

to pH 6.0 with concentrated hydriodic acid, filtered free of the homocystine which formed as a result of air oxidation, and then added to 3 liters of cold absolute ethanol. The precipitate was allowed to settle for several hours in a refrigerator, collected on a sintered glass filter and washed thoroughly with cold ethanol, yield 49 g. (52.5%). The product melted with decomposition at 234–235° (uncor.)<sup>4</sup> and was completely water soluble.

(4) V. Du Vigneaud, *ibid.*, **126**, 217 (1938).

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### Formylation of Amines with Chloral and Reduction of the N-Formyl Derivatives with Lithium Aluminum Hydride

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A formylation procedure, which seems to be practically unknown, was discovered by Hofmann<sup>2</sup> in 1872. He found that ethylenediamine reacted energetically with chloral to produce chloroform and another liquid product which he assumed was N,N'-diformylethylenediamine since, by hydrolysis, it was converted into ethylenediamine and formic acid. He stated that treatment of ethylamine with chloral converted it into ethylformamide, and he also mentioned that formamide can be obtained by this process but that in this instance the process is not an advantageous one.

In a German patent,<sup>3</sup> issued in 1921, it was stated that when N-methyl- $\alpha$ -methylhomopiperonylamine<sup>4</sup> and chloral hydrate were mixed, a spontaneous reaction took place, and N-methyl-N-formylhomopiperonylamine<sup>5</sup> was obtained in almost quantitative yield. Piperidine and chloral hydrate reacted, at a temperature below 50°, to form the N-formyl derivative in 95% yield.

Since we have been unable to find any other instances in the literature in which N-formylation was achieved by the use of chloral, it seemed desirable to determine whether or not the method had a wide range of usefulness. It was found that formylation with the aid of chloral is an excellent general procedure for the acylation of a strong organic base. A rapid reaction takes place at a low temperature, chloroform is the only by-product and the formyl derivative usually is obtained in good yield. The 12 amines which were formylated in order to test the procedure are shown in Table I.

The reduction of two N-formyl derivatives, in excellent yields, to the N-methyl compounds, by the use of lithium aluminum hydride, has been reported.<sup>6</sup> The formyl derivatives, described in this paper, were reduced to the N-methyl derivatives in fair to good yields<sup>7</sup> with lithium aluminum hydride.

(1) American Foundation for Pharmaceutical Education Fellow.

(2) A. W. Hofmann, *Ber.*, **5**, 247 (1872).

(3) German Patent 334,553; *Frdl.*, **13**, 835.

(4) Homopiperonylamine is  $\beta$ -(3,4-methylenedioxyphenyl)-ethylamine.

(5) It is evident that an error was made either in the name of the initial product or in the name of the reaction product.

(6) J. Ehrlich, *This Journal*, **70**, 2286 (1948); K. E. Hamlin and A. W. Weston, *ibid.*, **71**, 2210 (1949).

(7) We believe that in those instances in which the yields were below 80%, a further study, especially of the isolation procedures, would show that the yields could be increased.

TABLE I  
N-FORMYL DERIVATIVES OF AMINES

Derivative of	Yield, %	B.p., °C.	
		Found	Reported
1 Butylamine	83	122–123 (16 mm.) <sup>a</sup>	.....
2 Benzylamine	90	(M.p. 60–61°) <sup>b</sup>	(M.p. 49°) <sup>c</sup>
3 Cyclohexylamine	80	155–157 (22 mm.)	135–140 (10 mm.) <sup>d</sup>
4 $\beta$ -Hydroxyethylamine	75	145–148 (0.5 mm.)	191–193 (10 mm.) <sup>e</sup>
5 $\beta$ -Phenylethylamine	93	192–194 (20 mm.)	205 (15 mm.) <sup>f</sup>
6 Ethylenediamine <sup>g</sup>	95	(M.p. 110–111)	.....
7 Diethylamine	70	174–175 (745 mm.)	177–179 (atm.) <sup>h</sup>
8 N-Methyl- $\beta$ -phenylethylamine	94	110–112 (1 mm.) <sup>i</sup>	.....
9 Pyrrolidine	65	87–89 (16 mm.) <sup>j</sup>	.....
10 3-Methylpyrrolidine	71	100–102 (16 mm.) <sup>k</sup>	.....
11 Piperidine	90	104–105 (16 mm.)	108 (14–15 mm.) <sup>l</sup>
12 Morpholine	95	229–232 (745 mm.)	234 (760 mm.) <sup>m</sup>

