propiophenone (I) was dissolved by warming to 60° for ten minutes in 10 cc. of sodium methylate solution containing 0.46 g. (0.02 mole) of sodium and the orange-yellow solution was left for eighteen hours, it deposited on chilling 2.19 of α-aminobenzalacetophenone (IX); yield, 94%. The product, after crystallization from methyl alcohol, melted at 100–101°. This amino ketone, which had previously been prepared by a different method,[8] was identified by analysis, by the formation of a hydrochloride melting with decomposition at 180° (instantaneous melting point, 185°), and by hydrolysis on warming with dilute hydrochloric acid to phenylbenzylglyoxal which was isolated and characterized as the antimony derivative, m. p. and mixed m. p. 174–175°.

When 6.7 g. (0.02 mole) of β-phenyl-β-methoxyamino-p-bromopropiophenone (VI) was dissolved in 20 cc. of warm sodium methylate, containing 0.92 g. of sodium (0.04 mole), plus 20 cc. of absolute methyl alcohol and warmed for fifteen minutes the orange reaction mixture set solid on cooling. Chilling and filtering furnished 5.0 g. of α-aminobenzal-p-bromoacetophenone, a yield of 83%.

Summary

Methoxyamine adds to benzalacetophenone and its p or p' substituted analogs to furnish β-methoxyaminopropiophenones and β,β'-methoxyimino-bis-propiophenones. The same reagent adds also to benzoylphenylacetylene. The addition reaction has been shown to be reversible and the structures of the addition products have been established. The chemical behavior of the addition products has been described and it has been shown that the β-methoxyaminopropiophenones on treatment with strong bases lose a molecule of alcohol and rearrange to form α-amino unsaturated ketones.

FLUSHING, N. Y.   RECEIVED SEPTEMBER 27, 1939

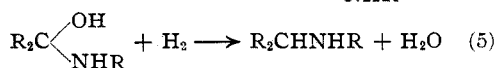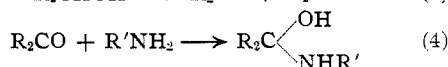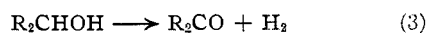[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Preparation of Certain Amines

BY EDWARD J. SCHWOEGLER AND HOMER ADKINS

Alcohols react with primary and secondary amines under the influence of such hydrogenating and dehydrogenating catalysts as nickel,[1,2] palladium[3] and copper chromite[4,5] with the formation of secondary and tertiary amines.

$$ROH + R'NH_2 \longrightarrow RNHR' + H_2O \quad (1)$$
$$ROH + R'_2NH \longrightarrow RNR'_2 + H_2O \quad (2)$$

Since tertiary alcohols do not show this type of reaction it is plausible to asume that the primary function of the catalyst is to dehydrogenate the alcohol to an aldehyde or ketone. The latter would then react with an amine to give a product which is readily hydrogenated to an amine.

$$R_2CHOH \longrightarrow R_2CO + H_2 \quad (3)$$

$$R_2CO + R'NH_2 \longrightarrow R_2C\begin{smallmatrix}OH\\ \\NHR'\end{smallmatrix} \quad (4)$$

$$R_2C\begin{smallmatrix}OH\\ \\NHR\end{smallmatrix} + H_2 \longrightarrow R_2CHNHR + H_2O \quad (5)$$

An alternative series of reactions depending upon the dehydrogenation of the original amine instead of the alcohol is not plausible for the product of reactions similar to (3), (4) and (5) would be an ether:
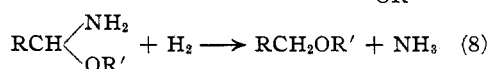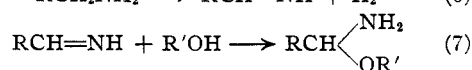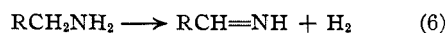
(1) Adkins and Cramer, THIS JOURNAL, **52**, 4350 (1930).
(2) Winans and Adkins, *ibid.*, **54**, 306 (1932).
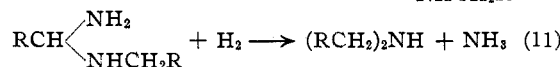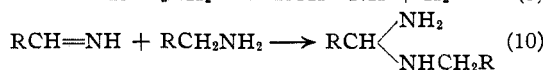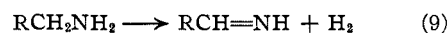(3) Kindler, *Ann.*, **485**, 113 (1931).
(4) Paden and Adkins, THIS JOURNAL, **58**, 2487 (1936).
(5) Hill and Adkins, *ibid.*, **60**, 1033 (1938).

