THE SYNTHESIS OF MERCAPTOINDOLES

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Received December 4, 1961

ABSTRACT

The 4-, 5-, 6-, and 7-mercaptoindoles have been prepared via the Reissert condensation of the isomeric benzylthio-*o*-nitrotoluenes. The latter were synthesized by diazotization of the corresponding 2-nitrotoluidines or by direct displacement of the halogen atom in monobrominated *o*-nitrotoluenes with the benzylmercapto group using dimethylformamide as solvent.

INTRODUCTION

Interest in the preparation of 4-mercaptoindole arose from the observation that the structurally analogous 6-mercaptopurine has been used successfully in the treatment of some forms of cancer (1, 2).

Apart from attempts to prepare 3-mercaptoindole, which oxidizes extremely easily to the diindolyl disulphide (3, 4), to our knowledge, no report exists in the literature concerning the remaining isomeric mercaptoindoles. Hence it was thought of interest to prepare the 4-, 5-, 6-, and 7-mercaptoindoles.

DISCUSSION

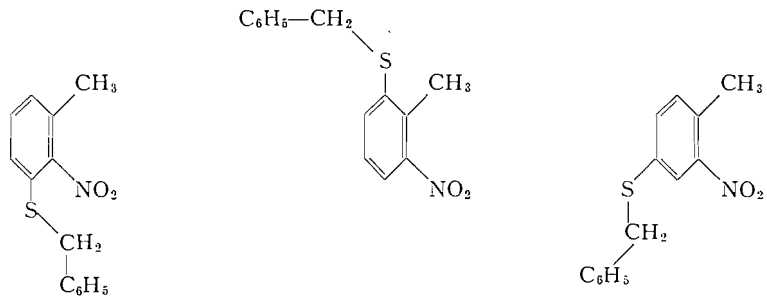
Attempts at direct replacement of nuclear bromine or chlorine in the benzene ring portion of indole by the mercapto group using potassium hydrogen sulphide or thiourea in various solvents met with failure, although similar procedures were successful when applied to 2-bromopyridine or to several chloropurines (5–7). Preparation of the mercaptophenylhydrazones which could be converted to the indole structure by Fischer's method (8) was quite unsatisfactory. However, since methoxy-*o*-nitrotoluenes and ethyl oxalate had been condensed and cyclized to methoxyindoles (9) via the Reissert procedure (10), the same approach was investigated in the present case and was found to be quite successful. Accordingly the isomeric 4-, 5-, 6-, and 7-benzylthio-2-nitrotoluenes were synthesized for this purpose.

The intermediate 4-benzylthio-2-nitrotoluene was prepared in 32% yield from 2-nitro-*p*-toluidine (11) by converting the latter to 4-mercapto-2-nitrotoluene via diazotization (12, 13) followed by treatment with base and benzyl chloride. The 5-benzylthio-2-nitrotoluene was obtained by nitration of aceto-*m*-toluidide according to the general method given by Fieser (14) and then conversion of the amine to the thioether as in the case of the 4-isomer.

The compound 6-nitro-*o*-toluidine required for the preparation of 2-benzylthio-6-nitrotoluene via the route indicated above could not be made satisfactorily by published procedures. Selective reduction of trinitrotoluene, reported to give 4-amino-2,6-dinitrotoluene (17), in our hands produced a substance which could be deaminated (18) only in very low yield. The crude 2,6-dinitrotoluene obtained from this reaction failed to reduce satisfactorily to 6-nitro-*o*-toluidine either with ammonium sulphide (19) or by electrolytic means (20). A more direct route to 6-benzylthio-2-nitrotoluene became available when it was found that the more nucleophylic potassium benzyl mercaptide displaced the halogen (21) in 2-bromo-6-nitrotoluene, especially if the reaction was carried out in dimethylformamide (22), yielding 26% of the thioether.

The fourth isomer, 3-benzylthio-2-nitrotoluene, necessary for the synthesis of 7-mercaptoindole, was obtained by two routes. The first involved the conversion of *m*-toluic acid to 2-nitro-*m*-toluic acid (23), which was then subjected to the Schmidt reaction (24), yielding 2-nitro-*m*-toluidine. This amine was converted to 3-benzylthio-2-nitrotoluene, in 19% yield, by the same method employed for the preparation of the 4- and 5-benzylthio-2-nitrotoluenes (12, 13). In the second route, the displacement of the halogen atom of 3-bromo-2-nitrotoluene (25) by treatment with potassium benzyl mercaptide in dimethylformamide gave the 3-benzylthio-2-nitrotoluene in 86% yield.

