Benzo[*b*]thiophene Formation in the Attempted Preparation of Products Related to the Metabolism of the Carcinogen, 4-Acetamidostilbene (1)

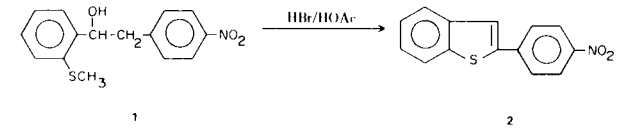
T. Lloyd Fletcher, Hsi-Lung Pan, Carol-Ann Cole and Moses J. Namkung

Pacific Northwest Research Foundation
(The Fred Hutchinson Cancer Research Center)
1102 Columbia Street, Seattle, Washington 98104 (2)

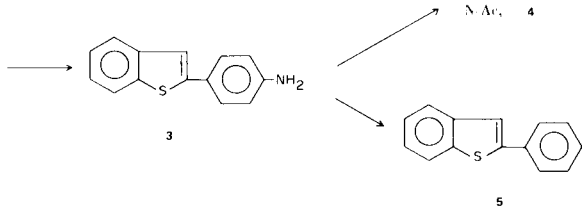
Received March 21, 1973 — Revised June 28, 1974

In a recent report we described the synthesis of ring methylthio-4-acetamidostilbenes (3), which were required in a study of the metabolism of the carcinogen, 4-acetamidostilbene (4-AAS), in rats.

In one case we had obtained the desired methylthionitrostilbene by facile dehydration of the appropriate 1,2-diphenylethanol in boiling dimethyl sulfoxide (3 hours). However, the attempt to thus dehydrate 1-(2-methylthiophenyl)-2-(4-nitrophenyl)ethanol (**1**) was not successful at first (4), and we turned to a more drastic method, the use of boiling hydrobromic acid in acetic acid. The product (**2**), of this reaction, however, when reduced to the amine (**3**), and the latter group acetylated gave **4**, which had a molecular weight (by mass spectrometry) of 267, sixteen mass units less than calculated for the desired stilbene derivative. Microanalyses agreed with a molecular formula lighter by CH_4 than that of a methylthio-4-AAS. The product was insoluble in alkaline



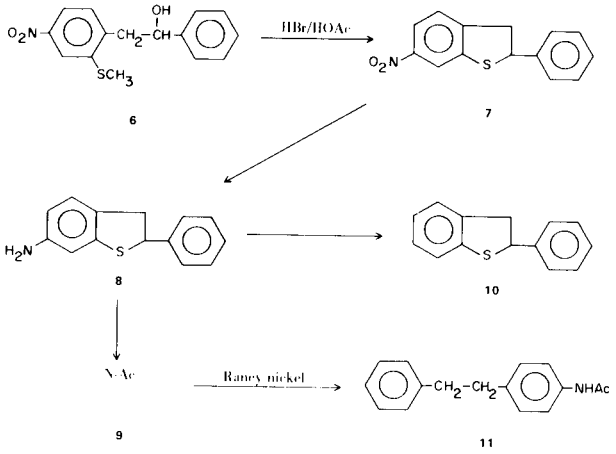
1 2



3 5

solution, thus showing absence of a thiol function. Deamination of **3** gave a known compound, 2-phenylbenzo[*b*]thiophene (**5**) which we confirmed by an alternate synthesis (5). We therefore had produced 2-(4-nitrophenyl)benzo[*b*]thiophene (**2**) from **1**. It should be noted that there was also recovered from the filtrate in the above reaction (**1** → **2**) a very small amount of the desired stilbene, 2′-methylthio-4-nitrostilbene (3).

Attempted dehydration of 2-(2-methylthio-4-nitrophenyl)-1-phenylethanol (**6**) (3), to a stilbene, in boiling acetic acid with hydrobromic acid also gave us an unexpected product (**7**). Reduction to **8** and acetylation to **9** produced a compound with a molecular weight 14 units lower than expected for a methylthio-AAS. Like **4**, **9** was insoluble in alkali.



6 7 8 10 9 11

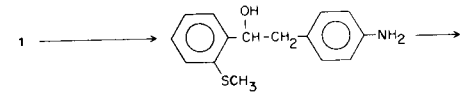
Deamination of **8** gave an oil. By preparative tlc we obtained a product which solidified in the freezer and did not remelt at cool room temperature. Analysis, nmr, and ir agree with the proposed structure (**10**), of a compound which does not appear to have been described hitherto.

