-β,β-dimethyl	$C_{17}H_{34}O_2N_2$	B 210–212 (2 mm.) M 39–41		9.38	9.55			
Di-N-pentamethylene-β,β-dimethyl	$C_{17}H_{30}O_2N_2$	B 183–187 (1 mm.)	1.5083	9.52	9.36			
Glutarimides (substituents)								
N-Phenethyl-β,β-dimethyl	$C_{16}H_{19}O_2N$	M 80.5–81.5		5.71	5.81			
N-*n*-Amyl-β,β-dimethyl	$C_{12}H_{21}O_2N$	B 115–116 (2 mm.)	1.4638	6.63	6.56			
N-Benzyl-β,β-dimethyl	$C_{14}H_{17}O_2N$	B 148–151 (2 mm.) M 63–64		6.06	6.25			
N-Benzyl-β-phenyl	$C_{16}H_{17}O_2N$	M 98–99		5.00	4.95			
N-Phenethyl-β-methyl	$C_{14}H_{17}O_2N$	M 98–100		6.06	6.20			
N-*n*-Amyl	$C_{10}H_{17}O_2N$	B 105–106 (1 mm.)	1.4754	7.64	7.58			
Piperidines (substituents)								
1-*n*-Amyl[7]	$C_{10}H_{21}N$	B 76–76.5 (13 mm.)	1.4616[8]			223–224		
1-Phenethyl[4b]	$C_{13}H_{19}N$	B 127–128 (10 mm.)				232–233	15.72	15.57
4-Methyl[5]	$C_6H_{13}N$					186–189.5	26.15	26.22
1-*n*-Amyl-2-methyl	$C_{11}H_{23}N$	B 92–93 (16 mm.)	1.4500	8.27	8.09	166.5–167.5	17.24	17.18
1-Phenethyl-4-methyl	$C_{14}H_{21}N$	B 141–142 (12 mm.)	1.5114	6.89	7.02	254–256	14.79	14.55
1-β-Cyclohexylethyl-4-methyl	$C_{14}H_{27}N$	B 135.5–137 (12 mm.)	1.4735	6.69	6.55	277–278	14.43	14.39
1-Benzyl-4-methyl	$C_{13}H_{19}N$	B 128–129 (14 mm.)	1.5126	7.40	7.36	166.5–168	15.72	15.46
1-*n*-Amyl-4-methyl	$C_{11}H_{23}N$	B 83–84 (10 mm.)	1.4443	8.27	8.36	239–241	17.24	17.16
1-Amyl-4,4-dimethyl	$C_{12}H_{25}N$	B 96–97 (12 mm.)	1.4445	7.64	7.80	302	16.16	16.17
1-Phenethyl-4,4-dimethyl	$C_{15}H_{23}N$	B 149–150 (12 mm.)	1.5074	6.45	6.63	252	14.00	13.85
1-Benzyl-4,4-dimethyl	$C_{14}H_{21}N$	B 114–115 (5 mm.)	1.4822	6.89	6.91	335–336	14.80	14.75
1-*n*-Amyl-4-phenyl	$C_{61}H_{25}N$	B 129–130 (1 mm.)	1.5113	6.06	5.88	245–246	13.28	13.18
1-Phenethyl-4-phenyl	$C_{19}H_{23}N$	B 170–174 (2 mm.) M 74–75		5.28	5.18	270–271	11.75	11.63
1-Benzyl-4-phenyl	$C_{18}H_{21}N$	B 157–159 (1 mm.)	1.5585	5.57	5.42	212–213	12.34	12.30
Pyrrolidines (substituents)								
1-β-Cyclohexylethyl	$C_{12}H_{23}N$	B 116–117 (12 mm.)	1.4748	7.75	7.62	224–225	16.29	16.20
1-Benzyl[6]	$C_{11}H_{15}N$	B 98–100 (10 mm.)				153.5–154.5	17.95	18.08
Hexahydroazepines (substituents)								
1-*n*-Amyl[c]	$C_{11}H_{23}N$	B 94–95 (13 mm.)	1.4551	8.27	8.20	217–218	17.24	17.40
1-Benzyl	$C_{13}H_{19}N$	B 130–132 (12 mm.)	1.5243	7.40	7.57	158.5–159.5	15.71	15.63

TABLE VIII (*Concluded*)

