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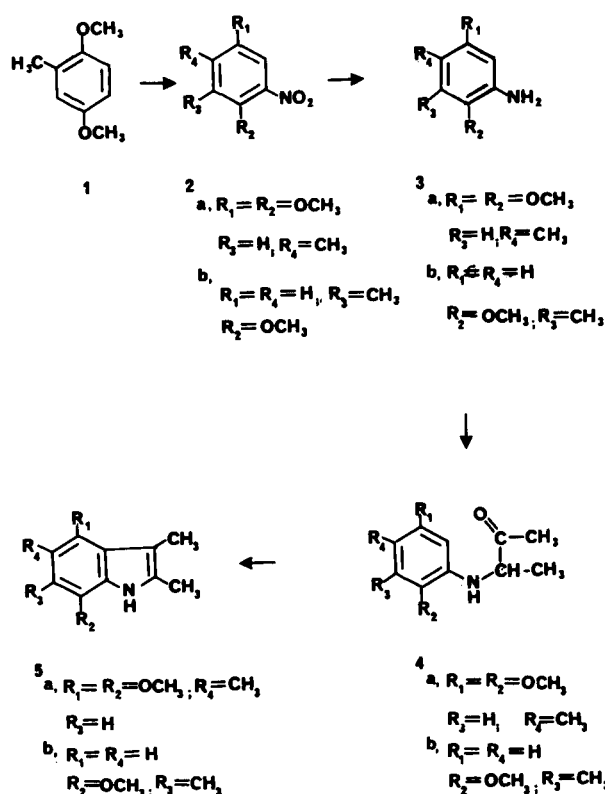
Condensation of arylamines with α -halogenoketone afforded the intermediate anilino-ketones which on direct cyclization furnished the corresponding alkylindoles. Synthesis of 2,3,5-trimethyl-4,7-dimethoxyindole (**5a**) and 2,3,6-trimethyl-7-methoxyindole (**5b**) is described. Earlier (1) synthesis of 2,3-dimethyl-4,7-dimethoxyindole and 1,2,3-trimethyl-4,7-dimethoxyindole is reported.

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In continuation of the work in this laboratory (1-2), it is the purpose of this work to report synthesis of very specific alkylindoles with relatively modified Bischler method (3). The Bischler reaction for the synthesis of indoles has been the subject of examination and discussion (4-9). Although a variety of indoles have been prepared from anilines, this method is found to be of disadvantage and inconvenience when dealing with costly and solid aryl amines as an excess of the amine is required to complete the reaction.

It is observed that refluxing an equimolar mixture of the arylamines and 3-bromobutanone in acetone in the presence of freshly ignited potassium carbonate, gave corresponding intermediate anilino ketones which were isolated and characterized. Cyclization of these anilino ketones with alcoholic zinc chloride (7) afforded corresponding indoles. Thus synthesis of 2,3,5-trimethyl-4,7-dimethoxyindole (**5a**) and 2,3,6-trimethyl-7-methoxyindole (**5b**) has been accomplished from the respective aryl amine derivatives (**3a**) and (**3b**). Synthesis of 2,3-dimethyl-4,7-dimethoxyindole and 1,2,3-trimethyl-4,7-dimethoxyindole is reported earlier (1). Direct cyclization of the intermediate anilino ketones to the indoles furnishes further evidence to the mechanism proposed for the Bischler reaction by Brown and Mann (7).

Nitration (10-11) of dimethoxytoluene (**1**) gave 2,5-dimethoxytoluene (**2a**). The location of the nitro group was further confirmed by nmr spectrum which indicated a pair of singlet, typical of *para* aromatic protons. Compound (**2a**) on reduction with iron-acetic acid afforded 2,5-dimethoxy-4-aminotoluene (**3a**). Earlier this compound has been reported by Gilman, *et al.* (11), however no attempt was made to purify the product. This compound has now been obtained as an analytically pure sample and has been well characterized. Reduction was also accomplished by hydrogenation at room temperature using Palladium-carbon as a catalyst to give **3a** in 94% yield. Condensation of **3a** with 3-bromobutanone in refluxing acetone, in the presence of potassium carbonate, resulted in the previously unknown 3-(2',5'-dimethoxy-4'-methyl-anilino)butanone (**4a**) which on subsequent indolization with alcoholic zinc chloride



(7) yielded 2,3,5-trimethyl-4,7-dimethoxyindole (**5a**). Attempts to isolate **4b** by reacting **3b** with 3-bromobutanone were unsuccessful, however, condensation was accomplished under the conditions of Bischler (3) to give directly 2,3,6-trimethyl-7-methoxyindole (**5b**). Compound **3b** was prepared from the corresponding nitro compound (**2b**) by reduction with iron-acetic acid.

