124. *Synthesis of Some 5-Substituted Benzo*[b]*thiophens Related to Gramine.*

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Some 5-substituted 3-dialkylaminomethylbenzo[*b*]thiophens have been prepared by reaction of the appropriate amines with the 3-bromomethylbenzo-[*b*]thiophen derivatives, which were obtained in high yield from the corresponding 5-substituted 3-methylbenzo[*b*]thiophens by the action of *N*-bromosuccinimide in carbon tetrachloride by use of a slight but important modification of Gaertner's method.

In contrast to the interest recently shown in the preparation of biologically active indole derivatives, the benzo[*b*]thiophen analogues have received relatively little attention. The plant-growth regulating properties of benzo[*b*]thiophenacetic acids have been studied,[1]

[1] *E.g.*, Crook, Davies, and Smith, *Nature*, 1937, **139**, 154; Crook and Davies, *J.*, 1937, 1697; Blicke and Sheets, *J. Amer. Chem. Soc.*, 1948, **70**, 3768; Kefford and Kelso, *Austral. J. Biol. Sci.*, 1957, **10**, 80.

the benzo[*b*]thiophen analogues of tryptophan [2] and tryptamine [3] have been reported, and a few other compounds related to tryptamine have been described.[4] In another field, *N*-ethyl-*N*-2′-halogenoethylbenzo[*b*]thienyl-3-methylamine hydrohalides were prepared.[5] Shirley and Cameron [6] first reported compounds related to gramine, and the preparation and pharmacological properties of some benzo[*b*]thiophen derivatives related to gramine and to serotonin have been described.[7] 3-Chloromethylbenzo[*b*]thiophen was obtained [7] by direct chloromethylation, and condensed with suitable amines to give compounds related to gramine. However, chloromethylation of benzo[*b*]thiophen gives only moderate yields (56%), and the chloromethyl compound reacts with amines with difficulty to give low yields of the products. The following procedure which we have used is widely applicable, and gives better yields than that outlined above. 5-Substituted 3-methylbenzo[*b*]-thiophens were prepared by Werner's method,[8] in which *p*-substituted thiophenols reacted with chloroacetone to give, in 90—97% yield, (arylthio)acetones which were cyclised with phosphorus pentoxide at 160—180°, in 50—70% yield. The 5-substituted 3-methylbenzo-[*b*]thiophens so produced were brominated by the gradual addition of *N*-bromosuccinimide to an irradiated boiling solution of the benzo[*b*]thiophen in carbon tetrachloride containing benzoyl peroxide. This modification of Gaertner's method [9] gave 80—90% yields of products sufficiently pure for further work. The bromomethyl compounds reacted rapidly in dry benzene with the secondary amines used, and the required tertiary amines (yield 70—100%), except for the dibenzylamino-compound, were isolated by distillation, and characterised as their hydrochlorides.

Experimental

Thiophenol, *p*-chloro- and *p*-methyl-thiophenol and *N*-bromosuccinimide were of commercial grade.

p-*Bromothiophenol.*—Finely-divided *p*-bromobenzenesulphonyl chloride (108·6 g., 0·425 mole) was added with vigorous stirring to a mixture of concentrated sulphuric acid (300 g., 2·93 moles) and crushed ice (900 g.) cooled to −5 to 0°, and zinc dust (150 g., 2·3 g.-atoms) was added at such a rate that the temperature did not rise above 0°. After a further 90 min. at 0°, the mixture was carefully warmed until an exothermic reaction began. External cooling was applied when necessary, and after the initial reaction had subsided the mixture was boiled until a clear solution was obtained. The product was steam-distilled, and extracted from the distillate with ether. Drying (Na_2SO_4) and distillation gave *p*-bromothiophenol (69·4 g., 86%), b. p. 106—108°/15 mm., m. p. 72—74° [from light petroleum (b. p. 60—80°)] (lit.,[10] 71—73°).

(*Arylthio*)*acetones.*—Chloroacetone (116·3 g., 1·26 moles) was added with stirring to a solution of thiophenol (137·5 g., 1·25 moles) in sodium hydroxide (50 g., 1·25 moles) and water (1500 ml.) at room temperature, and the mixture was stirred for 45 min. Extraction with ether, washing with water, drying (Na_2SO_4), and distillation gave (phenylthio)acetone (189 g., 91%), m. p. 32—34° [from light petroleum (b. p. 60—80°)], b. p. 135—137°/12 mm. (lit.,[8] 142°/17 mm.).

The following (arylthio)acetones were prepared similarly: p-*bromophenyl*- (90%), m. p. 62—65° [from light petroleum (b. p. 60—80°)], b. p. 176—178°/15 mm. (Found: C, 44·4; H, 3·4; Br, 32·8; S, 12·9. C_9H_9BrOS requires C, 44·1; H, 3·7; Br, 32·6; S, 13·1%); *p*-chloro-phenyl- (91%), pale yellow oil, b. p. 160—164°/12 mm. (lit.,[11] 170—173°/13 mm.); *p*-tolyl- (90%), pale yellow oil, b. p. 146—148°/12 mm. (lit.,[12] 164—168°/22 mm.), n_D^{26} 1·5610.