<sup>a</sup> *Anal.* Calcd. for C<sub>8</sub>H<sub>11</sub>ON: N, 13.84. Found: N, 13.65. <sup>b</sup> Recrystallized from petroleum ether (90–100°). <sup>c</sup> M. A. F. Holleman, *Rec. trav. chim.*, **13**, 411 (1894). <sup>d</sup> German Patent 454,495 (1927); *Frdl.*, **16**, 308. <sup>e</sup> H. Wenker, *This Journal*, **57**, 1079 (1935). <sup>f</sup> A. Bischler and B. Napieralski, *Ber.*, **26**, 1903 (1893). <sup>g</sup> N,N'-Diformyl. Recrystallized from ethyl acetate. *Anal.* Calcd. for C<sub>4</sub>H<sub>8</sub>O<sub>2</sub>N<sub>2</sub>: N, 24.10; Found: N, 24.02. In order to obtain ethylenediamine in anhydrous form, it was allowed to remain for some time over stick sodium hydroxide. It was then refluxed over sodium and distilled from the metal. <sup>h</sup> O. Wallach, *Ann.*, **214**, 240 (1882). <sup>i</sup> *Anal.* Calcd. for C<sub>10</sub>H<sub>13</sub>ON: N, 8.58. Found: N, 8.43. <sup>j</sup> The hydrochloride was obtained by treatment of an ethereal solution of the formyl derivative with hydrogen chloride whereupon the salt precipitated; it is hygroscopic and decomposes in moist air; m.p. 92–94° after recrystallization from ethyl acetate. *Anal.* Calcd. for C<sub>5</sub>H<sub>9</sub>ON·HCl: N, 10.33; Cl, 26.18. Found: N, 10.26; Cl, 26.02. <sup>k</sup> *Anal.* Calcd. for C<sub>6</sub>H<sub>11</sub>ON: N, 12.22. Found: N, 12.38. <sup>l</sup> O. Wallach and F. Lehmann, *Ann.*, **237**, 251 (1887). <sup>m</sup> Médard, *Bull. soc. chim.*, [5] **3**, 1343 (1936).

The two-step methylation procedure which has been described should be useful for the methylation of acid- and/or heat-sensitive compounds, and in instances in which the ordinary methylation processes are unsatisfactory—for example, in the methylation of mezcaine.<sup>8</sup>

In order to obtain 3-methylpyrrolidine, itaconic acid was hydrogenated to methylsuccinic acid, the latter substance was converted into methylsuccinimide and the imide was reduced with lithium aluminum hydride to the pyrrolidine.

#### Experimental Part

**Formylation.**—The solid amine, dissolved or suspended in chloroform, or the liquid amine, was placed in a 3-necked flask fitted with a stirrer, dropping funnel and a condenser to which a calcium chloride tube was attached. The mixture was stirred, cooled in an ice-bath, and one molecular equivalent of chloral<sup>9</sup> was added, dropwise. The mixture was then stirred for several hours at room temperature, and finally heated for one-half hour on a steam-bath; the chloroform was then removed. Liquid products were purified by distillation, solid products by recrystallization.

**Reduction of the Formyl Derivatives.**—Lithium aluminum hydride (0.1 mole) and a suitable amount of absolute ether were placed in the apparatus described above. The flask was cooled in an ice-bath, the mixture was stirred and the formyl compound (0.1 mole), dissolved in ether, was added, dropwise. After the addition was completed, the mixture was stirred and refluxed for 6 hours. The flask was cooled in an ice-bath, the mixture was stirred rapidly and enough water was added, dropwise, to destroy the excess lithium aluminum hydride. After the material had

(8) L. Reti and J. A. Castrillon, *This Journal*, **73**, 1767 (1951).

(9) Chloral was prepared by distillation from a mixture of equal weights of chloral hydrate and concentrated sulfuric acid.