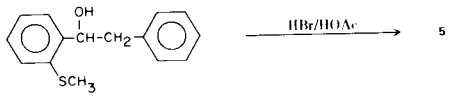
Desulfurization of **9** with Raney nickel gave predominantly 4-acetamidobibenzyl (**11**). Hydrodesulfurization of **4** likewise gave a mixture, which tlc showed to be largely **11**.

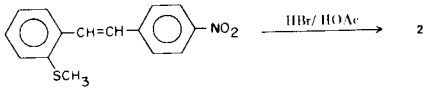
We were interested to learn whether the presence of the nitro group was necessary for the observed closures to take place, and also to learn whether the dehydration was an integral part of this reaction. To answer the first of these questions we reduced **1** (3) to the corresponding amine and then deaminated the latter to give 1-(2-methylthiophenyl)-2-phenylethanol(**12**). When **12** was refluxed

in acetic acid with 48% hydrobromic acid we obtained **5**, in somewhat smaller yield than was obtained in the reaction leading to **2**.

The second question was answered by treating 2′-methylthio-4-nitrostilbene (3) with hydrobromic acid in acetic acid thus obtaining **2**.







It is interesting to speculate on the reason for closure to the 2,3-dihydro hetero ring, when the methylthio and nitro groups are substituted in the ring which is on the β-carbon of the ethanol, but closure to the unsaturated hetero ring when these substituents are on different rings and when the methylthio bearing ring is on the α-carbon. Perhaps in the former case replacement of the hydroxyl group by bromine is followed by relatively rapid attack of the sulfide nucleophile on the α-carbon, with simultaneous elimination of Me bromide. In the latter closure a similar reaction would lead to a four-membered hetero ring. In this case, therefore, hydrogen bromide elimination takes place, followed by attack of sulfide on the more positive aliphatic carbon atom. The latter mechanism would be a way of rationalizing the closure of 2′-methylthio-4-nitrostilbene to **2**, and also the closure of **12** to **5**.

This appears to be a new method of preparation for 2-phenylbenzo[*b*]thiophenes and 2-phenyl-2,3-dihydrobenzo[*b*]thiophenes. Further study is required to show its usefulness with a variety of substituents and positions substituted.

EXPERIMENTAL

Melting points were taken on a Fisher-Johns block and are corrected to standards. Analyses were performed by A. Bernhardt, Elbach über Engelskirchen, West-Germany.

2-(4-Nitrophenyl)benzo[*b*]thiophene (**2**).

To a solution of 1-(2-methylthiophenyl)-2-(4-nitrophenyl)-ethanol (**1**) (3) (2 g., 0.007 mole) in glacial acetic acid (150 ml.), 48% hydrobromic acid (25 ml.) was added. The mixture was refluxed for 4 hours and cooled to room temperature. The yellow precipitate was collected and washed with a little acetic acid and dried, giving 1.2 g., m.p. 195-210°. Recrystallization from toluene (Darco) gave 0.9 g. (48%) of the product, m.p. 214-215°. Another recrystallization from toluene gave an analytical sample, m.p. 214-215°.

Anal. Calcd. for $C_{14}H_9NO_2S$: C, 65.87; H, 3.55; S, 12.56 Found: C, 65.96; H, 3.59; S, 12.71.

The filtrate from the reaction mixture was diluted with water to form a yellow precipitate. The precipitate was filtered off and dried, giving 0.6 g., m.p. 97-104°. Chromatography on neutral alumina with benzene as solvent and eluent gave 0.47 g. of bright yellow material, m.p. 102-104°. Mixture with authentic 2′-methylthio-4-nitrostilbene (3) melted at 106-109°. Thin layer Chromatography of this compound gave the same R_f value as that for 2′-methylthio-4-nitrostilbene.

2-(4-Aminophenyl)benzo[*b*]thiophene (**3**).

