

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Preparation of Mixed, Secondary Aliphatic Amines,  $RR'NH^{1,2}$ BY HENRY R. HENZE AND DAVID D. HUMPHREYS<sup>3</sup>

In connection with a program of synthesis of pharmaceutical products, a number of mixed, secondary amines were needed. Compounds of the type  $HNR'R''$  in which one group is aryl and the other alkyl are obtainable fairly readily by standard methods of synthesis, but those possessing two different alkyls are not so easily obtained. For production of this type three methods, perhaps, are used more commonly.

(1) The Hinsberg<sup>4</sup> method leads to the preparation of a pure mixed secondary amine but the procedure is somewhat involved, is not rapid and frequently the over-all yield is low.

(2) Stepwise alkylation of aniline with a subsequent nitrosation and alkaline hydrolysis<sup>5</sup> leads to the formation of a mixed, secondary amine in a state of purity dependent upon that of the mixed dialkyl aniline used.

(3) Interaction of a primary amine and a carbonyl compound with subsequent reduction of the imine.

(a) Reduction by means of sodium and alcohol<sup>6</sup> requires a separation and purification of the imine with a consequent loss of time and product.

(b) As reported by Skita and Keil,<sup>7</sup> reduction with colloidal platinum and hydrogen at room temperature and three atmospheres pressure for two to three hours produced, in satisfactory yield, several secondary amines of carbon content between  $C_9$  and  $C_{15}$ .

(c) Mailhe<sup>8</sup> stated that catalytic reduction of the imine derived from isovaleraldehyde and ethylamine, by passing its vapors over finely divided nickel in the presence of hydrogen at a temperature of 190–200°, yielded N-ethyl-isomethylamine as the principal product together with some diethylamine and triethylamine.

In all probability the infrequency of reference in the chemical literature to the use of mixed, secondary aliphatic amines is highly indicative of the

fact that these methods are neither very simple, rapid, nor productive of wholly satisfactory yields.

Because of the success in this Laboratory<sup>9</sup> in obtaining mixed secondary amines by reduction in the presence of Raney nickel catalyst of the Schiff bases formed by the interaction of benzaldehyde, or a derivative, with a primary amine, it was decided to study the analogous synthesis of mixed, secondary aliphatic amines in a similar manner.

It has been found that without preliminary isolation or purification, the products formed from the interaction of primary amines and simple aldehydes, except formaldehyde, or ketones in a hydrocarbon solvent can be hydrogenated in the presence of Raney nickel catalyst to produce mixed, secondary aliphatic amines in satisfactory yield.

In the preparation of seven of the mixed amines obtained during this investigation, *n*-butylamine was allowed to react with the appropriate carbonyl compound. However, in the case of N-methyl-*n*-butylamine the reactants were methylamine and *n*-butyraldehyde and here a significant amount of N-methyl-di-*n*-butylamine was formed also. The other preparations yielded various amounts of high boiling basic mixtures of indefinite composition.

In order to characterize them further and at the same time obtain substances useful for other syntheses, the amines were condensed with bromoacetone to form aminoacetones. The latter are colorless or faintly yellow, slightly viscous liquids having a characteristic odor and when impure they acquire a red color very rapidly. However, when pure they remain essentially colorless for long periods of time. They are quite soluble in the usual organic solvents, but are insoluble in water. The molecular refractions and parachors calculated from the densities, refractive indices, and surface tensions check quite closely with the sum of the atomic refractions<sup>10</sup> and the atomic parachors.<sup>11</sup> All attempts to form picrates of the aminoacetones resulted in the formation of oils which could not be solidified. Treatment of anhydrous ether

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(2) From the Ph. D. dissertation of D. D. Humphreys, June, 1941.

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(4) Hinsberg, *Ann.*, **265**, 178 (1891).

(5) Baeyer and Caro, *Ber.*, **7**, 963 (1874).

(6) Störmer and Leper, *ibid.*, **29**, 2110 (1896).

(7) Skita and Keil, *ibid.*, **61**, 1452, 1686 (1928).

(8) Mailhe, *Bull. soc. chim.*, [4] **25**, 321 (1919).

(9) Magee with Henze, *THIS JOURNAL*, **62**, 910 (1940).

(10) Landolt-Börnstein, "Physikalisch-chemische Tabellen," 5. Auflage, II, p. 985.

(11) Sugden, *J. Chem. Soc.*, **126**, 1180 (1924).

