

## NOTES

## 6-Aminoindole

BY R. K. BROWN AND N. A. NELSON

RECEIVED APRIL 28, 1954

The nitration of 3-carbethoxyindole in acetic acid solution has been shown by Majima and Kotake<sup>1</sup> to yield 6-nitro-3-carbethoxyindole. From this compound by hydrolysis and subsequent decarboxylation they obtained 6-nitroindole. Their reduction of 6-nitro-3-carbethoxyindole with stannous chloride and hydrochloric acid gave the stable and crystalline 6-amino-3-carbethoxyindole. The same reduction mixture produced from 6-nitroindole (after removal of the tin as the sulfide) a yellowish substance believed to be 6-aminoindole hydrochloride from which ammonia liberated a colorless, amorphous substance, apparently the 6-aminoindole. However, both the 6-aminoindole and its hydrochloride were found to be highly unstable during attempts at their purification, therefore no analytical data were obtained to confirm the findings.

Since a quantity of 6-aminoindole was required in this Laboratory for biological tests, its preparation was undertaken.

Reduction of 6-nitroindole with stannous chloride and concentrated hydrochloric acid gave an amorphous material more stable in alkaline than in neutral or acidic solution as shown by the greatly decreased rate of discoloration when the substance was suspended in dilute sodium hydroxide. The discoloration was quite marked when the material was exposed to air during its isolation. An attempt to avoid this apparent decomposition by drying the solid over phosphoric anhydride in an atmosphere of nitrogen was unsuccessful. Repeated efforts to purify the amine by crystallization also failed. Reduction of the 6-nitroindole with sodium hydrosulfite in alkaline solution by the method of Bauer and Strauss<sup>2</sup> gave no isolatable amine. However, following the modified sodium hydrosulfite reduction described by Shaw and Woolley<sup>3</sup> in their preparation of several substituted aminoindoles a 13% yield of 6-aminoindole was obtained.

Considerably more successful were two methods involving catalytic reduction with Raney nickel. Freshly prepared Raney nickel<sup>4</sup> with hydrogen at low pressures converted 6-nitroindole to the amine in 65% yield, whereas hydrazine in the presence of Raney nickel<sup>5,6</sup> afforded the amine in 76% yield. Moreover, reduction of 6-nitro-2,3-dimethylindole with Raney nickel and hydrazine gave the corresponding amine in larger yield (81%) than did methods previously reported.<sup>3,7</sup>

(1) R. Majima and M. Kotake, *Ber.*, **63**, 2237 (1930).(2) H. Bauer and E. Strauss, *ibid.*, **65**, 313 (1932).(3) E. Shaw and D. W. Woolley, *THIS JOURNAL*, **75**, 1877 (1953).(4) L. W. Covert and H. Adkins, *ibid.*, **54**, 4116 (1932).(5) I. P. Kuhn, *ibid.*, **73**, 1510 (1951).(6) D. Balcom and A. Furst, *ibid.*, **75**, 4334 (1953).(7) R. K. Brown, N. A. Nelson, R. B. Sandlin and K. G. Tanner, *ibid.*, **74**, 3934 (1952).

Correct analysis of the 6-aminoindole for carbon and hydrogen was attained only after the amine had been freed from adhering solvent by drying over phosphoric anhydride or sodium hydroxide pellets in a vacuum. However, when the amine was crystallized from dry benzene rather than aqueous alcohol, air drying was sufficient for good analyses.

Both 6-aminoindole and its hydrochloride could be preserved without decomposition if kept in stoppered containers away from light. The 6-acetaminoindole, readily prepared by normal procedures, was found to be quite stable.

## Experimental

All melting points are corrected.