EXPERIMENTAL

Melting points were taken on a Fisher Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckmann IR-33 Spectrometer. ^1H nmr spectra were obtained on a Varian-EM-360 instrument. Chemical shifts are in ppm (δ) relative to TMS as the internal standard. Electron impact mass spectra were recorded on a Dupont 21-492B mass spectrometer. 2,5-Dimethoxy-4-nitrotoluene (**2a**).

2,5-Dimethoxytoluene (**1**) was nitrated with nitric acid in

acetic acid at 0° as described in literature (10) to give **2a** in quantitative yield. It was recrystallized from ethanol, m.p. 115-116°, lit. (10) m.p. 117-118°; nmr (deuteriochloroform): δ 1.1 (3H, s, -CH₃), 2.65 (3H, s, -OCH₃), 2.75 (3H, s, -OCH₃), 5.70 (1H, s, aromatic proton), 6.20 (1H, s, aromatic proton).

2,5-Dimethoxy-4-aminotoluene (**3a**). Method a.

This compound was prepared in essential accordance with procedure described in literature (12). A stirred solution of 2,5-dimethoxy-4-nitrotoluene (10) (**2a**) (0.01 mole) in 50 ml. of glacial acetic acid and 10 ml. of water was heated to steam bath temperature and treated with 4 g. of iron powder over 90 minutes. Additional 10 ml. of water was added after 45 minutes. After cooling the reaction mixture was poured into a large volume of water.

This solution was extracted several times with methylene chloride and the combined extracts were washed successively with water, sodium carbonate solution and again with water. Evaporation of the dried organic solution gave **3a** in 60% yield. It was recrystallized from ethanol, m.p. 109°, lit. (11) m.p. 108-109°, nmr (carbon tetrachloride): δ 2.05 (3H, s, -CH₃), 3.50 (2H, s, -NH₂), 3.70 (3H, s, -OCH₃), 3.80 (3H, s, -OCH₃), 6.1 (1H, s, aromatic proton), 6.5 (1H, s, aromatic proton), ir (nujol) showed absorption at 3440 and 3460 cm⁻¹ (primary -NH₂), 2840 cm⁻¹ (-OCH₃).

Anal. Calcd. for C₉H₁₃O₂N: C, 64.67; H, 7.78; N, 8.38. Found: C, 64.48; H, 7.74; N, 8.31.

The amine should be stored in dark in a vacuum-desiccator as it darkened very rapidly upon exposure to air and light.

Method b.

A solution of **2a** (0.02 mole) in 200 ml. of ethanol was treated with hydrogen in the presence of 1 g. of 5% palladium carbon at room temperature and 5 atmospheric pressure on a Parr hydrogenator. After an absorption of quantitative hydrogen the catalyst was filtered off and the filtrate was evaporated on a rotatory evaporator. The white crystalline solid was collected and recrystallized from ethanol, m.p. 109°, yield 94%. It was identical with **3a** in all respects.

3-(2',5'-Dimethoxy-4'-methyl-anilino)butanone (**4a**).

2,5-Dimethoxy-4-aminotoluene (**3a**) (0.02 mole) was refluxed with 3-bromobutanone (0.015 mole) in 500 ml. of acetone for 40 hours in the presence of 15 g. of freshly heated potassium carbonate. The reaction mixture was filtered and the filtrate was collected. Evaporation of the solvent on a rotatory evaporator left a residue which was taken up in ether and treated with 10% hydrochloric acid. The aqueous layer was separated and made alkaline with sodium hydroxide solution. The separated product was extracted with ether. The ethereal layer was separated and dried over sodium sulfate. Evaporation of the solvent left a residue, which was chromatographed on a neutral silica gel 60 column and eluted with methylene chloride. Compound **4a** was isolated in 75% yield from the yellow fraction which eluted first. It was recrystallized from petroleum-ether, m.p. 54-56°, nmr (deuteriochloroform): δ 1.4 (3H, d, J = 7 cps, -CH-CH₃), 2.15 (3H, s, -CH₃), 2.20 (3H, s, -CH₃), 3.70 (1H, s, -NH), 3.80 (3H, s, -OCH₃ at 5'), 3.85 (3H, s, -OCH₃ at 2'), 3.90 (1H, q, -CH-CH₃), 6.15 (1H, s, aromatic proton), 6.65 (1H, s, aromatic proton); mass spectrum m/e 237 (M⁺).

Anal. Calcd. for C₁₃H₁₉O₃N: C, 65.82; H, 8.01; N, 5.90. Found: C, 65.75; H, 8.22; N, 5.70.

2,3,5-Trimethyl-4,7-dimethoxyindole (**5a**).