Although potassium ethoxide is a more effective base in the Reissert reaction of nitrotoluenes with ethyl oxalate (15), the cheaper sodium ethoxide was found to be quite satisfactory for the condensation of both 4- and 5-benzylthio-2-nitrotoluene with the ester. These conditions, when applied to the 3- and 6-benzylthio-2-nitrotoluenes, gave only small amounts of the pyruvate. However, use of potassium ethoxide as base and ether as solvent (15), along with extended reaction times of several days at room temperature, permitted the isolation of the potassium enolates of ethyl 3- and 6-benzylthio-2-nitrophenylpyruvate. The 6-benzylthio-2-nitrotoluene required, at the maximum, 6 days at room temperature to produce the enolate in 94% yield while the 3-benzylthio-2-nitrotoluene gave the condensation product in only 68% yield even after 16 days' reaction time. The greater difficulty which the 3- and 6-isomers find in undergoing the Reissert condensation might be attributed to the lower degree of activation which the methyl group experiences due to the ortho nitro group. If coplanarity of the nitro group with the ring is responsible, at least in part, for the activation of the methyl group and subsequent removal of a proton by base to form the carbanion, it is readily seen that the groups in the two positions ortho to the nitro substituent in 3-benzylthio-2-nitrotoluene (structure I) and the buttressing effect of the benzylthio group upon the methyl substituent in the 6-benzylthio-2-nitrotoluene (structure II) would indeed cause a marked restriction to the coplanarity of the nitro group with the ring as compared with that attainable in the 4- (and 5-) benzylthio-2-nitrotoluene (structure III). In support of this view it has been found that the position of the characteristic absorption bands in the infrared spectrum of the nitro group in these nitrotoluenes resemble those for the aliphatic nitro group in nitromethane to a progressively greater degree in the order 3-benzylthio-2-nitrotoluene > 6-benzylthio-2-nitrotoluene > 4-benzylthio-2-nitrotoluene (Table I). The order of the apparent ease of condensation of these toluenes with ethyl oxalate is 4-benzylthio-2-nitrotoluene > 6-benzylthio-2-nitrotoluene > 3-benzylthio-3-nitrotoluene.



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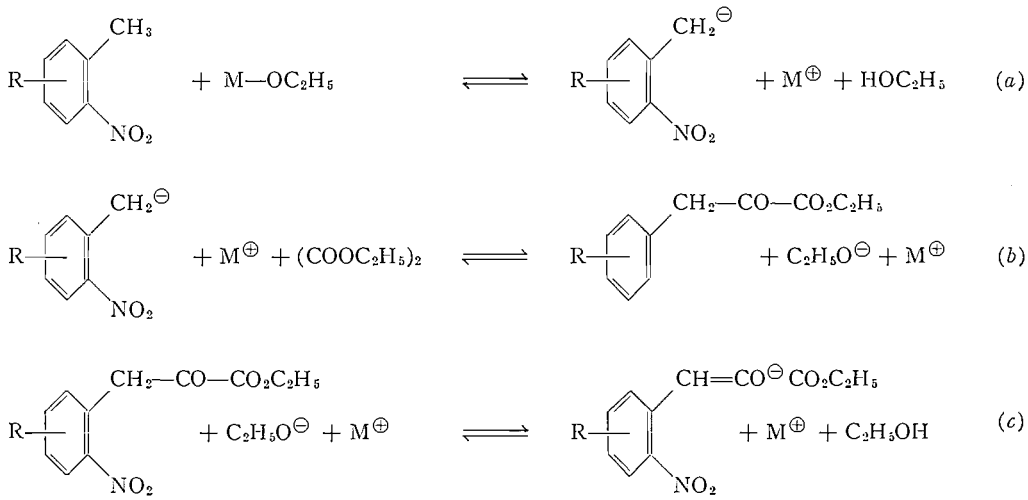
It is also possible that the greater difficulty in the formation of the pyruvate in the case of the 3- and 6-benzylthio-2-nitrotoluenes than for the 4- and 5-isomers may be due to an unfavorable shift in the equilibria indicated below.