**6-Aminoindole. (a) By Reduction with Hydrazine and Raney Nickel.**—To five grams of 6-nitroindole<sup>1</sup> dissolved in 150 ml. of methyl alcohol and containing approximately 2 g. of freshly prepared Raney nickel<sup>4</sup> was added diluted hydrazine (65% aqueous hydrazine in twice its volume of methyl alcohol) in small quantities at suitable intervals. Reduction progressed with evolution of nitrogen till its completion was indicated by the disappearance of the yellow color of the nitroindole. The solution was heated, if necessary, at 55–65° during the last stages of reduction to facilitate the reaction. After separation of the Raney nickel, the bulk of the alcohol was removed under vacuum. The remaining somewhat discolored liquid (about 50 ml.) was clarified with animal charcoal and further reduced in volume to about 40 ml. and then diluted with an equal volume of water. The solution, kept overnight in a refrigerator at zero degrees, deposited almost colorless crystals which (after air drying) weighed 3.1 g. (75.6%) and melted at 65–67°. Further dilution of the filtrate failed to precipitate more of the amine. Recrystallization from diluted methyl alcohol gave a melting point of 66–67°. Only after a 24-hour period of drying over phosphoric anhydride or sodium hydroxide pellets under vacuum, during which the amine liquefied and then became solid again, did the compound analyze correctly for 6-aminoindole. Crystallization from dry benzene-petroleum ether avoided this special drying and gave the pure amine directly.

*Anal.* Calcd. for C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>: C, 72.8; H, 6.10. Found: C, 72.9; H, 6.14.

**(b) By Reduction with Hydrogen and Raney Nickel.**—The 6-nitroindole (3 g.) dissolved in methyl alcohol (100 ml.) was shaken with Raney nickel (1.5 g.) and hydrogen (35 p.s.i.) until the yellow color of the solution disappeared. Isolation of the product as in the procedure described above gave 1.67 g. of amine melting at 64–67°. Crystallization from diluted methyl alcohol yielded 1.60 g. (65%) of 6-aminoindole, m.p. 66–67°.

**(c) By Reduction with Sodium Hydrosulfite.**—The 6-nitroindole (4 g.) was reduced according to published directions<sup>3</sup> and afforded 0.42 g. (13%) of the amine, m.p. 66–67°.

When the 6-aminoindole was dissolved in dry ether and treated with dried hydrogen chloride there was obtained an almost quantitative yield of the 6-aminoindole hydrochloride, m.p. 241–242°.

*Anal.* Calcd. for C<sub>8</sub>H<sub>9</sub>N<sub>2</sub>Cl: C, 57.0; H, 5.4. Found: C, 57.1; H, 5.3.

The faintly pink hydrochloride was stable when kept in a container away from light.

Treatment of 6-aminoindole (5.2 g.) in dry benzene with a slight excess of acetic anhydride gave a colorless precipitate of 6-acetaminoindole (5.7 g.) melting at 170–171°. Recrystallization from diluted ethyl alcohol did not alter the melting point.

*Anal.* Calcd. for C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O: C, 68.9; H, 5.80. Found: C, 68.9; H, 5.9.

The 6-acetaminoinidole was also obtained in good yield by treating an aqueous solution of 6-aminoindole hydrochloride with acetic anhydride and sodium acetate.<sup>8</sup>

**Acknowledgment.**—The authors wish to express their thanks to the National Cancer Institute of Canada for their continued support.

(8) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y.

DEPARTMENT OF CHEMISTRY  
UNIVERSITY OF ALBERTA  
EDMONTON, ALBERTA, CANADA

### Acylation of Alkyl Aryl Ethers with Iodine as Catalyst

BY XORGE ALEJANDRO DOMINGUEZ, BEATRIZ GÓMEZ, J. SLIM, DORA GIBSECKE AND ERNESTO URETA B.

RECEIVED APRIL 15, 1954

Acylation with iodine as a catalyst,<sup>1,2</sup> gives good yields of some alkoxy-substituted aceto-, propio-, isobutyro-, butyro- and caprophenones, although the acetylation of phenyl acetate, guaiacol, guaiacol acetate and bromo- and iodobenzene is unsuccessful. We have confirmed the report that anisole does not react with succinic anhydride in the presence of iodine.<sup>3</sup> The preparation of 4-methoxyacetophenone, reported by Chodroff and Klein,<sup>3</sup> who used a mole excess of anisole, has been improved.

Our experiments and those of Kaye, *et al.*,<sup>4</sup> indicate that iodine can be used as a catalyst for the acylation of aromatic ethers by aliphatic or aromatic monocarboxylchlorides or anhydrides, and that this method is better for the preparation of alkoxy aryl ketones than the conventional Friedel-Crafts procedure. In successful acylations, the violet colored vapor of the refluxing mixture disappeared after 15–30 minutes, but when there was no reaction, the color persisted.