To a solution of 2-(4-nitrophenyl)benzo[*b*]thiophene (**2**) (2.71 g., 0.01 mole) in a mixture of 100 ml. of toluene and 100 ml. of ethanol, 3 ml. of hydrazine hydrate (99-100%) and a small amount of palladium on charcoal (5%) were added and the mixture was boiled for 25 minutes. The catalyst was filtered off and the filtrate was boiled down to near dryness and cooled. The white precipitate was filtered off and washed with water and dried, giving 2.3 g. (96%) of the product, m.p. 155-156°. One recrystallization from ethanol gave an analytical sample with the same m.p.

Anal. Calcd. for $C_{14}H_{11}NS$: C, 74.64; H, 4.92; N, 6.22; S, 14.22. Found: C, 74.61; H, 5.04; N, 6.34; S, 14.16.

2-(4-Acetamidophenyl)benzo[*b*]thiophene (**4**).

Acetylation of the foregoing amine with acetic anhydride gave the amide, m.p. 269-271°. Recrystallization from ethanol-acetone (1:1 mixture) gave an analytical sample, m.p. 270-271° with sintering at 267°.

Anal. Calcd. for $C_{16}H_{13}NOS$: C, 71.89; H, 4.90; N, 5.24. Found: C, 71.86; H, 5.00; N, 5.05. The molecular weight was in agreement with theory, $M^+ = 267$ (7).

2-Phenylbenzo[*b*]thiophene (**5**).

a) To a solution of **3** (1.2 g., 0.053 mole) in tetrahydrofuran (6 ml.), concentrated hydrochloric acid (9 ml.) was added. The resulting amine hydrochloride was cooled in an ice (salt) bath and crushed ice (5 g.) was added. When the temperature of the mixture was -10°, an aqueous solution of sodium nitrite (0.6 g.) was added dropwise with stirring. The mixture was warmed gradually to 10°, and was allowed to stand at that temperature for 30 minutes. The clear brown solution was added to 50% hypophosphorous acid (60 ml.) with stirring. Reaction took place immediately with evolution of gas. The mixture was allowed to stand at room temperature overnight and the creamy white precipitate was filtered off, washed with water and dried, giving 1.0 g. (90%) of the crude product, m.p. 168-173°. Recrystallization from ethanol gave 0.8 g., m.p. 170-173°. Sublimation at a bath temperature of 150° (1 mm.), followed by recrystallization from ethyl acetate, gave shiny white crystals, m.p. 175-176° (lit. m.p. 176°) (8); nmr (DMSO-d_6): δ 7.08-7.92 (10H, m, aryl and C-3 position protons) (9). Compare reported value (10) for 2-*o*-nitrophenylbenzo[*b*]thiophene: τ (carbon tetrachloride): 2.15-2.90 (m, aromatic).

b) Compound **5** was also made by the method of Malte and Castro (5) from cuprous phenylacetylide (Willow Brook Laboratories) and *o*-bromothiophenol in pyridine. Recrystallization and sublimation gave a sample identical to **5**; m.p., mixture m.p., tlc and ir.

6-Nitro-2-phenyl-2,3-dihydrobenzo[*b*]thiophene (**7**).

To a hot solution of 2-(2-methylthio-4-nitrophenyl)-1-phenylethanol (**6**) (3) (3.7 g., 0.0128 mole) in glacial acetic acid (200 ml.), hydrobromic acid (48%) (30 ml.) was added and the mixture was refluxed for 2 hours, and then boiled down to a volume of 50 ml. Upon cooling this solution to room temperature a yellow precipitate was deposited which was filtered off and washed with glacial acetic acid, giving 2.8 g. (85%) of the product, m.p 93-94°. By concentrating the filtrate and cooling, a further 0.4 g. (12%) of the product was obtained, m.p. 92.5-94°. An analytical sample (m.p. 93-94°) was prepared by one recrystallization from ligroin (b.p. 60-90°).

Anal. Calcd. for $C_{14}H_{11}NO_2S$: C, 65.37; H, 4.31; N, 5.45; S, 12.45. Found: C, 65.43; H, 4.42; N, 5.57; S, 12.52.

6-Amino-2-phenyl-2,3-dihydrobenzo[*b*]thiophene (**8**).

The foregoing nitro compound (1.3 g., 0.005 mole) was dissolved in 30 ml. of ethanol and reduced with 2 ml. of hydrazine hydrate (99-100%) and 0.1 g. of palladium on charcoal (5%) by heating on a steam bath for 2 hours. The catalyst was filtered off and the filtrate was boiled down to near dryness and about 10 ml. of water was added. Upon stirring with a glass rod a white precipitate came out, giving 1.0 g. (88%) of the amino compound, m.p. 89.5-90°. One recrystallization from methanol gave an analytical sample with unchanged m.p.

