THE PREPARATION OF 3-ALKYLTHIOINDOLES[1]

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Dedicated to Professor R. B. Sandin on the Occasion of his Sixty-Eighth Birthday

ABSTRACT

3-Ethylthioindole has been prepared by Fischer cyclization of the condensation product of phenylhydrazine and ethylthioacetaldehyde diethyl acetal, and also by a route involving the reaction of ethyl iodide with the sodium borohydride reduction product of 1,2-dithiolo[4,3-*b*]indole-3-(4H)-thione. The last-named compound was obtained by reaction of 2-carbethoxyindoxyl with phosphorus pentasulfide.

INTRODUCTION

The need for a quantity of 3-indolylthioacetic acid evoked interest in the general problem of preparing 3-alkylthioindoles. Information in the literature concerning such compounds is meager. Several attempts have been made to prepare 3-mercaptoindole, from which, via a Williamson ether synthesis, the requisite 3-alkylthioindole might then be made. When indole magnesium bromide was treated with sulfur, 3,3′-diindolyl sulfide was obtained rather than the expected 3-mercaptoindole (1). Oddo and Mingoia (2) have recorded the preparation of 3- as well as some 2-benzoylthioindole when the indole Grignard reagent was allowed to react successively with sulfur and then benzoyl chloride. Hydrolysis of the resulting thiol esters led to 3- and 2-mercaptoindole.

The formation of thioethers from 3-mercaptoindole does not appear to be straightforward. Grant and Snyder (3), upon hydride reduction of 3,3′-diindolyl disulfide followed by addition of 2,4-dinitrochlorobenzene, quite readily obtained 3-(2,4-dinitrophenylthio)-indole, but when ethyl bromoacetate was used instead of the dinitrochlorobenzene there was obtained mainly unchanged 3,3′-diindolyl disulfide with only a trace of the expected 3-indolylthioacetic acid. These same authors were unable to isolate 3-mercaptoindole from hydride reduction of the disulfide, presumably because of the remarkably easy oxidation of 3-mercaptoindole back to the disulfide. Grant and Snyder, furthermore, have pointed out the similarity of the melting point of their 3,3′-diindolyl disulfide (m.p. 217–218°) to that of the reported (2) 3-mercaptoindole (235°). The 3,3′-diindolyl disulfide prepared by Woodbridge and Dougherty (4) is reported to melt at 227–229.5°. Hence, a doubt exists that 3-mercaptoindole (2) has actually been obtained. The 2-mercaptoindole, however, seems to be more readily isolated, since the compound reported by Oddo and Mingoia (2) melted at 148–150°, very close to that found for 2-mercaptoindole (m.p. 145°) easily prepared in 70% yield by treatment of oxindole with phosphorus pentasulfide (5).

Two reports of the preparation of 3-substituted 2-methylthioindoles have appeared (6, 7), but to our knowledge there is no account, other than those mentioned above, of the synthesis of 3-alkylthioindoles.

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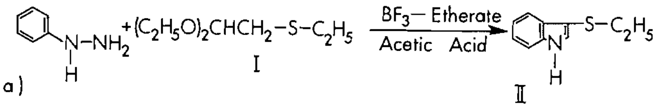
RESULTS AND DISCUSSION

3-Alkylthioindoles via the Fischer Indole Synthesis

When ethylthioacetaldehyde diethyl acetal (8) was condensed with phenylhydrazine in acetic acid in the presence of boron trifluoride etherate catalyst, a smooth exothermic reaction occurred (eq. [*a*]) and yielded 3-ethylthioindole (~60%). Elemental analysis,



(a)

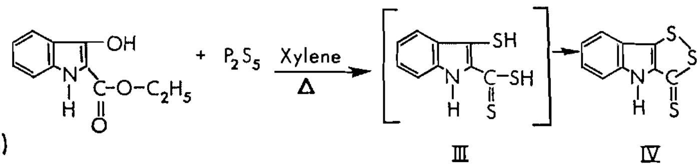
molecular weight (by mass spectrometry), and infrared and nuclear magnetic resonance (n.m.r.) spectra, as well as the method of synthesis, showed conclusively that the product was 3-ethylthioindole (II).