$$RCH_2NH_2 \longrightarrow RCH{=}NH + H_2 \quad (6)$$

$$RCH{=}NH + R'OH \longrightarrow RCH\begin{smallmatrix}NH_2\\ \\OR'\end{smallmatrix} \quad (7)$$

$$RCH\begin{smallmatrix}NH_2\\ \\OR'\end{smallmatrix} + H_2 \longrightarrow RCH_2OR' + NH_3 \quad (8)$$

However, a dehydrogenation as shown in (6) probably occurs, for secondary amines having the same alkyl groups as the primary amine are readily formed over palladium,[3] nickel[2] and copper chromite.[4] In fact this reaction constitutes an important side reaction when it is desired to combine an alcohol and an amine according to the type reactions (1) and (2). The series of probable reactions is

$$RCH_2NH_2 \longrightarrow RCH{=}NH + H_2 \quad (9)$$

$$RCH{=}NH + RCH_2NH_2 \longrightarrow RCH\begin{smallmatrix}NH_2\\ \\NHCH_2R\end{smallmatrix} \quad (10)$$

$$RCH\begin{smallmatrix}NH_2\\ \\NHCH_2R\end{smallmatrix} + H_2 \longrightarrow (RCH_2)_2NH + NH_3 \quad (11)$$

Reactions of the type shown in (1) and (2) go smoothly and almost quantitatively in certain cases, but this is by no means always true. It seemed desirable therefore to ascertain the optimum conditions for the reaction of representative alcohols and aliphatic amines. The data given in Table I indicate the yields which have been obtained under the specified conditions. A consid-

erable number of variations in the experimental conditions have been made and the ones specified for the various reactants gave the highest yields among those tried. It is probable that variations in the temperature and duration of reaction, ratio of catalyst to reactants, etc., would give even higher yields of the desired products.

The data in the table show very clearly that the optimum conditions vary with the alcohol and with the amine. The optimum yield varies over

TABLE I

YIELDS OF AMINES BY REACTION OF ALCOHOLS AND AMINES[a]

Alcohols	Amines			
	n-Amyl-amine	Piperidine	Phen-ethyl-amine	2-Me-4-amino-pentane
Ethyl	39% a	82% c	67% b	53% g
		31 d		
n-Propyl	15 a	63 d	26 b	61 a
i-Propyl	43 a	46 d	67 b	50 a
n-Butyl	6 a	70 c	60 b	48 j
		83 f		
n-Hexyl	....	84 d	....	...
Cyclohexyl	57 e	59 d	58 b	37 h
2-Ethylhexyl	....	29 i	....	....
n-Dodecyl	0 a	69 c	14 b	47 h
		78 d		

[a] Equimolecular quantities (usually 0.2 mole) of amine and alcohol and 4 g. of copper chromite were used except in (c) where 3 to 4 g. of Raney nickel and (f) and (j) where 8 g. of copper chromite was the catalyst. Eighty ml. of dioxane was used as a solvent for 0.2 mole of amine except in (c) where an excess of alcohol, and (a) and (g) where diethyl ether was the reaction medium. All reactions were carried out under 125 atm. of hydrogen at the temperatures and for the duration of time indicated below: (a) and (e) twelve hours at 180°, (b) and (c) three and one-half hours at 200°, (d) and (f) three and one-half hours at 250°, (g), (h) and (j) twelve hours at 200°, (i) twelve hours at 250°.

wide limits even if comparisons are made with the same amine and different alcohols or the same alcohol with different amines. Among the four amines, the best yields were with piperidine while the poorest were with n-amylamine. This may be correlated with the fact that higher temperatures could be used with piperidine than with n-amylamine. The higher temperature which may be used with piperidine as contrasted with the primary amines is probably due to the fact that the latter may form secondary amines through reactions (9), (10) and (11). For example, yields as high as 52% of diphenethylamine were obtained at 250° over copper chromite. At 200° no appreciable amount of diphenethylamine was formed.