Anal. Calcd. for $C_{14}H_{13}NS$: N, 6.16. Found: N, 6.02.

6-Acetamido-2-phenyl-2,3-dihydrobenzo[*b*]thiophene (**9**):

Acetylation of the foregoing amine with acetic anhydride gave the amide, m.p. 163-164°. Recrystallization from ethanol gave an analytical sample with the same m.p.

Anal. Calcd. for $C_{16}H_{15}NOS$: C, 71.35; H, 5.61; N, 5.20 Found: C, 71.24; H, 5.65; N, 5.17. The molecular weight was in agreement with theory, $M^+ = 269$(7).

2-Phenyl-2,3-dihydrobenzo[*b*]thiophene (**10**).

Compound **8** (1.2 g., 0.0525 mole) was diazotized with concentrated hydrochloric acid and sodium nitrite in the presence of tetrahydrofuran, and decomposed in 50% hypophosphorous acid in the same manner as for 2-(4-aminophenyl)benzo[*b*]thiophene. In this case, as the gas evolved, a dark oil separated. The oil was extracted with ether, dried over magnesium sulfate, and the ether was evaporated. Thin layer chromatography of the product showed the presence of impurity. The crude product was chromatographed through a neutral alumina column and eluted with benzene. A light brown band descended rapidly and was collected. Evaporation yielded 1.0 g. (90%) of a light yellow oil. Purification by preparative tlc on silica gel G yielded an oil which crystallized in a freezer and did not melt at cool room temperature, and which was analytically pure. The ir spectrum (potassium bromide disk) shows alkyl CH (2935-2820 cm^{-1}) as well as aryl CH (3060-3020 cm^{-1}). In contrast the spectrum of **5** shows all CH bands as aryl or conjugated (3080-3020 cm^{-1}); nmr (DMSO-d_6): δ 3.20-3.75 (2H, m, C-3 protons), 4.96-5.20 (1H, t, J = 4Hz, C-2 proton) (9).

Anal. Calcd. for $C_{14}H_{12}S$: C, 79.20; H, 5.70; S, 15.10. Found: C, 79.08; H, 5.70; S, 15.04.

4-Acetamidobibenzyl from 6-Acetamido-2-phenylbenzo[*b*]thiophene (**9**).

To a solution of **9** (0.3 g., 0.0011 mole) in 20 ml. of ethanol, 10 g. (wet) of freshly prepared Raney nickel (11) was added and the mixture was refluxed for 4.5 hours. The catalyst was filtered off and the filtrate was boiled down to near dryness and cooled. A white gel-like precipitate came out, giving <0.1 g. with a wide melting range up to 130°. Tlc on silica gel showed several components but principally one which corresponded to authentic 4-acetamidobibenzyl.

4-Acetamidobibenzyl from 2-(4-Acetamidophenyl)benzo[*b*]thiophene (**4**).

2-(4-Acetamidophenyl)benzo[*b*]thiophene (0.25 g.) was dissolved in hot 95% ethanol (60 ml.). The solution was cooled to ambient temperature and freshly prepared Raney nickel (11) (8 g., wet wt.) was added. The mixture was refluxed for 4.5 hours and the nickel catalyst was removed by filtration. The ethanol filtrate was concentrated to an oil which, in a vacuum, solidified to a waxy mass (0.25 g.). Tlc showed a principal spot which agreed (Rf) with 4-acetamidobibenzyl.

1-(2-Methylthiophenyl)-2-(4-aminophenyl)ethanol.

To a solution of **1** (3) (1 g., 0.052 mole) in 50 ml. of ethanol, 2 ml. of hydrazine hydrate (99-100%) and 0.2 g. of palladium on charcoal (5%) were added and the mixture was boiled on a steam bath for 1 hour, filtered to remove the catalyst, and boiled down to near dryness. A white precipitate was filtered off and dried, giving 1.1 g. (81%), m.p. 87-90°. One recrystallization from ethanol gave an analytical sample (0.9 g.), m.p. 89-90°.