TABLE I

Stretching bands of the nitro group in the infrared*
(Calibrated with polystyrene, 6.238 μ)

Compound	Stretching bands, μ	
	Asymmetric	Symmetric
o-Nitrotoluene	6.54	7.40
4-Benzylthio-2-nitrotoluene	6.53	7.40
6-Benzylthio-2-nitrotoluene	6.52	7.37
3-Benzylthio-2-nitrotoluene	6.50	7.29
Nitromethane	6.38	7.18

*Compare the data given for the infrared spectra of nitro compounds by R. N. Jones and C. Sandorfy in A. Weissburger's *Chemical applications of spectroscopy* (Interscience Publishers, Inc., New York. 1956. p. 540).



The requirement of a stronger base to shift the equilibrium to the right in equation (*c*) as well as solvent conditions which cause the precipitation of the enolate (step *c*) is therefore understandable. It has been found that in attempts at converting the potassium enolate of ethyl 6-benzylthio-2-nitrophenylpyruvate to the pyruvic acid by treatment with aqueous base some 6-benzylthio-2-nitrotoluene was obtained. Hence, for best results, the potassium enolate was used directly for the next step in the synthesis of the indole. In fact when pure 4-benzylthio-2-nitrophenylpyruvic acid was left in a solution of 95% ethanol (from which the acid could be crystallized) for a period of 4 weeks at room temperature, the bulk of the pyruvic acid reverted to 4-benzylthio-2-nitrotoluene. This clearly demonstrates the reversible nature of the Reissert reaction. The Reissert condensation appears to resemble the Claisen condensation in many respects (26). A detailed study of the Reissert reaction is at present under way in this laboratory.

The 4- and 5-benzylthio-2-nitrophenylpyruvic acids were reductively cyclized in the usual way with ferrous ammonium sulphate (9, 16). In the case of the potassium enolates of ethyl 3- (and 6-) benzylthio-2-nitrophenyl pyruvate, best results were obtained when a hot solution of the salt in dilute ammonium hydroxide was added to a boiling suspension of ferrous hydroxide. Following elimination of contaminating sulphate ion (16), decarboxylation of both 5- and 6-benzylthioindole-2-carboxylic acid was readily accomplished according to directions in the literature using a copper chromite catalyst (16). This

method, however, when applied to the 4- and 7-benzylthioindole-2-carboxylic acids gave low yields of products which were quite difficult to purify. In addition, considerable sulphur was lost as H_2S. A modified method of decarboxylation, recently described (27), using as catalyst a small amount of the copper salt of the respective indolecarboxylic acid, gave excellent yields of easily purified 4- and 7-benzylthioindoles.

Cleavage of the thioethers with sodium in liquid ammonia to the respective mercaptoindoles followed published directions with some slight modifications (28, 29).

EXPERIMENTAL

All melting points are uncorrected.

4-Benzylthio-2-nitrotoluene

Fifty-four grams (0.355 mole) of 2-nitro-*p*-toluidine, prepared by the method of Cohen and Dakin (11), was diazotized and converted to the xanthogenic ester according to Bennett and Berry (12, 13). The crude ester was hydrolyzed in a refluxing solution made from 20 g of sodium in 200 ml of ethanol to which 40 ml of water was added. An atmosphere of oxygen-free nitrogen was employed to minimize oxidation of the mercaptan to the disulphide. After 1 hour's reflux the solution was diluted with an equal volume of boiled distilled water (N_2) and poured into a separatory funnel previously flushed out with nitrogen. After the addition of 50 g of benzyl chloride, the mixture was shaken vigorously for 5 minutes. A further addition of 10 g of benzyl chloride was made and the mixture again shaken for 5 minutes. During this time enough 6 *N* sodium hydroxide was introduced periodically to maintain an alkaline condition. Combined ether extracts of the cooled solution were washed with water and dried (Na_2SO_4). Removal of the ether left an oil which was fractionally distilled under vacuum to yield 29 g (32%) of 4-benzylthio-2-nitrotoluene, b.p. 143° at 0.2 mm, m.p. 78°. The thioether crystallized well from 95% ethanol. Calc. for $C_{14}H_{13}O_2NS$: S, 12.37. Found: S, 12.23.