Attempts to form the N-acetyl derivative with either acetic anhydride in benzene or acetyl chloride in pyridine gave only unchanged thioether. This agrees with a similar resistance to N-acylation shown by 3,3′-diindolyl sulfide (1). When II was treated with an alcoholic solution of mercuric chloride, a precipitate of ethylthiomercuric chloride (9) was obtained, a reaction characteristic of a number of alkyl aryl and aryl aralkyl thioethers (10).

The utility of this reaction in preparing 3-alkylthioindoles is obviously dependent upon the availability of the appropriate alkylthioacetaldehyde diethyl acetal (I).

3-Alkylthioindoles via Reaction of P_2S_5 with 2-Carbethoxyindoxyl

Since the reaction of oxindole with phosphorus pentasulfide is known to produce 2-mercaptoindole (5), 2-carbethoxyindoxyl was treated with phosphorus pentasulfide in boiling xylene (eq. [*b*]). From the reaction mixture was isolated in 11% yield the compound 1,2-dithiolo[4,3-*b*]indole-3(4H)-thione (IV).*



(b)

The isolation of IV (the oxidized form of III) rather than the 3-mercaptoindole (III) is analogous to the reported isolation of 3,3′-diindolyl disulfide rather than the expected 3-mercaptoindole upon reduction of this disulfide (3). Elemental analysis, molecular weight, and infrared and nuclear magnetic resonance spectra, as well as a negative Ehrlich test (11, 12), supported structure IV for this product. In addition, Raney nickel desulfurization (13) of IV afforded a compound whose infrared spectrum was identical with that of authentic 2-methylindole (14).

Reduction of IV, with sodium borohydride in ethanol, followed by reaction of the product with ethyl iodide (eq. [*c*]) gave an 84% yield of ethyl 3-ethylthio-2-indoledithiocarboxylate (V), whose structure was corroborated by elemental analysis and infrared and

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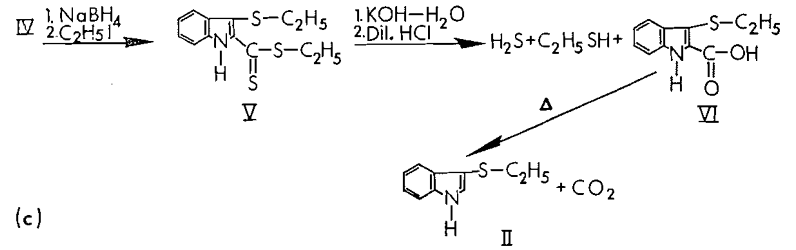
**The reaction of β-ketoesters (N. Lozac'h and L. Legrand, Compt. Rend. 234, 1291 (1952); A. Luttringhaus, H. Trefzger, and U. Schmidt, Angew. Chem. 67, 274 (1955)) and of aromatic o-hydroxycarboxylic acids (L. Katz, W. Schroeder, and M. Cohen, J. Org. Chem. 19, 711 (1954)) with* P_2S_5 *has been shown to produce the stable 1,2-dithiolo-3-thione structure found in compound IV.*



(c)

nuclear magnetic resonance spectra. Hydrolysis of V gave hydrogen sulfide, ethyl mercaptan, and 3-ethylthioindole-2-carboxylic acid (VI). Compound VI readily decarboxylated and distilled when heated under vacuum, producing 3-ethylthioindole (II), identical with that prepared by the Fischer reaction.

EXPERIMENTAL

Infrared spectra were obtained with Perkin–Elmer instruments, models 21, 221G, and 421. Nuclear magnetic resonance spectra were provided by a Varian Associates instrument, model A-60. Mass spectra were obtained with a MS2-H Metropolitan-Vickers instrument. Gas–liquid chromatography was carried out on a Burrell K-2 Kromo-Tog using a 2½-m column containing a packing of 20% Apiezon L on Kromat F.B. (30–60 mesh) and employing helium as carrier gas.

3-Ethylthioindole (II) by Fischer Cyclization

A mixture of 17.8 g (0.1 mole) of ethylthioacetaldehyde diethyl acetal (8) and 10.8 g (0.1 mole) of phenylhydrazine was added to 100 ml of glacial acetic acid at room temperature. A slightly exothermic reaction took place. Addition of 15.1 g (0.1 mole) of boron trifluoride etherate caused a rise in temperature to 90°. The mixture was maintained at this temperature for 1 h, then poured into 1 l of cold water, and extracted with ether (3 × 200 ml). The combined ether extracts were neutralized with sodium bicarbonate and then washed successively with water (1 × 300 ml), 1 *N* HCl (3 × 300 ml), and water (3 × 300 ml). The dried ethereal solution ($MgSO_4$) was freed from solvent and afforded 12 g (67.5%) of red oil which was shown by gas–liquid chromatography to be reasonably pure 3-ethylthioindole.