#### Experimental<sup>5</sup>

**General Procedure, 4-Methoxyacetophenone.**—A mixture of 21.6 g. (0.2 mole) of anisole, 22.5 g. (0.22 mole) of acetic anhydride and 1.0 g. (0.004 mole) of iodine was refluxed for three hours. The dark brown solution was poured into 100 ml. of water. The mixture was extracted with ether; the ether solution was washed successively with dilute sodium carbonate, sodium bisulfite and water and then dried over sodium sulfate. After removal of the solvent and distillation of the residue under vacuum, 24 g. (80%) of 4-methoxyacetophenone was obtained, b.p. 120–125° (5 mm.). The yield was 50% when acetyl chloride was used. After crystallization from aqueous methanol the compound melted at 37–38° and its semicarbazone at 197–198°; reported in p. 38°, semicarbazone m.p. 198–198.5°.<sup>3</sup>

In the presence of 0.8 g. (0.00278 mole), 1.2 g. (0.0047 mole), 1.6 g. (0.0063 mole), 0.2 g. (0.00079 mole) of iodine, a mixture of 0.2 mole of anisole and 0.22 mole of acetic anhydride, gave yields of 68.7, 66, 61.2 and 45%, respectively.

**2-Methoxy-1-acetylnaphthalene.**—A mixture of 15.8 g. (0.1 mole) of 2-methoxynaphthalene, 11.3 g. (0.11 mole) of acetic anhydride and 0.5 g. (0.00196 mole) of iodine gave after recrystallization from dilute alcohol, 13.2 g. (63%) of 2-methoxy-1-acetylnaphthalene, m.p. 57°; its mixed m.p. with an authentic specimen was 57–58°; reported by Noller and Adams,<sup>6</sup> 57–58°.

(1) H. D. Hartough and A. I. Kosak, *THIS JOURNAL*, **68**, 2639 (1946).

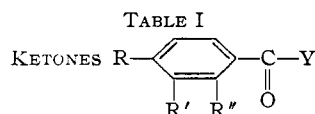
(2) A. I. Kosak and H. D. Hartough, *ibid.*, **69**, 3144 (1947).

(3) S. Chodroff and H. C. Klein, *ibid.*, **70**, 1647 (1948).

(4) I. A. Kaye, H. C. Klein and W. J. Burlant, *ibid.*, **75**, 745 (1953).

(5) The melting points are uncorrected.

(6) C. R. Noller and R. Adams, *THIS JOURNAL*, **46**, 1889 (1924).



R'	R''	Y	Yield, %	M.p., °C.	Semicarbazone m.p., °C.	
CH <sub>3</sub> O	CH <sub>3</sub> O	H	Methyl	66.5	47–48 <sup>b</sup>	209–211 <sup>c</sup>
CH <sub>3</sub> O	H	CH <sub>3</sub> O	Methyl	71	42–43.5 <sup>d</sup>	211–213 <sup>e</sup>
C <sub>2</sub> H <sub>5</sub> O	H	H	Methyl	66	36–37.5 <sup>f</sup>	179–180 <sup>g</sup>
CH <sub>3</sub> O	H	H	Ethyl	50	26–27 <sup>h</sup>	171–172 <sup>i</sup>
CH <sub>3</sub> O	CH <sub>3</sub> O	H	Ethyl	46.5	56–58 <sup>j</sup>	191 <sup>k</sup>
C <sub>2</sub> H <sub>5</sub> O	H	H	Ethyl	57	29–30 <sup>l</sup>	181–183 <sup>m</sup>
CH <sub>3</sub> O	H	H	Propyl	68	19–21 <sup>n</sup>	179–181 <sup>o</sup>
CH <sub>3</sub> O	CH <sub>3</sub> O	H	Propyl	74	59–61 <sup>p</sup>	178–180 <sup>q</sup>
CH <sub>3</sub> O	H	H	<i>i</i> -Propyl	42	<sup>r</sup>	202–203 <sup>s</sup>
CH <sub>3</sub> O	H	H	Pentyl	49.3	38–30 <sup>t</sup>	143 <sup>u</sup>