6-Nitro-m-toluidine

m-Toluidine was acetylated (ref. 14, p. 165) and the resulting *m*-acetotoluidide nitrated by the general method given by Fieser (ref. 14, p. 170). The crude product obtained proved to be a mixture of acetylated and unacetylated 6-nitro-*m*-toluidine. This material, without further purification, was hydrolyzed in 20-gram batches by refluxing with 1200 ml of a 1:1 mixture of concentrated hydrochloric acid and water containing enough ethanol to dissolve the solid when hot. Following a 1-hour reflux period, the solution was cooled and neutralized with solid sodium carbonate. The precipitate was removed and extracted with boiling dilute hydrochloric acid. (Any solid not soluble in the hot dilute acid was subjected to further hydrolysis as above.) The precipitate obtained from basification of the combined extracts was washed with water and air dried. The crude material melted at 129–130° (lit. 133–134° (30)) and was quite satisfactory for the next reaction.

5-Benzylthio-2-nitrotoluene

By the same method employed above 54 g of 6-nitro-*m*-toluidine was converted to 26.5 g (29%) of 5-benzylthio-2-nitrotoluene, m.p. 55.5–57°. Calc. for $C_{14}H_{13}O_2NS$: S, 12.37. Found: S, 12.28.

2-Bromo-6-nitrotoluene

o-Nitrotoluene was brominated by published procedures (32). The 2-bromo-6-nitrotoluene was separated from the 4-bromo-2-nitrotoluene by fractionation under reduced pressure with a meter-length column containing a stainless steel packing. The 2-bromo-6-nitrotoluene distilled over first and the product solidified in the receiver. The next fraction came over as an oil and proved to be a mixture of the two isomers. Recrystallization of the solid 2-bromo-6-nitrotoluene from ethanol containing a small amount of water gave a 26% yield of pure product. B.p. 108–110° at 3.3 mm; m.p. 41–42°, lit. 42° (19).

6-Benzylthio-2-nitrotoluene

Powdered potassium carbonate (38.8 g, 0.28 mole) was stirred into 50 ml of dimethylformamide containing 55 g (0.25 mole) of 2-bromo-6-nitrotoluene. To this was added 31.3 g (0.25 mole) of benzyl mercaptan (33) all at once. The stirred reaction mixture, kept under nitrogen, was heated for 4 hours at 50–55° and then stirred at room temperature for 14 hours. The addition of an equal volume of water, followed by cooling to 0°, produced a yellow solid which was triturated with dilute sodium hydroxide and then with water. Crystallization from ethanol gave 17.5 g (26%) of yellow needles, m.p. 102–103°. Calc. for $C_{14}H_{13}O_2NS$: C, 64.86; H, 5.02; N, 5.41; S, 12.35. Found: C, 64.72; H, 5.27; N, 5.38; S, 12.42.

3-Benzylthio-2-nitrotoluene

Following the same procedure outlined above, 17.0 g (0.079 mole) of 3-bromo-2-nitrotoluene (25) afforded 17.5 g (86%) of 3-benzylthio-2-nitrotoluene melting at 53–54°. Anal. Found: C, 64.56; H, 5.48; N, 5.27; S, 12.47.

4-Benzylthio-2-nitrophenylpyruvic Acid

To a solution of 6.9 g (0.30 mole) of sodium in 170 ml of anhydrous ethanol were added 44 g (0.30 mole) of diethyl oxalate and 77 g (0.30 mole) of 4-benzylthio-2-nitrotoluene. The reaction mixture, which rapidly became dark red, was refluxed for 1 hour, cooled, diluted with twice its volume of water, and then thrice extracted with ether. The aqueous layer was acidified to Congo red with concentrated hydrochloric acid. Air was blown through the solution to remove residual ether, whereupon crystallization occurred. The solid was separated, dissolved in dilute ammonium hydroxide, and again reprecipitated with hydrochloric acid. Crystallization from an alcohol–water mixture gave 66 g of 4-benzylthio-2-nitrophenylpyruvic acid which melted at 166–167° with decomposition. From the ethereal extract was recovered 9 g of unchanged 4-benzylthio-2-nitrotoluene. Yield, based upon the thioether consumed, 75%.

5-Benzylthio-2-nitrophenylpyruvic Acid

By the same method described above, 5-benzylthio-2-nitrotoluene afforded an oil which failed to solidify. It was therefore purified further by solution in cold dilute ammonium hydroxide followed by precipitation with concentrated hydrochloric acid. An ether extract of the oil was dried (Na_2SO_4), freed of solvent, and the residual oil subjected to the reductive cyclization step in the synthesis.