Benzo[b]*thiophens.*—(Phenylthio)acetone (55·3 g., 0·33 mole) was added to phosphorus

[2] *E.g.*, Avakian, Moss, and Martin, *J. Amer. Chem. Soc.*, 1948, **70**, 3075.
[3] *E.g.*, Herz, *J. Amer. Chem. Soc.*, 1950, **72**, 4999.
[4] (*a*) Cagniant, *Bull. Soc. chim. France*, 1949, 382; (*b*) Capps and Hamilton, *J. Amer. Chem. Soc.*, 1953, **75**, 697; (*c*) Edgerton, U.S.P. 2,916,595/1959; (*d*) Anderson, U.S.P. 3,070,606/1962; B.P. 855,115/1960.
[5] Avakian and Martin, U.S.P. 2,553,495/1950; Chapman and Tompsett, *J.*, 1961, 1291.
[6] Shirley and Cameron, *J. Amer. Chem. Soc.*, 1952, **74**, 664.
[7] Lewis, Martin-Smith, Muir, Nanjappa, and Reid, *J. Medicin. Chem.*, 1963, **1**, 50.
[8] Werner, *Rec. Trav. chim.*, 1949, **68**, 509.
[9] Gaertner, *J. Amer. Chem. Soc.*, 1952, **74**, 4950.
[10] Kharasch and Swidler, *J. Org. Chem.*, 1954, **19**, 1704.
[11] B.P. 721,263/1955.
[12] Banfield, Davies, Gamble, and Middleton, *J.*, 1956, 4791.

pentoxide (71 g., 0·50 mole), and the mixture was slowly heated to 160—180° with vigorous stirring. More (phenylthio)acetone (110·6 g., 0·66 mole) was added followed by more phosphorus pentoxide (25 g., 0·176 mole). The mixture was kept at 160—180° for 45 min. and cooled, and most of the product was extracted with ether. The residue in the flask was decomposed with hot water and filtered through Celite. The solid residue was washed thoroughly with ether, the aqueous filtrate was shaken with ether, the combined extracts were dried (Na_2SO_4), and the ether was removed. 3-Methylbenzo[*b*]thiophen (70%) was obtained as a colourless oil, b. p. 106—110°/12 mm. (lit.,[13] 112°/12 mm.).

The following benzo[*b*]thiophens were prepared similarly: 5-*bromo*-3-*methyl*- (47%), b. p. 153—158°/12 mm., *picrate* (from ethanol), m. p. 89—90° (Found: C, 39·7; H, 2·5; N, 9·5; S, 7·2. $C_{15}H_{10}BrN_3O_7S$ requires C, 39·5; H, 2·2; N, 9·2; S, 7·0%); 5-chloro-3-methyl- (55%), m. p. 32—34°, b. p. 142—144°/14 mm. (lit.,[4d] 92—93°/0·3 mm.); 3,5-dimethyl- (69%), a colourless oil, b. p. 123—125°/12 mm. (lit.,[13] 127°/14 mm.).

5-*Substituted* 3-*Bromomethylbenzo*[b]*thiophens*.—Benzoyl peroxide (5·0 g.) was added to a vigorously stirred solution of the 5-substituted 3-methylbenzo[*b*]thiophen (0·50 mole) in pure dry carbon tetrachloride (1200 ml.). *N*-Bromosuccinimide (89 g., 0·50 mole) was added in small portions to the boiling mixture which was irradiated by two 200 w electric bulbs. The mixture was boiled for a further 90 min., cooled, and filtered from succinimide. Concentration of the filtrate to about 100 ml. caused separation of most of the bromomethyl compound. The rest was obtained by removing all the solvent and triturating the residue with light petroleum (b. p. 60—80°). All the materials obtained in this way were sufficiently pure for use in the next stage of the synthesis. Samples for analysis were recrystallised from light petroleum (b. p. 60—80°). In this way the following benzo[*b*]thiophens were prepared: 5-*bromo*-3-*bromomethyl*- (80%), m. p. 127—128·5° (Found: C, 35·4; H, 1·9; Br, 52·6. $C_9H_6Br_2S$ requires C, 35·3; H, 2·0; Br, 52·2%); 5-*chloro*-3-*bromomethyl*- (91%), m. p. 128—130° (Found: C, 41·3; H, 2·5;

5-Substituted 3-dialkylaminomethylbenzo[*b*]thiophen hydrochlorides, 5-X·C_8H_4S·CH_2·NR_2,HCl, and related compounds.