<sup>a</sup> All compounds were recrystallized from aqueous methanol. <sup>b</sup> C. Mannich, *Arch. Pharm.*, **248**, 137 (1910), reports m.p. 48°. <sup>c</sup> Ref. b, m.p. 211°. <sup>d</sup> J. Tambor, *Ber.*, **43**, 188<sup>+</sup> (1910), reports 44°. <sup>e</sup> *Anal.* Calcd. for C<sub>11</sub>H<sub>15</sub>O<sub>3</sub>N<sub>3</sub> (237.25); N, 17.71. Found: N, 17.64. <sup>f</sup> F. Unger, *Ann.*, **504**, 267 (1933), reports m.p. 37–38°. <sup>g</sup> Ref. f, m.p. 181.5°. <sup>h</sup> Ref. f, m.p. 29°. <sup>i</sup> Ref. f, m.p. 172°; F. v. Wessely, *et al.*, *Monatsh.*, **73**, 127 (1940), give m.p. 175°. <sup>j</sup> R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, **809** (1938), reports m.p. 58–59°. <sup>k</sup> E. Martegiani, *Gazz. chim. ital.*, **42**, II, 348 (1912), reports m.p. 190–192°. <sup>l</sup> L. Gattermann, R. Ehrhardt and H. Maisch, *Ber.*, **23**, 1205 (1890), reports m.p. 30°. <sup>m</sup> *Anal.* Calcd. for C<sub>12</sub>H<sub>17</sub>O<sub>3</sub>N<sub>3</sub> (235.28); N, 17.46. Found: N, 17.31. The *p*-nitrophenylhydrazones melted at 163–164°. <sup>n</sup> *Anal.* Calcd. for C<sub>17</sub>H<sub>19</sub>O<sub>3</sub>N<sub>3</sub> (314.32); N, 13.37. Found: N, 13.30. <sup>o</sup> P. M. Baranger, *Bull. soc. chim.*, [4] **49**, 1213 (1931), reports m.p. 21–22°. <sup>p</sup> Ref. n, m.p. 183°; ref. f, m.p. 173.5°. <sup>q</sup> *Anal.* Calcd. for C<sub>12</sub>H<sub>16</sub>O<sub>3</sub> (208.29): C, 69.21; H, 7.74. Found: C, 69.30; H, 7.55. <sup>r</sup> *Anal.* Calcd. for C<sub>13</sub>H<sub>19</sub>O<sub>3</sub>N<sub>3</sub> (265.29); N, 15.84. Found: N, 15.63. <sup>s</sup> B.p. 188–190° (40 mm.); A. Sosa, *Ann. chim.*, **14**, 5 (1940), reports b.p. 158.5–159.5° (12 mm.). <sup>t</sup> Ref. r, m.p. 193–194° (heating block) and 206°. <sup>u</sup> S. Skraup and F. Nielsen, *Ber.*, **57**, 1295 (1924), report m.p. 41°. <sup>v</sup> Ref. f, m.p. 142.5°.

**Acknowledgment.**—We express our appreciation to Ings. Carlos Lopez, Carlos Duhne and Elliot Camarena for their interest and invaluable collaboration and to Amelia Saldaña and Ernesto Alatorre for their assistance.

LABORATORIO DE QUIMICA ORGANICA, INSTITUTO TECNOLÓGICO Y DE ESTUDIOS SUPERIORES DE MONTERREY MONTERREY, N. L., MEXICO

### Furfuryl Esters of Some Dicarboxylic Acids

BY W. R. EDWARDS, JR., AND M. J. MITCHELL<sup>1</sup>

RECEIVED FEBRUARY 1, 1954

Earlier authors<sup>2–7</sup> have prepared furfuryl esters of monocarboxylic acids by a variety of methods, none of which appears to be suitable for the difurfuryl esters of dicarboxylic acids. The reactions of furfuryl alcohol with phthalic and succinic anhydrides give the mono esters. In the present work we found that the difurfuryl esters lacked sufficient volatility and thermal stability to make

(1) From the M.S. thesis of M. J. Mitchell, Louisiana State University, June, 1952.

(2) L. von Wissell and B. Tollens, *Ann.*, **272**, 291 (1893).

(3) J. E. Zanetti, *THIS JOURNAL*, **47**, 536 (1925).

(4) W. R. Edwards, Jr., and L. H. Reeves, *ibid.*, **64**, 1583 (1942).

(5) J. E. Zanetti, *ibid.*, **47**, 1452 (1925).

(6) F. A. Norris and D. E. Terry, *Oil and Soap*, **21**, 193 (1944).

(7) G. Calingaert, H. Soroos, V. Hnizda and H. Shapiro, *THIS JOURNAL*, **62**, 1545 (1940).