Potassium Enolate of Ethyl 3-Benzylthio-2-nitrophenylpyruvate

Potassium (4.7 g, 0.12 mole) was dissolved in 20 ml of anhydrous ethanol. To this solution, diluted with 150 ml of dry ether, was added 17.5 g (0.12 mole) of diethyl oxalate, followed 15 minutes later by an anhydrous ether solution of 3-benzylthio-2-nitrotoluene (26 g, 0.10 mole). A deep orange solution resulted which, when left at room temperature for 16 days, slowly deposited the potassium enolate as an orange precipitate. The solid, collected and washed thoroughly with anhydrous ether and then air dried, weighed 27.0 g (68% crude yield). This salt was used directly in the reductive cyclization step.

Potassium Enolate of Ethyl 6-Benzylthio-2-nitrophenylpyruvate

This salt was obtained in 94% yield from 6-benzylthio-2-nitrotoluene by the method described above. The reaction time required in this case was 6 days rather than 16.

6-Benzylthioindole-2-carboxylic Acid

The reductive cyclization of 4-benzylthio-2-nitrophenylpyruvic acid was accomplished according to published procedures (9). The resulting 6-benzylthioindole-2-carboxylic acid was freed from sulphate ion and purified according to Rydon and Tweddle (16). The solid acid obtained after removal of the ether was taken up in cold dilute ammonium hydroxide. Upon acidification (HCl) and cooling, the solution deposited a solid which was air dried. From 15 g of the pyruvic acid there was obtained 8 g (62%) of the indolecarboxylic acid, m.p. 215°. Calc. for $C_{16}H_{13}O_2NS$: S, 11.35. Found: S, 11.32.

5-Benzylthioindole-2-carboxylic Acid

The same method of reductive ring closure converted the crude, oily 5-benzylthio-2-nitrophenylpyruvic acid to 5-benzylthioindole-2-carboxylic acid, m.p. 210–211° (decomp.). Calc. for $C_{16}H_{13}O_2NS$: S, 11.35. Found: S, 11.40. Yield, based upon 45 g of 5-benzylthio-2-nitrotoluene used in the Reissert condensation reaction from which 19 g of the toluene was recovered unchanged, 15.2 g (54%).

7-Benzylthioindole-2-carboxylic Acid

For best results, the usual reductive cyclization (9, 16) was modified as follows. A solution of the potassium enolate of ethyl 3-benzylthio-2-nitrophenylpyruvate (10.0 g, 0.025 mole) in hot (80°) 4 *N* ammonium hydroxide (250 ml) was added slowly with stirring to a boiling suspension of ferrous hydroxide. (The latter was obtained by the addition of 25 ml of ammonium hydroxide, $d = 0.90$, to a boiling solution of ferrous sulphate heptahydrate, 45 g, 0.16 mole, in 300 ml of water.) The resulting mixture was boiled for 90 minutes and then filtered. The ferric oxide sludge was repeatedly extracted with boiling 2 *N* ammonium hydroxide until acidification of an aliquot of the extract failed to precipitate the indolecarboxylic acid. The combined extracts were cooled to 5°, filtered, and washed several times with ether. Upon acidification a solid appeared which when dried gave 2.2 g (31%) of 7-benzylthioindole-2-carboxylic acid melting at 165–166°. Calc. for $C_{16}H_{13}O_2NS$: C, 67.84; H, 4.59; N, 4.95; S, 11.31. Found: C, 67.59; H, 4.75; N, 5.05; S, 11.54.

4-Benzylthioindole-2-carboxylic Acid

This compound was prepared similarly in 56% yield from the potassium enolate of ethyl 6-benzylthio-2-nitrophenylpyruvate. Purification as above gave a brown solid melting at 185–186°. Anal. Found: C, 67.84; H, 4.63; N, 4.96; S, 11.22.

6-Benzylthioindole

Decarboxylation was carried out essentially according to published directions (16) using quinoline and copper chromite (31). Thirty-two grams of 6-benzylthioindole-2-carboxylic acid in 320 ml of distilled quinoline containing 5 g of copper chromite catalyst was heated 16 hours at 200°. The crude indole obtained from this reaction was dissolved in ethanol and clarified with charcoal. Three crops of product were obtained

by successive reductions in the volume of the solvent. The combined precipitates, crystallized from an alcohol–water mixture, afforded 18 g (67%) of 6-benzylthioindole, m.p. 106.5–107°. Calc. for $C_{15}H_{13}NS$: S, 13.41. Found: S, 13.32.