Mignonac was the first to prepare amines by the hydrogenation of aqueous ammoniacal or amine solutions of aldehydes and ketones.[6] Later it was shown that better yields of the amines were obtained if the ammonia or amine addition product of the aldehyde were isolated and the hydrogenation carried out in an organic solvent.[7] However, there has been described no practical method for preparing primary amines directly from aldehydes or ketones and ammonia.[8] The most satisfactory method for converting an aldehyde or ketone to a primary amine has been through the preparation of the oxime.[7,9]

Representative ketones and aldehydes have now been converted in good yields to the corresponding primary amines by dissolving the carbonyl compound in a mixture of methanol and liquid ammonia and hydrogenating over Raney nickel. The reaction mixture in most cases consisted of 0.5 mole of carbonyl compound, 0.7 mole of ammonia, 50 ml. of methanol and 3 to 4 g. of Raney nickel under 150 atm. of hydrogen. Preparations were also made on a slightly smaller scale and on quantities six times as large as those specified above. Except for benzaldehyde (125°) and furfural (125 to 140°) the temperature for reaction was 150°. The period of reaction was usually about one hour, though furfural was complete after ten minutes, while benzophenone was heated for three and one-half hours before the absorption of hydrogen ceased.

Among the compounds which have given good results are heptaldehyde, benzaldehyde, acetophenone, pinacolone and several dialkyl ketones. The yields of various amines were as follows: 2-methyl-4-aminopentane, 65%; α-phenethylamine, 64%; benzhydrylamine, 19%; 2,2-dimethyl-3-aminobutane, 51%; 5-aminononane, 72%; 2,4-dimethyl-3-aminopentane, 48%; benzylamine, 48%; n-heptylamine, 59%; and furfurylamine, 60%. Acetonylacetone under the same conditions gave 2,5-dimethylpyrrolidine, 28%, and 2,5-dimethylpyrrole, 59%, while acetylacetone underwent aminolysis to give acetamide in quantitative yield.

Secondary amines are formed in very consider-

(6) Mignonac, Compt. rend., 172, 275 (1921).

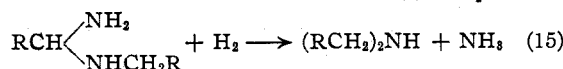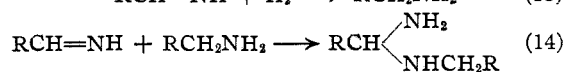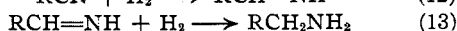(7) Winans and Adkins, THIS JOURNAL, 55, 2051 (1933).

(8) Since the completion of the experimental work described herein a U. S. patent 2,109,159, Feb. 22, 1938, has been issued to C. F. Winans covering the hydrogenation of a mixture of furfural and ammonia in an inert organic solvent with the production of furfuryl-amines.

(9) Martha E. Smith and Adkins, THIS JOURNAL, 60, 660 (1938).