Pentanes (substituents)	Formula	B. p. or m. p.,[a] °C.	$n^{25}D$	Nitrogen, % Calcd.	Found	Hydrochloride M. p., °C.	Analysis for chlorine Calcd.	Found
1,5-Di-N-piperidino[9d]	$C_{15}H_{30}N_2$	B 130–131 (2 mm.)				252–253	22.83	22.79
1,5-Di-N-piperidino-3-methyl	$C_{16}H_{32}N_2$	B 123–125 (1 mm.)	1.4810	11.10	11.02	246–248	21.82	21.77
1,5-Di-N-piperidino-3,3-dimethyl	$C_{17}H_{34}N_2$	B 133–134 (1 mm.)	1.4839	10.52	10.48	314–316	20.90	20.77
Miscellaneous compounds								
N-β-Cyclohexylethylsuccinimide	$C_{12}H_{19}O_2N$	B 145–148 (2 mm.) M 53–54		6.70	6.78			
1-β-Cyclohexylethylpyrrolidone-2	$C_{12}H_{21}ON$	B 136–138 (2.5 mm.)	1.4907	7.18	7.29			
1-n-Amylpyrrolidone-2	$C_9H_{17}ON$	B 87–88.5 (1 mm.)	1.4619	9.03	9.18			
1-β-Cyclohexylethyl-4-methylpiperidone-2	$C_{14}H_{25}ON$	B 146–149 (2 mm.)	1.4872	6.27	6.17			
4-(N-Phenethylamino)-butanol-1	$C_{12}H_{19}ON$	B 176–178 (9 mm.)	1.5243	7.25	7.30	127–128	15.45	15.33
4-(N-Phenethylamino)-butyl benzoate	$C_{19}H_{23}O_2N$					153–155	10.31	10.73
4-Phenylpiperidine-benzenesulfonamide	$C_{17}H_{19}O_2NS$	M 108–109		4.65	4.79			

[a] All melting points below 250° are corrected. [b] The picrate melted at 147–148°. Pollard and Robinson[19] gave 144–145°. [c] The picrate melted at 109–110°. [d] Melting point of the picrate, 188–189°; von Braun, Kühn and Goll[9] gave 185°.

sponds to 0.064 g. of 4-phenylpiperidine in 2.00 g. of the mixture, or 3.2%.

The following fractions were obtained from the reaction of **phenethylamine** and **butanediol-1,4** at 200°:

	B. p., °C.	M.	G.	Product
1	79– 81	9	7.8	43% Phenethylamine
2	110–119	9	10.6	1-Phenethylpyrrolidine + butanediol-1,4
3	175–179	9	10.1	35% 4-(N-Phenethylamino)-butanol-1

Fraction 2 was extracted three times with ether (15-cc. portions), the glycol being mostly insoluble. This ether solution of **1-phenethylpyrrolidine** was dried over sodium sulfate and filtered. Into the ether solution a stream of dry hydrogen chloride was passed. A liquid layer separated which solidified in an ice-bath. It was filtered and recrystallized, m. p. and mixed m. p. 159–170°.[11] The yield was 4.3 g. or 14%. This amount of hydrochloride corresponds to 3.8 g. of the free amine so that fraction (2) contained, by difference, 10.8 − 3.6 = 7.2 g. of butanediol-1,4, which would be 55% of the starting amount. Since, however, 35 + 14 = 49% of the glycol is accounted for in the two amines, it is evident that this makes a total of 104% of butanediol. The discrepancy is probably due to incomplete recovery of 1-phenethylpyrrolidine from fraction (2). Assuming that an amount of diol corresponding to the phenethylamine (43%) was unreacted, we obtain a yield of 23% for 1-phenethylpyrrolidine. The average of 14 and 23% is reported as the yield of the pyrrolidine in the table. The hydrochloride of the benzoate of 4-(N-phenethylamino)-butanol-1 was prepared by heating 1.0 g. of the amino alcohol with 1.0 g. of benzoyl chloride at 175° for 1 hour.[20] On cooling, the product was recrystallized from absolute alcohol and ether.

(20) McElvain, THIS JOURNAL, **48**, 2182 (1926).

