

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>
9	60	Chloroplatinate	205-207	206-208 <sup>j</sup>
		Picrate	221-222	221 <sup>b</sup>
10	50	Picrate	180-182	181-182 <sup>k</sup>
11	90	Picrate	218-220 <sup>l</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>10</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>12</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>4</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*-nitrophenylhydrazone,<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 phenylhydrazone. Cyclization of the hydrazone 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**, 2152 (1913).

(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. Paper, *Biochem. J.*, **8**, 326 (1914), m.p. 115°.

of the nitroindole in acetic acid solution with stannous chloride in hydrochloric acid. However, when the crude amine was acylated by the method devised by Lumière and Barbier<sup>9</sup> 6-acetamino-2,3-dimethylindole was obtained in 78% yield. Attempts to prepare the free amine in higher yield by alkaline hydrolysis of the acylated amine gave only an uncrystallizable tarry material.

#### Experimental<sup>10</sup>

**6-Amino-2,3-dimethylindole.**—2,3-Dimethylindole<sup>8</sup> was nitrated according to the directions of Plant and Tomlinson.<sup>1</sup> A solution of the 6-nitro-2,3-dimethylindole (10 g.) in 100 ml. of glacial acetic acid was cooled to 30° and 20 g. of stannous chloride dihydrate in 100 ml. of concentrated hydrochloric acid was slowly added, with stirring, so that a sharp rise in temperature of the reaction mixture was avoided. The mixture was then allowed to stand until the reaction temperature began to fall whereupon the clear, reddish solution was heated for one hour on a steam-bath. When cooled in ice, the solution deposited a brown tin double salt which was removed, washed with cold acetic acid and then dispersed in ice-water. Enough 40% sodium hydroxide was added to make the solution basic and remove the tin as the soluble sodium salts. The liberated amine remained in this alkaline solution for 12 hours to permit complete penetration of the solid particles. The greyish amine, which had suffered no apparent change in color during this period, was removed, washed thoroughly with water and dried as rapidly as possible between filter paper. The dried amine was dissolved in benzene and decolorized twice with norite. The clear solution when cooled deposited 1.1 g. (13%) of tan crystals, melting sharply at 119–120°. Since the amine discolors markedly on exposure to air, the filtrations and crystallizations of the benzene solutions were carried out under an atmosphere of nitrogen. However, even after one week's exposure, accompanied by extensive discoloration, the solid amine showed practically no change in its melting point from that of the freshly prepared material.

*Anal.* Calcd. for C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>: C, 75.0; H, 7.6. Found: C, 74.9; H, 7.6.

**6-Acetamino-2,3-dimethylindole.** (a) From 6-Amino-2,3-dimethylindole.—To 6-amino-2,3-dimethylindole (0.35 g.), dissolved in 20 ml. of dry benzene, was added 0.5 ml. of acetic anhydride. A slight rise in temperature occurred while the pale yellow solution first turned reddish, then deposited a colorless precipitate. Ten minutes later the mixture was cooled and the solid separated, washed with benzene and air-dried. The crude material (0.4 g., m.p. 210–212°) when recrystallized from diluted alcohol gave 0.32 g. (72%) of colorless needles melting at 211–212°.

*Anal.* Calcd. for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O: C, 71.3; H, 7.0. Found: C, 71.0, 71.1; H, 7.0, 6.9.

(b) From 6-Nitro-2,3-dimethylindole.—The crude amine, obtained from the reduction of 44 g. of 6-nitro-2,3-dimethylindole as described above, was dissolved in a slight excess of dilute hydrochloric acid. The clear solution heated to 60° was treated with norite and filtered. To the colorless filtrate was added in succession a slight excess of acetic anhydride, then excess sodium acetate dissolved in water, to liberate the amine from its hydrochloric acid salt.<sup>9</sup> The crude acylated amine was removed from the cooled solution and air dried (37 g., m.p. 197–200°). Crystallization from diluted alcohol gave 29 g. (62%) of pure, colorless 6-acetamino-2,3-dimethylindole melting at 211–212°. A mixed melting point with the product obtained by method (a) showed no depression.

Two grams of the 6-acetamino-2,3-dimethylindole was refluxed for 2 hours with 100 ml. of 2.5 N aqueous alcohol (2:1). From the cooled solution was obtained 50 mg. of a brown amorphous powder which did not melt under 330°. Evaporation of the liquor to one-third its volume gave a dark precipitate which yielded only a small amount of the original 6-acetamino-2,3-dimethylindole and a tarry material from which no amine could be isolated.

(9) A. Lumière, L. Lumière and H. Barbier, *Bull. soc. chim.*, [3] **33**, 783 (1903); L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., New York, N. Y., 1941, p. 165.

(10) Melting points are corrected.

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### Preparation of a Series of Carbethoxymethyl Alkanoates<sup>1</sup>

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Heintz<sup>2</sup> was able to prepare carbethoxymethyl acetate by the interaction of sodium acetate and ethyl monochloroacetate in a sealed tube. The same compound was obtained by Gal<sup>3</sup> using the monobromo instead of the monochloro derivative, and he also prepared carbethoxymethyl butyrate from ethyl monobromoacetate and sodium butyrate. This reaction was further studied by Senff<sup>4</sup> who prepared the corresponding derivatives from the sodium salts of propionic, butyric, isobutyric, benzoic, phthalic and salicylic acids, but did not purify the diester derivatives of the last three acids cited. Though he reported a reaction with sodium stearate, he was not able to isolate the ester.

When sodium iodide was used as a catalyst, it was found that the reaction of ethyl monochloroacetate with sodium acetate and sodium propionate showed an apparent increase in reaction rate over the uncatalyzed reaction as shown in Table I. However, it was found difficult to separate the diesters from the ethyl iodoacetate (b.p. 178–180°) formed in the course of the reaction. Since the reaction was found to take place at atmospheric pressure on continued refluxing, the carbethoxymethyl alkanoates were obtained in higher purity by the latter method without using a catalyst.

During the course of this investigation it was noted that the rate of reaction increased with increasing length of the carbon chain of the fatty acid. Branching of the carbon chain resulted in a large increase in the speed of the reaction.

#### Experimental

**Ethyl Monochloroacetate.**—This compound was prepared in an 85.5% yield, b.p. 136–136.6° (646 mm.), from the esterification of monochloroacetic acid using a modification of the procedure of Vanino.<sup>5</sup>

**Sodium Salts of Fatty Acids.**—Commercial sodium acetate was fused, cooled, ground in a mortar and used as such. The other salts of fatty acids used in this investigation were prepared from commercially available acids which were purified by careful rectification in a packed column. The slightly acid salts were pulverized in a mortar and dried in a vacuum drying oven for 12 hours at 95° (4 mm.) to remove excess water and acid before being used.

**Carbethoxymethyl Alkanoates.**—A 500-ml., 3-necked, round-bottomed flask with ground glass joints was equipped with a reflux condenser, a motor-driven Monel metal

(1) This paper contains material abstracted from the thesis of Wynn B. Fife submitted to the faculty of the Utah State Agricultural College in partial fulfillment of the requirements for the degree of Master of Science, June, 1951.

(2) K. Heintz, *Ann.*, **123**, 338 (1862).

(3) H. Gal, *ibid.*, **142**, 371 (1867).

(4) M. Senff, *ibid.*, **208**, 270 (1881).

(5) L. Vanino, "Präparativen Chemie," II Band, Organischen Teil, Verlag von Ferdinand Enke, Stuttgart, Germany, 1937, p. 107.