An analytical sample was prepared by passing a portion of the oil through a column of neutral alumina (activity grade 1)* using benzene as eluant. The benzene eluate was freed from solvent and the residual oil distilled at 95° at 1.5 mm pressure. Much decomposition accompanied distillation but the product came over as a light yellow oil, η_D^{24} 1.6285.

Anal. Calcd. for $C_{10}H_{11}NS$: C, 67.8; H, 6.26; N, 7.95; S, 18.07. Found: C, 67.54; H, 6.19; N, 7.74; S, 18.27.

Infrared absorption (neat) at 3 405 cm^{-1} indicated N—H stretching characteristic of indoles (15). Aliphatic C—H absorption occurred at 2 885, 2 910, and 2 985 cm^{-1}. The n.m.r. spectrum obtained in deuterochloroform showed a triplet centered at 8.80 τ (J = 7 c.p.s.) and a quartet centered at 7.3 τ (J = 7 c.p.s.), both characteristic of an ethyl group. Signals at 2.0–3.0 τ were attributed to aromatic protons and, according to the integrated area, also included the C_2 proton signal shifted downfield from its normal position at about 2.9–3.4 τ (16, 17) as a result of the combined inductive effects of the nitrogen and the C_3 sulfur substituent. Analysis of the compound by mass spectrometry gave a molecular weight of 177. The empirical formula calculated from mass spectrometric data by the method of Silverstein and Bassler (18) was $C_{10}H_{11}NS$.

Acetylation of 3-ethylthioindole with either acetic anhydride in benzene or acetyl chloride in pyridine failed. Only unchanged 3-ethylthioindole was recovered.

Treatment of 3-ethylthioindole with an ethanolic solution of picric acid gave an amorphous precipitate; attempts at crystallization failed to improve this precipitate. The substance melted over the range −10 to 0°.

When 55 mg (2.55×10^{-4} mole) of pure 3-ethylthioindole was treated with 69 mg (2.55×10^{-4} mole) of mercuric chloride in 1 ml of 95% ethanol and the solution allowed to stand overnight at room temperature, 50 mg of ethylthiomercuric chloride was deposited. This gave an infrared spectrum in Nujol identical with that of an authentic specimen (9). Thin-layer chromatography of the remaining ethanolic solution showed spots, developed by Ehrlich's reagent (11, 12), whose R_f values were identical with those of authentic samples of indole and 3-ethoxyindole (19, 20).

3-Ethylthioindole via Reaction of P_2S_5 with 2-Carbethoxyindoxyl

1,2-Dithiolo[4,3-b]indole-3(4H)-thione (IV)

To 10 g (0.028 mole) of 2-carbethoxyindoxyl (20) in 150 ml of practical grade xylene was added 20 g (0.09 mole) of phosphorus pentasulfide and the resulting mixture heated to reflux for 2.5 h. The solution was

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then filtered hot, and the filtrate reduced in volume to 50 ml and chromatographed on a column of neutral alumina (activity grade 1) using ether as eluant. Removal of the ether from the eluate deposited deep orange crystals which were recrystallized from toluene. Yield, 1.2 g (11%); m.p. 208° (decomp.). Molecular weight by Rast, 231; by mass spectrometry, 223.

Anal. Calcd. for $C_9H_5NS_3$: C, 48.40; H, 2.24; N, 6.28; S, 43.10. Found: C, 48.53; H, 2.35; N, 6.42; S, 43.07.

The infrared spectrum showed absorption at 3 310 cm^{-1} (indolic NH) (14) but no carbonyl absorption between 1 600 and 1 735 cm^{-1} (21). No absorption bands could be clearly discerned as being due to $>C{=}S$, usually found at 1 050 – 1 200 cm^{-1} (15, p. 357). The n.m.r. spectrum in dimethyl sulfoxide showed a N—H signal at -2.34 τ and aromatic absorption at 1.83–3.0 τ, while in pyridine a signal at -2.79 τ occurred for N—H, and between 2 and 3 τ for aromatic absorption, but no signals were found above 3.0 τ.

Compound IV gave a negative Ehrlich test, indicating that both C_2 and C_3 positions of the indole ring were blocked by substituents (11, 12).