The main fraction from the reaction of **benzylamine** with **hexanediol-1,6** distilled at 119–133° (9 mm.) and weighed 12.5 g. Twelve grams of this fraction was treated with 20.0 g. of benzoyl chloride and 100 cc. of 10% sodium hydroxide and shaken for thirty minutes. It was then warmed on the steam-bath for half an hour to hydrolyze all the benzoyl chloride. On cooling, the alkaline solution was extracted three times with ether, and the unreacted amine extracted from the ether with 5% hydrochloric acid. This solution was made alkaline, the insoluble layer separated and the aqueous layer extracted three times with ether. The ethereal solution of the amine was dried, the ether distilled and the residue fractionated under reduced pressure. Eight and two-tenths grams of **1-benzylhexahydroazepine** was obtained, b. p. 131–134° (13 mm.). This corresponded to 8.55 g. in the original fraction, or a yield of 23% of the theoretical. On refractionation, this substance distilled at 130–132° (12 mm.).

To prove the structure of this substance, the benzyl group was removed by treatment with copper–chromium oxide at 275° for six and one-half hours. Five and three-tenths grams of the material in 9.7 cc. of dioxane was hydrogenated in a small bomb designed for quantitative hydrogenations. One and four-tenths moles of hydrogen per mole of compound instead of the calculated value of 1.0 was absorbed. This excess of hydrogen was undoubtedly due to reaction of the dioxane with hydrogen, which proved to be very detrimental in this case.

After all the material was distilled which would come over at atmospheric pressure (with the oil-bath at 20°), there remained 5.1 g. of high boiling residue, of which 2.0 g. distilled between 130 and 217° at 2 mm. The residue was even higher boiling. This material was probably formed by alkylation of the hydroxyl groups, formed in the reaction of dioxane with hydrogen, with the amino group in the hexahydroazepine formed.

However, when dry hydrogen chloride was passed into the dioxane fraction and the solvent removed under reduced pressure, 0.25 g., 6.6% of **hexahydroazepine** hydrochloride remained. After two recrystallizations it melted at 229–231° (corr.). Müller and Sauerwald give the melting point of this substance as 236° (corr.). Von Braun and Goll give the melting point as 222° while Wallach gives 221–224°. This substance could not be either 2-, 3- or 4-methylpiperidine hydrochloride because samples of the 2- and 4-derivatives were available for comparison and 3-methylpiperidine hydrochloride melts at 171–172°. Also, it apparently is not 2-ethylpyrrolidine hydrochloride because this substance is described as a hygroscopic solid which melts below 100°.

The *p*-toluenesulfonamide melted at 75° in agreement with the value of 75° reported in the literature by Ziegler,[21] and the chloroplatinate melted at 199° (corr.). Müller and Sauerwald[22] gave the melting point at 197° (corr.).

A sample of 2-ethylpyrrolidine was prepared in this Laboratory by Mr. James Rainey, by the hydrogenation of 2-acetylpyrrole. The picrate of this substance melted at 85–86° and the chloroplatinate at 190–191°. Both of these melting points agree with those reported by Müller and Wachs.[23] The chloroplatinate apparently was pure since the melting point was not raised by further recrystallization. The melting point was not depressed by mixing with the chloroplatinate of hexahydroazepine, however. The mixed melting point was 193°.

Preparation of Amides and Imides

In making simple amides, the ester was treated with gaseous ammonia in a bomb at 250° (Table V). The ammonia was introduced into a bomb as a liquid. The ester was placed in a test-tube in a bomb, and the latter was cooled in an ice–calcium chloride bath for about three hours. Then liquid ammonia was run into the bomb slowly until the interior was well cooled. The ammonia was then run in rapidly and the bomb closed immediately. No hydrogen was placed in the bomb in these experiments. When either an amide or imide is prepared (under pressure) from the free acid (Table VI), it is necessary to use dioxane as a diluent for the water formed.

If the amides prepared as above were solids in the bomb they were removed, cooled, filtered and recrystallized from the solvent indicated in Table V. The ethyl alcohol and excess of amine from the filtrate of the reaction product were removed under reduced pressure and the residue purified by recrystallizing. The products which were present as liquids when the bomb was opened were purified by fractionation.

N-Benzyl-β-phenylglutarimide and N-*n*-amylglutarimide were purified by fractionation through a Widmer column. N-Phenethyl-β-methylglutarimide was separated from the amide by fractional crystallization from methyl alcohol. Since the imide is more soluble than the amide it could not be freed entirely from the latter.