NR_2	X	Yield * (%)	M. p.†	Found (%) C	H	N	Required (%) C	H	N
NMe_2	H	91	211—212°	57·8	6·4	6·1	58·0	6·2	6·2
NEt_2	H	85	181·5—182·5	61·3	6·8	5·3	61·0	7·1	5·5
$N(CH_2Ph)_2$	H	86	199·5—201	72·6	5·9	3·5	72·7	5·8	3·7
Pyrrolidino	H	82	186—187	61·4	6·4	5·8	61·5	6·4	5·5
Piperidino	H	92	201—203	63·3	6·8	5·3	62·8	6·8	5·2
Morpholino	H	80	217—219	58·0	5·6	5·0	57·9	6·0	5·2
NMe_2	Me	80	200—202 (d.) ‡	45·3	5·2	3·9	45·0	5·2	4·0
NEt_2	Me ¶	78	163—166 §	62·2	7·7	5·0	62·3	7·5	5·2
Pyrrolidino	Me ¶	81	200—202	62·7	6·6	4·9	62·8	6·8	5·2
Piperidino	Me ¶	71	198—200 §	63·4	7·2	4·9	63·9	7·2	5·0
Morpholino	Me ¶	72	180—182 §	59·6	6·5	5·1	59·2	6·4	4·9
NMe_2	Cl	86	217—218	50·2	5·1	5·7	50·4	5·0	5·3
NEt_2	Cl	78	207—208	53·5	5·5	4·8	53·8	5·9	4·8
$N(CH_2Ph)_2$	Cl	100	182—184	66·9	5·7	3·2	66·7	5·1	3·4
Pyrrolidino	Cl	90	222—223·5	54·3	5·4	4·5	54·2	5·2	4·9
Piperidino	Cl	92	224—226	55·7	5·8	5·0	55·6	5·7	4·6
Morpholino	Cl	75	228—229	51·1	5·1	4·2	51·3	5·0	4·6
NMe_2	Br	83	225—226	43·1	4·2	4·5	43·1	4·3	4·6
NEt_2	Br	77	215—216	47·1	4·8	3·9	46·6	5·1	4·2
$N(CH_2Ph)_2$	Br	100	186—187	60·6	4·9	2·8	60·2	4·6	3·1
Pyrrolidino	Br	71	224—225	46·7	4·5	4·3	47·0	4·6	4·2
Piperidino	Br	68	212—213	48·6	4·9	4·5	48·5	4·9	4·0
Morpholino	Br	72	235—237	44·6	4·3	4·3	44·8	4·3	4·0

* Based upon crude starting material. † Most of the compounds soften below the m. p., and some decompose on melting. ‡ Rapid heating. Characterised as the methiodide. § Recrystallised from dry ethanol–ether. ¶ Prepared by Mr. K. A. H. Walker.

Br, 30·6. C_9H_6BrClS requires C, 41·3; H, 2·3; Br, 30·6%); 5-*methyl*-3-*bromomethyl*- (92%), m. p. 99·5—101·5° (Found: C, 50·0; H, 4·1; Br, 32·8. $C_{10}H_9BrS$ requires C, 49·8; H, 3·8; Br, 33·1%). 3-Bromomethylbenzo[*b*]thiophen (82%), m. p. 64—66°, was too unstable for analysis. All these compounds were skin irritants and lachrymators.

[13] Faller and Cagniant, *Bull. Soc. chim. France*, 1963, 30.

5-*Substituted* 3-*Aminomethylbenzo*[b]*thiophen Hydrochlorides*.—The following method was used for all the gramine analogues except the 3-dibenzylaminomethyl derivatives.

The 5-substituted 3-bromomethylbenzo[*b*]thiophen (0·050 mole) was dissolved in dry benzene (300 ml.), and the appropriate amine (dimethylamine, diethylamine, piperidine, morpholine, or pyrrolidine) (0·10 mole) was added. The solution was set aside at room temperature for 30 min. and boiled for 30 min. Ether (300 ml.) was added and the mixture was washed with water to remove the amine hydrobromide and unchanged amine. The solution was dried (Na_2SO_4), and distillation under reduced pressure gave the required products as almost colourless oils. The hydrochlorides (see Table) were prepared (~100%) by adding a dry ethereal solution of the compound to dry ethereal hydrogen chloride, and were recrystallised from dry ethanol.

5-*Substituted* 3-*Dibenzylaminomethylbenzo*[b]*thiophens*.—The 5-substituted 3-bromomethylbenzo[*b*]thiophen (0·050 mole) was boiled for 90 min. with dibenzylamine (19·7 g., 0·10 mole) in dry benzene (500 ml.). The mixture was cooled, the dibenzylamine hydrobromide filtered off, and the benzene removed under reduced pressure. The residue was shaken with dry ether (500 ml.), the mixture filtered, and the filtrate treated with dry ethereal hydrogen chloride. The resulting hydrochlorides (see Table) were recrystallised from dry ethanol.

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