A solution of 300 mg (0.0013 mole) of 1,2-dithiolo[4,3-*b*]indole-3(4H)-thione in 200 ml of 95% ethyl alcohol, containing 40 g of active Raney nickel (13), was refluxed for 24 h. The hot solution was separated from the nickel by filtration and the sludge extracted with hot alcohol (3 × 100 ml). The combined alcohol solutions were freed from solvent, giving 10 mg of a compound whose infrared spectrum was identical with that of authentic 2-methylindole (14).

Ethyl 3-(Ethylthio)-2-indoledithiocarboxylate (V)

A solution of IV (0.445 g, 0.0021 mole) in 12.5 ml of 95% ethyl alcohol and 2.5 ml of water containing 0.2 g of sodium carbonate was treated with 0.25 g (0.0066 mole) of sodium borohydride under an atmosphere of nitrogen. The mixture was then heated to reflux for 30 min and cooled. To this ice-cold solution was then added 1 ml of ethyl iodide and the resulting mixture brought to reflux for an additional 30 min. The originally dark red solution became light orange. The reaction mixture was then filtered free from solid, and the filtrate diluted with water and extracted with ether (2 × 50 ml). The ether extract was washed with water and dried ($MgSO_4$). Upon removal of the ether the residue was taken up in hexane and the solution chromatographed on 20 g of neutral alumina. Elution with a benzene–hexane mixture (1:1) gave 440 mg of a red-orange oil upon removal of the solvent. On standing, it solidified. Recrystallization was best accomplished from a minimum amount of toluene (2 ml) diluted with *n*-pentane (25 ml). Upon standing overnight at −20°, the solution deposited fine orange needles melting at 49–50°. Yield, 0.356 g (61%).

Anal. Calcd. for $C_{13}H_{15}NS_3$: C, 55.50; H, 5.34; N, 4.98; S, 34.15. Found: C, 55.66; H, 5.15; N, 4.86; S, 34.50.

The infrared spectrum (Nujol) showed a band at 3 340 cm^{-1} for indolic N—H (15). The signals and integrated area of the n.m.r. spectrum in deuterochloroform were consistent with structure V, showing two triplets centered at 8.58 τ (J = 7.5 c.p.s.) and 8.8. τ (J = 7.5 c.p.s.) and two quartets centered at 6.6 τ (J = 7.5 c.p.s.) and 7.1 τ (J = 7.5 c.p.s.) respectively, thereby indicating two differently located ethyl groups. Aromatic proton absorption occurred at 2–3 τ.

Hydrolysis of V to 3-Ethylthioindole-2-carboxylic Acid (VI)

To a solution of ethyl 3-(ethylthio)-2-indoledithiocarboxylate (V) (0.362 g) in 10 ml of 95% ethanol was added 1 ml of water containing 1 g of potassium hydroxide. The mixture was stirred and refluxed for 7 h under an atmosphere of nitrogen. Ethyl mercaptan was evolved and could be detected by the white precipitate which occcurred when it was passed through a solution of mercuric chloride. The reaction mixture was then cooled, diluted with a small amount of water, and then filtered to remove suspended particles. The cooled filtrate (ice) was acidified with 4 ml of 6 N hydrochloric acid. Hydrogen sulfide was liberated. After the solution had stood for an hour, 245 mg (86%) of crude yellow material, m.p. 97–100°, was deposited. Solution of this material in 5 ml of benzene followed by addition of hexane (35 ml) and cooling of the resulting solution gave dark yellow needles melting at 105–106°. Yield, 185 mg (65%). The solid was soluble in dilute aqueous sodium hydroxide. A 10-mg sample required 9.9 ml of 0.00441 N sodium hydroxide, giving a neutral equivalent of 229 (theoretical, 221).

An infrared spectrum in Nujol showed indolic N—H absorption at 3 310 cm^{-1} and carbonyl absorption at 1 710 cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}O_2NS$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.51; H, 5.26; N, 6.47.

3-Ethylthioindole (II)

3-Ethylthioindole-2-carboxylic acid (380 mg) was heated at 150° at 6 mm pressure. A gas was evolved (CO_2) and a liquid was distilled under these conditions, giving 85 mg (26.6%) of pure 3-ethylthioindole identical in boiling point and infrared and n.m.r. spectra with those of an authentic sample prepared by Fischer cyclization.

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