The amide present as an impurity was neither converted into the imide nor hydrogenated under the conditions used (Table II), and was recovered unchanged. Some of the amide was insoluble in the dioxane, so when the bomb was opened after hydrogenation of this compound reported in Table II, the catalyst and amide were filtered off. The amide was dissolved immediately in 95% ethyl alcohol and the catalyst filtered off. The two filtrates were combined and fractionated. There was obtained 18.7 g. of 1-β-cyclohexylethyl-4-methylpiperidone-2, b. p. 158–162° (3 mm.). The residue from the first fractionation was 3.9 g. On recrystallization from methyl alcohol it melted at 180–185°, and mixed with di-N-phenethyl-β-methylglutaramide it melted at 186–188°. Since 30.1 g. of the mixture of amide and imide was used, 13% of the mixture was amide. Thus 26.2 g. of imide was present in the mixture, and the yield of piperidone calculated on this basis was 74%.

All the **amides, and the imides of β,β-dimethylglutaric acid,** were prepared by heating the corresponding diethyl ester (1 mol) with four moles of the amine at temperatures of from 180–250° under 125 atm. of hydrogen. Twice the calculated amount of amine is necessary because some of it is alkylated by the ethyl alcohol set free.[24] The esters were previously treated with about 5% of their weight of Raney nickel under 100 atm. of hydrogen at 150° for about six hours to remove any impurities which might poison a catalyst, and to ensure the purity of the amides. It was found that in most cases a temperature of 200° was sufficient for the preparation of amides, but since there were a few exceptions it was considered preferable to carry out the reactions at 250°. Also, most of the reactions were probably complete in much less than the time indicated, but since longer heating does no harm, no particular attempt was made to stop the reactions as soon as they were complete.

β-Phenylglutarimide, m. p. 174–175° (from methanol), was prepared by the method of Vorländer[15] in yields of 62 to 72%. β-Methylglutarimide, m. p. 144–145° (from acetone and ether), was similarly prepared in 72% yield.[13]

Preparation of Acids, Esters and Glycols

Diethyl glutarate was prepared by the hydrolysis of ethyl methylene–dimalonate with 38% sulfuric acid.[25] By this procedure 67–75% of the ester could be obtained directly. Three hundred thirty-two grams (1.0 mole) of the ester and 532 g. of 38% sulfuric acid (prepared from 330 cc. of water and 110 cc. of concentrated sulfuric acid, sp. gr. 1.84) were placed in a 2-liter round-bottomed flask and refluxed vigorously for ten hours. The contents of the flask should be shaken vigorously several times until refluxing starts. Otherwise the bottom layer may become greatly superheated, causing the material to boil out through the condenser. The solution became clear in six hours, but if the reaction was stopped at this point the yields were greatly reduced. When the contents of the flask had cooled to room temperature, the oily layer was separated and the aqueous layer extracted three times with 150-cc. portions of benzene. The benzene and ester were combined, dried over anhydrous sodium sulfate and the benzene distilled at atmospheric pressure. The residue was placed in a flask under a Widmer column and heated in an oil-bath at 150° under reduced pressure until the evolution of carbon dioxide ceased. The ester was then fractionated. This distillation is accompanied by con-

(21) Ziegler and Orth, *Ber.*, **66B**, 1867 (1933).
(22) Müller and Sauerwald, *Monatsh.*, **48**, 526, 730 (1927).
(23) Müller and Wachs, *ibid.*, **53**, 420 (1929).
(24) Winans and Adkins, THIS JOURNAL, **54**, 306 (1932).
(25) Welch, *J. Chem. Soc.*, 673 (1931).

siderable foaming so a column of some sort is necessary. The material boiling at 104–108° (8 mm.) was collected. On refractionation the ester boils at 105–106° (8 mm.). The refractionation of four runs of the size described above gave 563 g. (75% of theoretical) of pure diethyl glutarate, b. p. 105–106° (8 mm.).

β-Phenylglutaric acid was prepared from benzylidenebismalonic ester by hydrolysis with hydrochloric acid.[26] The reaction was carried out in a manner similar to that described in "Organic Syntheses" for the preparation of tricarballylic acid.[27] Three hundred and seventy grams (0.9 mole) of the ester, 125 cc. of water, and 125 cc. of concentrated hydrochloric acid were placed in a 2-liter round-bottomed flask carrying a Widmer column and a condenser set for downward distillation. The mixture was boiled at such a rate that the temperature at the head of the column remained at 80–100°. In this manner the alcohol was removed as formed, but very little water was allowed to distil. This was continued until the solution became clear and no more carbon dioxide was evolved (thirty hours). Twice during this time further 100-cc. portions consisting of 50 cc. of water and 50 cc. of concentrated hydrochloric acid were added.