5-Benzylthioindole

5-Benzylthioindole-2-carboxylic acid (15 g) was similarly decarboxylated by heating for 11 hours at 200–210° and gave 6.6 g (52%) of 5-benzylthioindole melting sharply at 74–75°. Calc. for $C_{15}H_{13}NS$: S, 13.41. Found: S, 13.62.

7-Benzylthioindole

Since decarboxylation of 7-benzylthioindole-2-carboxylic acid by the usual procedure (16), employed successfully for the 5- and 6-isomers, proved to be quite unsatisfactory, giving poor yields even after extended times of reaction and also causing some loss of sulphur as H_2S, a modified procedure recently described (27) which avoids these difficulties was employed. From 2.83 g (0.01 mole) of the acid there was obtained 2.05 g (85%) of 7-benzylthioindole melting at 52–53° (from skellysolve B). Calc. for $C_{15}H_{13}NS$: C, 75.27; H, 5.47; N, 5.85; S, 13.40. Found: C, 75.36; H, 5.42; N, 5.93; S, 13.71.

4-Benzylthioindole

This compound was prepared in 80% yield from the corresponding indolecarboxylic acid as described above. It melted at 35–36° (from ethanol). Anal. Found: C, 75.49; H, 5.42; N, 5.98; S, 13.36.

6-Mercaptoindole

This compound was prepared by a modification of the procedure reported by du Vigneaud *et al.* (28, 29). Commercial anhydrous liquid ammonia (125 ml) was placed in a 50×150 mm test tube supported in a Dewar flask by means of a cork ring. To the ammonia was added 5 g (0.02 mole) of 6-benzylthioindole. Small pieces of freshly cut sodium metal were stirred into the ammonia until a blue color of 5–10 minutes' duration was obtained. Excess sodium was then destroyed by ammonium iodide, added until the blue color just disappeared. The reaction tube was then removed from the Dewar flask and the ammonia driven off under a blanket of purified nitrogen. Distilled water (125 ml), previously boiled and cooled, was added to the tube, along with sufficient 3 *N* hydrochloric acid to acidify the solution. The solid which appeared when the solution was cooled was removed and taken up in dilute sodium hydroxide and again precipitated with acid. When washed with water and dried in a desiccator over P_2O_5 (N_2) it melted sharply at 70–71°. Yield, 1.5 g (47%). Calc. for C_8H_7NS: S, 21.49. Found: S, 21.30.

5-Mercaptoindole

Debenzylation of 4 g of 5-benzylthioindole as above afforded 1.5 g (60%) of the mercaptan, which melted at 75–76°. Anal. Found: S, 21.48.

4-Mercaptoindole

Debenzylation of 3.57 g (0.15 mole) of 4-benzylthioindole followed the procedure described above but with the following changes. The ammonia was kept in an Erlenmeyer flask surrounded by dry ice. The flask was kept stoppered throughout the reaction as much as possible to minimize absorption of CO_2 by the liquid ammonia. Following the removal of ammonia, and addition of water to the ammonium salt of the mercaptan, the resulting aqueous solution was washed several times with ether to remove unreduced material. Acidification at 0° gave a solid which was dried in a desiccator under vacuum over dry calcium chloride. The substance was an oil at room temperature, but was readily crystallized from Skellysolve B at dry ice temperatures. Yield 1.5 g (68%). Calc. for C_8H_7NS: C, 64.39; H, 4.73; N, 9.39; S, 21.49. Found: C, 64.37; H, 4.93; N, 9.49; S, 21.08.

7-Mercaptoindole

Debenzylation of 3.3 g (0.014 mole) of 7-benzylthioindole by the same procedure as employed for the 4-benzylthioindole gave 1.8 g (87%) of the pure mercaptan melting at 57–58° (from Skellysolve B). Anal. Found: C, 64.25; H, 4.69; N, 9.31; S, 21.45.

ACKNOWLEDGMENTS

The authors wish to thank the Hercules Powder Company for the donation of a quantity of *m*-toluic acid. Grateful acknowledgment is made to the National Cancer Institute of Canada and to the National Research Council of Canada for continued financial support during the course of this work.

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