TABLE I  
 N-ALKYL-*n*-BUTYLAMINES, R—NH—C<sub>4</sub>H<sub>9</sub>

	Yield, %	B. p. °C. (cor.)	mm.	<i>d</i> <sup>20</sup> <sub>4</sub>	<i>n</i> <sup>20</sup> <sub>D</sub>	Mol. refract.		$\gamma^{20}$
						Calcd.	Found	
Methyl <sup>a</sup>	26	89-91	750	0.7377	1.4011	28.89	28.71	22.46
Ethyl <sup>b</sup>	31	111-112	747	.7398	1.4040	33.51	33.45	22.52
<i>n</i> -Propyl <sup>c</sup>	31	138-139	745	.7497	1.4127	38.13	38.30	23.30
Isopropyl	52	124-125	748	.7408	1.4050	38.13	38.12	21.92
Isobutyl	56	150-151	738	.7519	1.4120	42.75	42.74	22.85
<i>s</i> -Butyl	51	149-149.5	751	.7568	1.4150	42.75	42.76	23.39
<i>n</i> -Amyl <sup>d</sup>	51	180-182	743	.7667	1.4230	47.36	47.59	24.50
Isoamyl <sup>e</sup>	41	175-177	745	.7658	1.4200	47.36	47.34	24.17

	Carbon, %		Hydrogen, %		Nitrogen, %		Parachor		Free surface energy
	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	
Methyl							258.8	259.3	540.8
Ethyl	71.21	70.98	14.94	14.96	13.85	13.92	297.8	298.0	597.8
<i>n</i> -Propyl	72.97	72.90	14.88	15.04	12.16	11.95	336.8	337.7	668.5
Isopropyl	72.97	72.72	14.88	14.85	12.16	12.25	336.8	336.5	634.0
Isobutyl	74.34	73.90	14.82	14.79	10.84	10.49	375.8	375.8	706.4
<i>s</i> -Butyl	74.34	74.27	14.82	15.01	10.84	11.14	375.8	375.5	720.0
<i>n</i> -Amyl	75.44	75.29	14.78	14.74	9.78	10.43	414.8	415.0	816.6
Isoamyl	75.44	75.70	14.78	14.97	9.78	10.01	414.8	414.8	790.6

<sup>a</sup> Franchimont and v. Erp, ref. 12a, reported *d*<sup>16</sup> 0.7375; b. p. 90.5-91.5°; Löffler and Freytag, ref. 12b, recorded *d*<sup>15</sup>, 0.7367; b. p. 90-91°; picrate, m. p. 111-112°; we find picrate, m. p. 112.5-113.5° (cor.). <sup>b</sup> Brill, ref. 13, reported b. p. 108-109°. <sup>c</sup> v. Braun and Weismantel, ref. 14, reported b. p. 134-135°. <sup>d</sup> Ochiai and Tsuda, ref. 15, listed b. p. 94° (45 mm.); Lazier and Adkins, ref. 16, recorded preparation of this amine but noted no data for its physical properties. <sup>e</sup> Ochiai and Tsuda, ref. 15, recorded b. p. 89° (45 mm.) and 85° (40 mm.).

solutions of these ketoamines with dry hydrogen chloride yielded no solid hydrochloride.

Where high pressure hydrogenation apparatus is available it is our belief that the method to be described below represents a simpler and more rapid procedure for preparing mixed, secondary, aliphatic amines in satisfactory yields than the older methods.

### Experimental

**Aldimines.**—Half-mole quantities of amine and aldehyde are separately dissolved in 25-cc. portions of Skellysolve. The solutions are chilled in a salt-ice mixture (except that of methylamine which is chilled to -15° with a bath of acetone chilled with solid carbon dioxide) and the solution of aldehyde is added slowly to that of the amine while shaking the mixture. Water begins to separate after approximately one-half of the aldehyde has been added. The reaction mixture is allowed to stand for one hour in the ice box and the water is separated. The hydrocarbon solution is dried over anhydrous potassium carbonate or sodium sulfate before hydrogenation.

**Ketimines.**—Half-mole quantities of amine and ketone are mixed with 50 cc. of Skellysolve and the clear, homogeneous solution is hydrogenated without any attempt at dehydration.

**Hydrogenation.**—The Skellysolve solutions as prepared above are hydrogenated at 75° in the Adkins apparatus using 10 g. of Raney nickel catalyst, and an initial hydrogen pressure of 3000 lb./sq. in. Separation of water occurs during the hydrogenation of the ketone-amine solution. The hydrogenation of the aldimines is practically complete within three hours, but that of the ketimine solutions requires three to four times that period.

**Isolation of the Amines.**—The hydrogenation solution is filtered from the catalyst and the amine is extracted with a slight excess of 6 *N* hydrochloric acid. After washing the acid solution with ether, it is made strongly alkaline with 40% sodium hydroxide and ether extracted. The ether solution of basic material is dried with anhydrous potassium carbonate, and after removal of the ether the crude amine is partially purified by distillation. The distillate is dried over sodium and fractionated to obtain the pure amine.

The *N*-alkyl-*n*-butylamines prepared by this procedure are the methyl, ethyl, *n*-propyl, isopropyl, isobutyl, sec-butyl, *n*-amyl and isoamyl compounds. In this series, synthesis of the methyl,<sup>12</sup> ethyl,<sup>13</sup> *n*-propyl,<sup>14</sup> *n*-amyl<sup>15,16</sup> and iso-amyl<sup>16</sup> members has been reported previously, but their characterization is incomplete.