The flask was cooled in an ice-bath and the crystals were filtered and dried by suction. The dried acid was dissolved in 200 cc. of hot acetone, treated with charcoal and filtered. Half the acetone was distilled and an equal volume of benzene added. One hundred twenty-five grams (67%) of pure β-phenylglutaric acid separated, m. p. 139–140°. (Melting points of 138 and 143° are given in the literature.) The filtrate gave an additional 44.5 g. of acid, m. p. 138–139° (24%). The total yield was 91% of the theoretical.

In preparing diethyl β-phenylglutarate the above procedure was followed except that the crude acid was not purified. Four hundred five grams (1 mole) of benzylidenebismalonic ester was hydrolyzed as above. To the crude, dry acid was added a mixture of 460 cc. of 95% ethyl alcohol and 25 cc. of concentrated sulfuric acid. The mixture was refluxed for six hours on the steam-bath. Then the excess alcohol and the water formed were removed under reduced pressure by warming on the steam-bath until the temperature of the residue was 50° (20 mm.). Then 200 cc. of absolute ethyl alcohol and an additional 10 cc. of concentrated sulfuric acid was added and the mixture refluxed for three hours. The excess alcohol was removed under reduced pressure and the residue poured into water. The oily layer was separated and the aqueous layer extracted twice with ether. The ether solution of the ester was extracted twice with 5% sodium carbonate solution, twice with water and dried over anhydrous sodium sulfate. The ether was removed at atmospheric pressure and the residue distilled *in vacuo*. One hundred sixty grams of ester was obtained (85%) which distilled at 143–145° (1.5 mm.); von Braun and Weissbach[28] report the boiling point of this ester as 148–150° at 0.5 mm.

β-Methylglutaric acid was made as by Boorman, Linstead and Rydon except that the triethyl 2-methylpropanetricarboxylate obtained as an intermediate was purified before hydrolysis. The triester b. p. 117–119° was obtained in 80–85% yield. The yield of acid m. p. 86.5–87.5° was 80%, based on the triester used.[29]

Diethyl-β-methylglutarate was prepared in a manner analogous to that used in the preparation of diethyl-β-phenylglutarate, in a yield of 90% from the pure acid. It boils at 117–118° (13 mm.).

Diethyl-β,β-dimethylglutarate was obtained through the kindness of Dr. Roger Adams.

β-Methylglutaric anhydride was prepared by the method of Darbishire and Thorpe[30] in a yield of 92%, b. p. 141–142° (8 mm.) and m. p. 41–43°.

The glycols were prepared by the hydrogenation of esters.[31]

Summary

Glutaramide gave a 70% yield of piperidine by treatment with hydrogen under 200–400 atm. pressure over copper–chromium oxide at 250° in dioxane solution. Eight N-monosubstituted amides of glutaric, β-methyl-, β-phenyl- and β,β-dimethylglutaric acid in which the substituents on the nitrogen atom were the *n*-amyl, benzyl or phenethyl group, gave 65–80% yields of piperidines substituted in the 1 and 4 positions. Glutarimides gave yields of piperidines of the same order of magnitude. The di-N-pentamethylene amides of glutaric, β-methyl- and β,β-dimethylglutaric acid gave rise to 45–71% yields of di-N-pentamethylenecadaverines.

Under the same conditions two 2-pyrrolidones and one 2-piperidone have been converted to the corresponding pyrrolidines and piperidine in yields of 88–96%.

Primary amines have been found to react with 1,4- or 1,5-glycols under the conditions used for the hydrogenation of amides, to give 68–77% yields of pyrrolidines or piperidines.

The hydrogenation of di-N-*n*-amyladipamide was shown to give a 45% yield of 1-*n*-amylhexahydroazepine. Thirty-four per cent. of this material was isolated in the pure state from the di-*n*-amylamine which was formed to the extent of 41%.

Treatment of hexanediol-1,6 with benzylamine gave a 23% yield of 1-benzylhexahydroazepine which was converted to hexahydroazepine by treatment with hydrogen over copper–chromium oxide at 275°.