TABLE II  
 N-METHYL DERIVATIVES OF AMINES

Derivative of	Yield, %	Salt	M.p., °C.	
			Found	Reported
1 <sup>a</sup>	87	Hydrochloride	173-174	170-171 <sup>b</sup>
2	85	Hydrochloride	172-174	174-175 <sup>c</sup>
3	80	Hydrochloride	175-178	176 <sup>d</sup>
5	84	Hydrochloride	162-164	152-154 <sup>e</sup>
		Chloroplatinate	211-212	212 <sup>e</sup>
6	60	Dihydrochloride	235-236	235-236 <sup>f</sup>
7	64	Picrate	185-186	182 <sup>g</sup>
8	83	Hydrochloride	164-165 <sup>h</sup>	205 <sup>i</sup>
		Picrate	136-138	133-134 <sup>j</sup>
		Chloroplatinate	205-207	206-208 <sup>j</sup>
9	60	Picrate	221-222	221 <sup>b</sup>
10	50	Picrate	180-182	181-182 <sup>k</sup>
11	90	Picrate	218-220 <sup>i</sup>	148 <sup>m</sup>
		Chloroplatinate	195-196	195-196 <sup>m</sup>
		Chloroaurate	199-200	201 <sup>m</sup>
12	61	Picrate	225-226	225-226 <sup>n</sup>

<sup>a</sup> These numbers refer to the parent compounds listed in Table I under the same number. <sup>b</sup> K. Löffler, *Ber.*, **42**, 3429 (1909). <sup>c</sup> H. Emde, *Arch. Pharm.*, **247**, 366 (1909). <sup>d</sup> A. Skita and H. Rolfes, *Ber.*, **53**, 1249 (1920). <sup>e</sup> T. B. Johnson and H. H. Guest, *Am. Chem. J.*, **42**, 350 (1909). <sup>f</sup> R. Schneider, *Ber.*, **28**, 3074 (1895). <sup>g</sup> A. Ries, *Z. Krystal. Mineral.*, **55**, 474 (1920). <sup>h</sup> Recrystallized from isopropyl alcohol. *Anal.* Calcd. for C<sub>10</sub>H<sub>16</sub>NCl: N, 7.54; Cl, 19.09. Found: N, 7.49; Cl, 18.86. The base boiled at 202-204° (750 mm.); 81-83° (10 mm.). <sup>i</sup> T. B. Johnson and H. H. Guest, *THIS JOURNAL*, **32**, 766 (1910). <sup>j</sup> H. Decker and P. Becker, *Ber.*, **45**, 2407 (1912). <sup>k</sup> K. Löffler, *ibid.*, **43**, 2044 (1910). <sup>l</sup> Melts with decomposition. *Anal.* Calcd. for C<sub>12</sub>H<sub>16</sub>O<sub>7</sub>N: N, 17.06. Found: N, 16.92. <sup>m</sup> F. Haase and R. Wolfenstein, *ibid.*, **37**, 3228 (1904). <sup>n</sup> L. Knorr, *Ann.*, **301**, 12 (1898).

been stirred for one-half hour at room temperature, it was filtered through a sintered glass funnel, and the inorganic matter was washed thoroughly with ether. After removal of the ether from the dried solution, the product was distilled or recrystallized.

In the case of formyl derivatives which are only slightly soluble in ether, the derivative can be placed in the thimble of a modified Soxhlet extractor.<sup>10</sup>

The reduction of an ether-insoluble formyl derivative, such as N,N'-diformylethylenediamine, is described below. Lithium aluminum hydride (20 g., 0.5 mole), 300 cc. of absolute ether and 400 cc. of pure dioxane were placed in a 3-necked flask fitted with a stirrer and a condenser to which a soda-lime tube was attached. Finely powdered N,N'-diformylethylenediamine (30 g., 0.26 mole) was added, in small portions, through the neck of the flask while the mixture was stirred rapidly. A thermometer was placed in the mixture and the latter was stirred and heated at 75° for 2 days. The mixture was cooled in an ice-bath, stirred rapidly and 100 cc. of water was added, dropwise. The mixture was steam distilled until the distillate which dropped from the condenser was no longer alkaline. The distilled liquid was acidified with hydrochloric acid, and the solvent was removed under reduced pressure; yield 24.5 g. (60%); m.p. 235-236° after recrystallization from alcohol.

**Methylsuccinic Acid.**—Itaconic acid (26 g.) was dissolved in 200 cc. of 85% ethanol and, after the addition of 0.5 g. of platinum oxide catalyst, was hydrogenated, under an initial pressure of 50 pounds, until the calculated amount of hydrogen had been absorbed. The yield was 17.6 g. after recrystallization from a mixture of 175 cc. of benzene and 15 cc. of ethanol; m.p. 115-116°<sup>11</sup>; an additional 9.3 g. (m.p. 112-113°) was obtained upon concentration of the mother liquor.