TABLE II
PHYSICAL PROPERTIES AND ANALYTICAL DATA

Amine	Formula	Amines B. p., °C.	Mm.	$n^{25}D$	Nitrogen, % Calcd.	Found	Hydrochlorides M. p., °C.	Chlorine, % Calcd.	Found
N-2-Ethylhexylpiperidine	$C_{13}H_{17}N$	141	42	1.4520	7.10	6.99	162–163	15.17	15.24
N-n-Propyl-β-phenethylamine	$C_{11}H_{17}N$	102	16	1.4998	8.59	8.47	218	17.76	17.81
N-Isopropyl-β-phenethylamine	$C_{11}H_{17}N$	112	21	1.4990	8.59	8.44	163–164	17.76	17.59
N-Ethyl-n-amylamine	$C_7H_{17}N$	136		1.4111	12.17	12.38	195	23.48	23.51
N-n-Propyl-n-amylamine	$C_8H_{19}N$	155		1.4161	10.85	11.01	247(d)	21.41	21.21
N-Isopropyl-n-amylamine	$C_8H_{19}N$	146		1.4113	10.85	10.81	167–167.5	21.41	21.45
N-Cyclohexyl-n-amylamine	$C_{11}H_{23}N$	118	30	1.4500	8.28	8.08			
N-Ethyl-2-Me-4-aminopentane	$C_8H_{19}N$	136		1.4105	10.84	10.67	144–145	21.41	21.55
N-n-Propyl-2-Me-4-aminopentane	$C_9H_{21}N$	162		1.4148	9.78	9.73	139	19.73	19.59
N-n-Butyl-2-Me-4-aminopentane	$C_{10}H_{23}N$	179		1.4192	8.91	8.79	149–150	18.31	18.23
N-Dodecyl-2-Me-4-aminopentane	$C_{18}H_{39}N$	170–172	12	1.4410	5.20	5.04	124.5–125	11.60	11.66
N-Cyclohexyl-2-Me-4-aminopentane	$C_{12}H_{25}N$	106	21	1.4530	7.65	7.91	198–199	16.07	16.03
N-Isopropyl-2-Me-4-aminopentane	$C_9H_{21}N$	146		1.4098	9.78	9.80	158.5	19.73	19.88
2-Me-4-aminopentane	$C_6H_{15}N$	108–109		1.4063			139.5	25.77	25.76
N-Ethyl-β-phenethylamine	$C_{10}H_{15}N$	85 / 81	8 / 6				183.5–184	19.11	19.00
N-n-Butyl-β-phenethylamine	$C_{12}H_{19}N$	113.5	6					16.60	16.44
2,4-Di-Me-3-aminopentane	$C_7H_{17}N$	129					196	25.77	25.75
2,2-Di-Me-3-aminobutane	$C_6H_{15}N$	102					296–297 (subl.)	25.77	25.78
2,5-Di-Me-pyrrolidine	$C_6H_{13}N$	113–118					201–202	26.15	26.20
Picrate of isopropylpiperidine	$C_{14}H_{20}N_4O_4$	(M. p.) 153			15.73	15.91			
Phenyl isocyanate deriv. of N-cyclohexyl-n-amylamine	$C_{18}H_{28}N_2O$	(M. p.) 110			9.72	9.78			

able yields through the hydrogenation of cyanides. Seldom is the ratio of primary to secondary amine greater than 3 to 1 and in some instances it is not more than 2 to 1. The formation of the secondary amine probably results from the following series of reactions as originally suggested by von Braun[2]

$$RCN + H_2 \longrightarrow RCH=NH \quad (12)$$
$$RCH=NH + H_2 \longrightarrow RCH_2NH_2 \quad (13)$$
$$RCH=NH + RCH_2NH_2 \longrightarrow RCH\diagdown{NH_2 \atop NHCH_2R} \quad (14)$$
$$RCH\diagdown{NH_2 \atop NHCH_2R} + H_2 \longrightarrow (RCH_2)_2NH + NH_3 \quad (15)$$

It seemed possible therefore to minimize the formation of secondary amines by carrying out the hydrogenation in the presence of ammonia. The imine formed according to reaction (12) would then have less opportunity to undergo reaction (13) because ammonia would also add to the imine

$$RCH=NH + NH_3 \longrightarrow RCH\diagdown{NH_2 \atop NH_2} \quad (16)$$
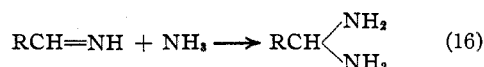
The hydrogenolysis (17) of the product of reaction (16) would give a primary amine and not a secondary amine as would be produced by reac-

tion (15) from the addition product of reaction (14).[10]

$$RCH\diagdown{NH_2 \atop NH_2} + H_2 \longrightarrow RCH_2NH_2 + NH_3 \quad (17)$$
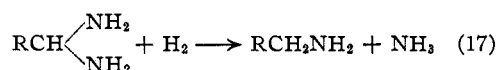
The results of hydrogenating n-butyl cyanide and n-hexyl cyanide in the presence of ammonia at 125° over Raney nickel supported this hypothesis. The yields of secondary amine were less than 5% and the yields of the primary amines, $C_5H_{11}NH_2$ and $C_7H_{15}NH_2$, were from 90 to 95%. In these experiments from 0.4 to 0.7 mole of the cyanide was hydrogenated mixed with from 0.9 to 1.6 mole of ammonia.

The reactions were carried out in steel reaction vessels using standard equipment, procedures and catalysts.[11] The products were usually separated by fractionation through a modified Widmer column having a spiral 18 cm. in length with one turn of the helix per cm.[9] The technique for

(10) There is no evidence as to whether the reactions shown in (5), (11), (15) and (17) proceed through hydrogenolysis as indicated or through a loss of ammonia and the hydrogenation of the resulting imine.