Two N-substituted succinimides and one glutarimide have been converted to the corre-

(26) Kötz, *J. prakt. Chem.*, [2] **75**, 486 (1907).

(27) "Organic Syntheses," 508 (1932).

(28) Von Braun and Weissbach, *Ber.*, **64**, 1787 (1931).

(29) Auwers, Köbner and Meyerburg, *ibid.*, **24**, 2888 (1891); Day and Thorpe, *J. Chem. Soc.*, **117**, 1469 (1920); Boorman, Linstead and Rydon, *ibid.*, 573 (1933).

(30) Darbishire and Thorpe, *ibid.*, **87**, 1717 (1905).

(31) Adkins, Folkers and Wojcik, THIS JOURNAL, **54**, 1145, 4939 (1932).

sponding pyrrolidone-2 or piperidone-2 by treatment with hydrogen over Raney nickel at 200–220°.

When diethyl glutarate, or diethyl β-methyl- or β-phenyl-glutarate, was heated with four moles of a primary amine at 250°, amides were formed to the extent of 83–94%. When diethyl β,β-dimethylglutarate was so treated, yields of 39–71% of the glutarimides were formed.

Glutarimides were formed in yields of 42 to 62% by heating glutaric, β-methyl- or β-phenyl-glutaric acid with one mole of primary amine at 250°. This is appreciably less than the yields of succinimides obtained from succinic acid and primary amines.

An improved method for preparing diethyl glutarate has been developed.

MADISON, WIS. RECEIVED OCTOBER 1, 1936

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Rates of Alcoholysis of Acyl Chlorides

G. E. K. BRANCH AND A. C. NIXON

We have recently published the results of a study[1] in which we investigated the effect of the para-substitution of certain groups on the rates of alcoholysis of triphenylmethyl chlorides. In this paper we pointed out that predictions concerning rates in which I and T effects are used merely on the direction of electrical forces tending to prevent or assist the separation of an ion are not necessarily sound, although the actual results we obtained with the trityl chlorides could have been predicted on this basis. As we strongly suspected that this crude method of using I and T effects would be entirely erroneous when applied to the alcoholysis of acyl chlorides, we have used an identical method to measure the rates of alcoholysis of some acyl chlorides. The compounds studied are mainly para substituted benzoyl chlorides but measurements on some aliphatic compounds are also included.

We employed the same solvent as before, namely, a mixture containing by volume at 25°, 60% ether and 40% absolute ethyl alcohol. The reactions were followed by observing the rate of change of the electrical conductivity of solutions containing acid chloride. This method was used on the assumption that the hydrochloric acid produced had a much higher conductivity than any of the other constituents of the solution and hence the concentration of the acid could be determined from the conductivity of the solution by reference to a previously determined conductivity–concentration curve for hydrochloric acid. The concentration of the organic chloride at any time could then be determined as the difference between the hydrochloric acid concentration at that time and the final hydrochloric acid concentration after completion of the reaction. This method is very suitable for measuring low concentrations. We used concentrations around 0.001 *M*, and could follow the reactions accurately to more than 95% completion.

The reaction was found to be irreversible at the concentrations used since the conductivity of a 0.001 *N* hydrochloric acid in the alcohol–ether mixture was found to be unchanged by the addition of an equivalent quantity of ethyl *p*-nitrobenzoate. The irreversibility of the reaction has been shown more definitely by Norris and his co-workers,[2] who showed that ethyl *p*-nitrobenzoate was unaffected when hydrogen chloride gas was bubbled through the molten ester. Their tests also showed the absence of side reactions.

A detailed description of the method and apparatus used is given in our previous communication.[1] The method consisted essentially of mixing 20 cc. (25°) of alcohol with 30 cc. (25°) of an ether solution of the chloride at the bath temperature and then measuring the resistance of the solution at convenient intervals. The cell resistance was determined by means of the usual Wheatstone bridge arrangement, an a. c. galvanometer being used as a null instrument.

Preparation of Materials

(a) Alcohol and Ether.—These were prepared as reported previously and had within limits of error the same physical constants.

(1) A. C. Nixon and G. E. K. Branch, THIS JOURNAL, **58**, 492 (1936).

(2) J. F. Norris, E. V. Fasce and C. J. Staud, *ibid.*, **57**, 1415 (1935).