Anal. Calcd. for $C_{15}H_{17}NOS$: C, 69.47; H, 6.61; N, 5.40. Found: C, 69.30; H, 6.65; N, 5.52.

Synthesis of **5** by Condensation of Deaminated 1-(2-Methylthiophenyl)-2-(4-aminophenyl)ethanol.

The foregoing amino compound (0.8 g., 0.003 mole) was diazotized with dilute hydrochloric acid (10 ml. of concentrated hydrochloric acid containing 20 g. of cracked ice) and an aqueous solution of sodium nitrite (0.25 g.). After the mixture had stood at room temperature for 1 hour, the diazonium salt solution was poured into 50 ml. of 50% hypophosphorous acid. Accompanied by evolution of gas, a thick oil separated. The mixture was allowed to stand for three days and the product was extracted with benzene, dried over magnesium sulfate, and put through a neutral alumina column (benzene). The light brown main band was collected and evaporated to give a thick oil, which slowly solidified in a refrigerator (0.3 g.), m.p. 35-37°, with softening at 30°.

This was dissolved in acetic acid (20 ml.) and 48% aqueous hydrobromic acid (4 ml.) was added. The mixture was refluxed for 4 hours and cooled. No crystalline solid was obtained. The solution was then boiled down to half of its original volume and a mixture of acetic acid (8 ml.) and 48% aqueous hydrobromic acid (2 ml.) was added and refluxing was continued for 3.5 hours. The solution was cooled and the crystalline precipitate (0.1 g.) was found (tlc) to be a mixture of **5**, some of the unreacted diphenylethanol, and one other component.

The filtrate was mixed with more 48% aqueous hydrobromic acid (3 ml.) and refluxed for 22 hours and cooled. The precipitated product (0.1 g.) was recrystallized twice from methanol giving 0.05 g., m.p., mixture m.p., and tlc identified the product as **5**.

2-(4-Nitrophenyl)benzo[*b*]thiophene (**2**) from 2-Methylthio-4′-nitrostilbene (3).

2-Methylthio-4′-nitrostilbene (0.3 g., 0.0011 mole) was dissolved in warm acetic acid (25 ml.) and 48% aqueous hydrobromic acid (5 ml.) was added. The mixture was refluxed for 4 hours and cooled. The product was collected by filtration and recrystallized

from toluene giving 0.05 g., m.p. and mixture m.p. 212-214°. It was also identified by tlc.

REFERENCES

(1) This investigation was supported in part by research grant No. CA-14500 (formerly CA01744) from the National Cancer Institute.

(2) The work described was begun at the University of Washington, School of Medicine, with the same financial support.

(3) T. L. Fletcher, M. J. Namkung, H.-L. Pan, and C.-A. Cole, *J. Med. Chem.*, **14**, 1113 (1971).

(4) Later it was found that refluxing this diphenylethanol, and also compound **6**, in boiling DMSO for 18-24 hours gave the desired stilbenes (3).

(5) A. M. Malte and C. E. Castro, *J. Am. Chem. Soc.*, **89**, 6770 (1967).

(6) It is of interest that Meerwein arylation of *p*-nitrocinnamic acid with diazotized 1-methylthioaniline also gave us **2** instead of the expected stilbene. The mechanism for this might well be the addition of aryl and chlorine across the double bond followed by nucleophilic attack of sulfur on the carbon adjacent to the nitrated ring, with elimination of the CH_3 and Cl moieties. (H. Krauch and W. Kunz, "Organic Name Reactions", John Wiley and Sons, Inc., New York, N. Y., 1964, p. 310).

(7) We are grateful to Dr. J. A. Miller at the McArdle Institute, University of Wisconsin, for determining these molecular weights by mass spectral analysis.

(8) L. Vio, *Compt. Rend.*, **257**, 459 (1963).

(9) The nmr spectra were run on a Varian Ha-100 by Mr. B. J. Nist, Department of Chemistry, University of Washington.

(10) K. E. Chippendale, B. Iddon, and H. Suschitzy, *J. Chem. Soc. (Perkin I)*, 2023 (1972).

(11) Raney nickel was essentially the W-2 type ("Org. Synth.", Coll. Vol III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 181), but modified for use in desulfurization as described in R. Mozingo, D. E. Wolfe, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).