This compound was prepared according to the method of Brown and Mann (7). Compound **4a** (0.01 mole) was refluxed for 10 hours with freshly fused zinc chloride (0.05 mole) in 30 ml. of absolute ethanol under a nitrogen atmosphere. The reaction mixture was poured into 100 ml. of dilute hydrochloric acid with cooling. The separated compound was extracted with ether. The ethereal layer was separated and dried over calcium chloride. Evaporation of the solvent left a solid which was recrystallized from petroleum ether in greenish yellow needles, m.p. 130-131°, yield 30-40%; nmr (deuteriochloroform): δ 2.25 (3H, s, -CH₃ 5), 2.33 (6H, s, 2 -CH₃ at 2 and 3), 3.78 (3H, s, -OCH₃ at 4), 3.85 (3H, s, -OCH₃ at 7), 6.30 (1H, s, aromatic proton), 7.50 (1H, s, broad, -NH).

Anal. Calcd. for C₁₃H₁₇O₂N: C, 71.23; H, 7.76; N, 6.39. Found: C, 71.20; H, 7.86; N, 6.30.

2-Methoxy-3-aminotoluene (**3b**).

A stirred solution of 2-methoxy-3-nitrotoluene (13) (**2b**) (0.02 mole) in 150 ml. of glacial acetic acid and 15 ml. of water was heated to steam bath temperature and treated with 6 g. of iron powder over 90 minutes. On working out the reaction as described earlier, there was obtained **3c** as liquid in 68% yield. The compound was found to be identical to that reported in literature (13), nmr (deuteriochloroform): δ 2.10 (3H, s, -CH₃), 3.50 (2H, s, -NH₂), 3.60 (3H, s, -OCH₃) 6.30 to 6.80 (3H, m, aromatic protons); ir showed strong absorption at 3400 and 3310 cm⁻¹ (primary -NH₂), 2880 cm⁻¹ (-OCH₃).

2,3,6-Trimethyl-7-methoxyindole (**5b**).

An intimate mixture of 2-methoxy-3-aminotoluene (**3b**) (0.02 mole) and 3-bromobutanone (0.005 mole) was heated in an oil bath at 180° for 15 minutes. The reaction mixture was poured into 100 ml. of 10% hydrochloric acid with cooling and was left overnight. The separated compound was extracted with ether. The ethereal layer was washed with water and dried over sodium sulfate. Evaporation of the solvent left a solid which was recrystallized from hexane. Two additional recrystallizations from hexane gave an analytically pure sample, m.p. 99-100°, yield 20%; nmr (deuteriochloroform): δ 2.20 (3H, s, -CH₃ at 6), 2.35 (3H, s, -CH₃ at 2 or 3), 2.41 (3H, s, CH₃ at 2 or 3), 3.9 (3H, s, -OCH₃), 6.9 (1H, d, J = 8 cps, aromatic proton), 7.20 (1H, d, J = 8 cps, aromatic proton), 7.90 (1H, s, broad, -NH); ir (nujol) showed sharp absorption at 3340 cm⁻¹ (-NH-), 2900 cm⁻¹ (-OCH₃). It was homogenous (tlc) in benzene-chloroform-methanol, 8:2:1.

Anal. Calcd. for C₁₂H₁₅ON: C, 76.19; H, 7.93; N, 7.40. Found C, 76.03; H, 7.70; N, 7.12.

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REFERENCES AND NOTES

- (1) Y. Shaikh, *Org. Prep. Proc. Int.*, **8**, 293 (1976).
- (2) U. Hornemann, Y. Ho, J. Mackey and S. Srivastava, *J. Am. Chem. Soc.*, **98**, 7069 (1976).
- (3) A. Bichler, *Ber.*, **25**, 2860 (1892).
- (4) P. Verkade and E. Janetzky, *Rec. Trav. Chim.*, **62**, 763, 775 (1943).
- (5) A. Crowther, F. Mann and D. Purdie, *J. Chem. Soc.*, **58** (1953).

- (6) P. Julian, F. Meyer, A. Magnani and W. Cole, *J. Am. Chem. Soc.*, **67**, 1203 (1945).
- (7) F. Brown and F. Mann, *J. Chem. Soc.*, 847, 858 (1948).
- (8) F. Weygand and E. Richter, *Chem. Ber.*, **88**, 499 (1955).
- (9) K. Nelson and R. Seefeld, *J. Am. Chem. Soc.*, **80**, 5957 (1958).
- (10) H. G. Erdtman, *Proc. Roy. Soc. (London)*, **A143**, 191 (1933).
- (11) H. Gilman, J. Swiss, H. Willis and A. Yeoman, *J. Am. Chem. Soc.*, **66**, 798 (1944).
- (12) G. Allen, L. Binovi and M. Weiss, *J. Med. Chem.*, **10**, 13 (1967).
- (13) Vladislav Mraz, *Sb. Pr. Vyzk, Chem. Využití Uhlí, Dehtu Ropy*, **7**, 21 (1967); *Chem. Abstr.*, **68**, 95436n (1968).