**Preparation of Aminoacetones.**—The conversion of the amines to aminoacetones is accomplished by one of the methods used by Magee,<sup>9</sup> namely, the condensation of two-tenths mole of amine dissolved in 200 cc. of anhydrous ether with one-tenth mole of bromoacetone dissolved in 25 cc. of ether. The amine precipitated as hydrobromide is recovered and treated with another portion of bromoacetone until three reaction mixtures have been obtained. The combined ether solutions are washed with water, then the basic material is extracted with a slight excess of 6 *N* hydrochloric acid solution. The acid solution is washed with ether, then made alkaline with a considerable excess

(12) (a) Franchimont and v. Erp, *Rec. trav. chim.*, **14**, 317 (1894); (b) Löffler and Freytag, *Ber.*, **42**, 3429 (1909); (c) Graymore, *J. Chem. Soc.*, 1353 (1932).

(13) Brill, *THIS JOURNAL*, **54**, 2484 (1932).

(14) von Braun and Weismantel, *Ber.*, **55**, 3165 (1922).

(15) Ochiai and Tsuda, *J. Phar. Soc. Japan*, **56**, 357 (1936); through *C. A.*, **30**, 6363 (1936).

(16) Lazier and Adkins, *THIS JOURNAL*, **46**, 741 (1924).

TABLE II  
N-ALKYL-*n*-BUTYLAMINOACETONES.  $R(n-C_4H_9)NCH_2COCH_3$

--R	Yield, %	B. p.		$d_4^{20}$	$n_D^{20}$	$\gamma_D^{20}$	Mol. refract.	
		$^{\circ}C.$ (cor.)	mm.				Calcd.	Found
Methyl	68	76	19	0.8551	1.4720	27.96	43.10	43.01
Ethyl	41	87-88	17	.8537	1.4305	27.72	47.71	47.63
<i>n</i> -Propyl	74	90-91	12	.8512	1.4321	27.90	52.33	52.19
Isopropyl	55	92-94.5	13	.8576	1.4338	27.69	52.33	51.99
Isobutyl	55	106-107	14	.8476	1.4331	27.21	56.95	56.83
<i>s</i> -Butyl	57	105-106	12	.8610	1.4381	28.35	56.95	56.53
<i>n</i> -Amyl	65	110-111	6	.8508	1.4362	28.33	61.57	61.28
Isoamyl	62	80-82	3	.8441	1.4350	27.47	61.57	61.62

  

--R	Carbon, %		Hydrogen, %		Nitrogen, %		Parachor		Free surface energy
	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	
Methyl	67.08	66.74	11.97	12.27	9.78	9.64	384.8	385.4	849.6
Ethyl	68.74	68.45	12.18	12.27	8.91	10.93	423.8	432.7	897.4
<i>n</i> -Propyl	70.12	70.17	12.36	12.88	8.19	8.32	462.8	462.4	958.1
Isopropyl	70.12	69.72	12.36	12.51	8.19	8.26	462.8	458.2	946.2
Isobutyl	71.29	71.34	12.51	12.84	7.56	7.71	501.8	499.3	987.5
<i>s</i> -Butyl	71.29	70.86	12.51	12.55	7.56	8.01	501.8	496.6	1012.2
<i>n</i> -Amyl	72.30	72.11	12.62	12.68	7.03	7.77	540.8	540.5	1077.5
Isoamyl	72.30	72.56	12.62	12.84	7.03	7.07	540.8	540.7	1025.4

TABLE III  
SEMICARBAZONES OF N-ALKYL-*n*-BUTYLAMINOACETONES  
 $R(n-C_4H_9)NCH_2(CH_3)C=NNHCONH_2$

--R	Yield, %	M. p. $^{\circ}C.$ (cor.)	Nitrogen, %	
			Calcd.	Found
Methyl	69	104.0-104.5	27.78	27.76
Ethyl	62	126.5-127.5	26.15	25.95
<i>n</i> -Propyl	51	130.5-131.0	24.54	24.82
Isopropyl		151.0-152.0	24.54	25.43
Isobutyl	27	139.0-139.5	23.12	23.74
<i>s</i> -Butyl	72	172.0-172.5	23.12	23.41
<i>n</i> -Amyl	27	107.5-108.5	21.85	21.93
Isoamyl	32	116.0-117.0	21.85	21.63

of 40% sodium hydroxide solution. The basic material is extracted with ether and after drying over anhydrous potassium carbonate or sodium sulfate the ether is removed leaving the crude aminoacetone to be purified by fractional distillation. When the aminoacetones are not to be used for synthesis immediately they should be stored in a desiccator over potassium carbonate.

In Table I are included data for certain physical properties, values derived from them by calculation, and the results of analyses of the *N*-alkyl-*n*-butylamines.

Data for the new aminoacetones prepared in this investigation are tabulated in Table II, and for the semicarbazones of these ketones in Table III.

### Summary

1. A simple, rapid method of preparing mixed, secondary aliphatic amines in satisfactory yield has been tested by synthesizing eight examples of *N*-alkyl-*n*-butylamines. The method involves high pressure hydrogenation of aldimines or ketimines in the presence of Raney nickel.

2. These amines have been converted into eight new disubstituted aminoacetones of the type  $CH_3COCH_2NRR'$ .

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