**3-Methylsuccinimide and 3-Methylpyrrolidine.**—3-Methylsuccinimide was obtained in 66% yield from ammonium

3-methylsuccinate by the procedure described in reference 12 for the preparation of succinimide; b.p. 275-283°<sup>13</sup>; m.p. 65-66° after recrystallization from absolute ethanol.

In the manner which has been described, 25.5 g. (0.23 mole) of 3-methylsuccinimide was reduced with 20 g. (0.52 mole) of lithium aluminum hydride and 600 cc. of ether. The 3-methylpyrrolidine (12.3 g., 67%) boiled at 92-94°<sup>14</sup>; the picrate, obtained by the addition of an alcoholic solution of picric acid to the base dissolved in ether, softened at 105° and melted at 110-111°<sup>14</sup> after recrystallization from absolute ethanol.

*Anal.* Calcd. for C<sub>11</sub>H<sub>14</sub>O<sub>7</sub>N<sub>2</sub>: C, 42.04; H, 4.49; N, 17.83. Found: C, 42.45; H, 4.30; N, 17.66.

(12) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 562.

(13) A. E. Arppe, *Ann.*, **87**, 230, 236 (1853), b.p. 280°, m.p. 66°.

(14) H. Oldach, *Ber.*, **20**, 1657 (1887), b.p. 103-105°.

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### 6-Amino-2,3-dimethylindole

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Although 6-nitro-2,3-dimethylindole has been prepared by nitration of 1-acetyl-2,3-dimethylindole<sup>1-3</sup> as well as by Fischer cyclization of methyl ethyl ketone *m*-nitrophenylhydrazones<sup>1,3,4</sup> to our knowledge the successful reduction of this compound to 6-amino-2,3-dimethylindole has not been reported.

By the action of tin and hydrochloric acid on an alcoholic solution of 7-chloro-4-nitro-2,3-dimethylindole, Plant and Whitaker obtained 4-amino-2,3-dimethylindole. However, attempted reductions of 6-nitro-2,3-dimethylindole by the same method yielded only a gum which could not be crystallized.<sup>2</sup> The apparent instability of the reduction product of 6-nitro-2,3-dimethylindole led Plant and Whitaker to believe that the nitro group in their nitrated 2,3-dimethylindole was indeed in the 6-position even before they had confirmed this fact by oxidative means.

A number of observations have been made on the unstable nature of the aminoindoles<sup>2,4,5</sup> and it appears that the 6- and 7-aminoindoles are more difficult to prepare and preserve<sup>3,5,7</sup> than the 3-, 4- and 5-aminoindoles.<sup>2,4,6</sup>

This paper reports the preparation of 6-amino-2,3-dimethylindole and 6-acetamino-2,3-dimethylindole from methyl ethyl ketone phenylhydrazones. Cyclization of the hydrazones with an ethereal solution of boron trifluoride according to the directions of Snyder and Smith<sup>8</sup> gave 2,3-dimethylindole in excellent yield. This was acylated and converted to 6-nitro-2,3-dimethylindole as described by Plant and Tomlinson.<sup>1</sup> The corresponding amine was prepared in 13% yield by reduction

(1) S. G. P. Plant and M. L. Tomlinson, *J. Chem. Soc.*, 955 (1933).

(2) S. G. P. Plant and W. D. Whitaker, *ibid.*, 283 (1940).

(3) K. Schofield and R. S. Theobald, *ibid.*, 796 (1949).

(4) H. Bauer and E. Strauss, *Ber.*, **65**, 308 (1932).

(5) R. Majima and M. Kotake, *ibid.*, **63**, 2227 (1930).

(6) P. Ruggli and R. Grand, *Helv. Chim. Acta*, **20**, 373 (1937); *cf.*, *C. A.*, **31**, 7422.

(7) G. K. Hughes, F. Lions and E. Ritchie, *J. Proc. Roy. Soc., N. S. Wales*, **72**, 209 (1939); *cf. C. A.*, **33**, 6837.

(8) H. R. Snyder and C. W. Smith, *THIS JOURNAL*, **65**, 2452 (1943).

(10) The siphon tube is removed and a new connection made in such a manner that the liquid which drops from the condenser will not accumulate in the extractor but will drop immediately into the reaction mixture.

(11) H. S. Faper, *Biochem. J.*, **8**, 326 (1914), m.p. 115°.