(11) Adkins, "Reactions of Hydrogen, etc.," University of Wisconsin Press, Madison. Wisconsin. 1937.

using liquid ammonia has been described in connection with the preparation of diacetoneamine.[12]

Alcohols, amines, ketones, aldehydes and cyanides were freed of any halogen-containing impurity by means of Raney nickel before they were submitted to reaction. In other respects these compounds were prepared and purified by the usual procedures.

Amines distilling over with solvents were recovered as the hydrochlorides and the amines regenerated with alkali and purified by fractional distillation. Amines were characterized by analysis and by the formation of solid derivatives. Neutral equivalents were determined upon all the amines reported.

Analytical data and physical properties of several amines and their derivatives not previously reported are given in Table II. References for certain other amines and their derivatives are given herewith: N-ethylpiperidine,[13] N-n-propylpiperidine,[13] N-i-propylpiperidine,[13] N-n-butyl-piperidine,[14] N-n-hexylpiperidine,[15] N-cyclohexyl-piperidine,[2] N-n-dodecylpiperidine,[16] N-cyclohexyl-phenethylamine,[17] N-n-dodecylphenethylamine.[18]

(12) Martha E. Smith and Adkins, THIS JOURNAL, 60, 408 (1938).
(13) Evans, J. Chem. Soc., 71, 524 (1897).
(14) Von Braun, Ber., 40, 3930 (1907).
(15) Von Braun and Buckman, ibid., 64B, 2610 (1931).
(16) Wojcik and Adkins, THIS JOURNAL, 56, 2419 (1934).
(17) Wieland, Schopf and Hermsen, Ann., 444, 40 (1925).
(18) Wojcik and Adkins, THIS JOURNAL, 56, 2424 (1934).

α-phenethylamine,[19] benzhydrylamine,[20] 5-amino-nonane,[21] benzylamine,[22] n-heptylamine,[23] furfurylamine,[8] 2,5-di-Me-pyrrole, N-n-butyl-n-amyl-amine,[24] 2,2-di-Me-3-aminopentane,[25] 2,4-di-Me-3-aminopentane.[26]

Summary

Favorable conditions for the reaction of eight representative alcohols with four different amines to give secondary and tertiary amines have been ascertained.

It has been found that representative aldehydes, dialkyl ketones and alkyl aryl ketones may be directly converted in good yields to primary amines by hydrogenating them over Raney nickel in an ammonia–methanol mixture.

The formation of secondary amines in the hydrogenation of cyanides over Raney nickel may be almost entirely prevented by carrying out the hydrogenation in the presence of sufficient ammonia.

(19) Tafel, Ber., 19, 1929 (1886).
(20) Heilbron, "Dictionary of Organic Compounds," Vol. I, Eyre and Spottiswoode, London, 1934, p. 49.
(21) Unpublished work by G. M. Whitman.
(22) Hoogewerff, Rec. trav. chim., 5, 253 (1886).
(23) Mulliken, "Identification of Pure Organic Compounds," Vol. II, John Wiley and Sons, New York, N. Y., 1916, p. 140.
(24) Ochiai and Tsuda, J. Pharm. Soc. Japan, 56, 352 (1936).
(25) Markownikoff, Ber., 32, 1448 (1899).
(26) Mailhe, Bull. soc. chim,. 27, 541 (1920).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Conjugation of Amino Acids with Isocyanates of the Anthracene and 1,2-Benzanthracene Series[1]

BY LOUIS F. FIESER AND HUGH J. CREECH[2]

This communication describes results obtained in an extension of the program of research initiated by Franks and one of us[3,4,5] on the problem of conjugating carcinogenic hydrocarbons with proteins and investigating their possible immunizing action against hydrocarbon carcinogenesis. In the previous work the meso isocyanate derivatives of anthracene and 1,2,5,6-dibenzanthracene were prepared, characterized by reaction with simple amines and

alcohols, and linked to various proteins by interaction in aqueous dioxane solution. The conjugated proteins were found to possess definite antigenic properties, varying with the nature of the prosthetic group, and experiments with preparations of 1,2,5,6-dibenzanthryl-9-carbamido-casein afforded some indications of an immunization against the action of dibenzanthracene. The material was also found to be mildly carcinogenic, and this property was discovered also in the conjugate from dibenzanthryl isocyanate and glycine.

As one step in the extension of this work we have prepared and characterized the isocyanates resulting from the interaction of phosgene with