

SYNTHESIS OF BENZOTHIOPHENES

547.73

BY

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Four methylbenzothiophenes and two methylnaphthothiophenes were synthesized by cyclization of arylketosulphides (obtained by reaction of α -halogen ketones on thiophenols) in the presence of zinc chloride or phosphorus pentoxide.

U.V. absorption spectra of the benzo and naphthothiophenes and their dioxides were measured to be used for the identification of benzothiophenes in mixtures with other compounds.

Introduction.

Descriptions of the preparation of alkylbenzothiophenes (or thio-naphthenes) are found only sporadically in the literature. Thus far they were prepared by reduction either of thioindoxyl derivatives¹⁾ or of the benzothieryl ketones obtained by acylation of benzothiophene²⁾.

However, the first method can hardly be regarded as general because the starting materials are, as a rule, difficult to obtain, while the reduction yields are rather low.

The base material used in the second method is benzothiophene itself, which can be obtained e.g. from coal tar or by synthesis from styrene and hydrogen sulphide³⁾.

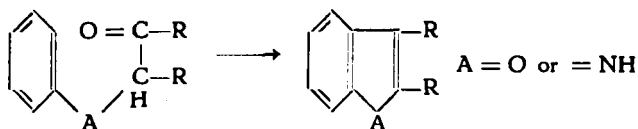
It is a known fact that the oxygen and nitrogen compounds corresponding to the benzothiophenes, viz. the coumarones and indols, can be obtained by cyclodehydration of arylketoethers and arylketoamines respectively⁴⁾:

¹⁾ e.g. C. E. Dalgliesh and F. G. Mann, J. Chem. Soc. 1945, 893; D. S. Tarbell and D. K. Fukushima, J. Am. Chem. Soc. 68, 1456 (1946); C. Hansch and H.G. Lindwall, J. Org. Chem. 10, 381 (1945).

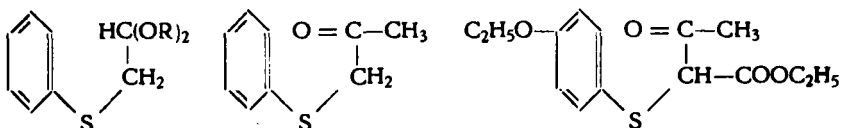
²⁾ e.g. N. P. Buu-Hoi and P. Cagniant, Rec. trav. chim. 67, 64 (1948).

³⁾ R. J. Moore and B. S. Greensfelder, J. Am. Chem. Soc. 69, 2008 (1947).

⁴⁾ C. K. Bradsher, Chem. Rev. 38, 447 (1946).

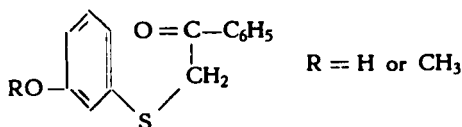


*Autenrieth*⁵⁾, and *Delisle* and *Schwalm*⁶⁾, already attempted an analogous preparation of benzothiophenes by cyclization of 2-phenylthioethanal acetals, of phenylthioacetone or of (3'-ethoxyphenylthio)-1-acetoacetic ester.



They were, however, not successful, which was attributed partly to the fact that some of the arylketosulphides are easily convertible into aryldisulphides, partly to the poor activation of the ortho position by the —SR group.

Fries et al.⁷⁾ succeeded in cyclizing the following two ketosulphides, the ortho position of which was activated by the presence of a hydroxy or methoxy group.



As it seemed that this reaction had been investigated with only a few ketosulphides, we thought it useful once more to study the possibility of applying it as a more general method of preparing benzothiophenes substituted with alkyl or other groups; the more so as the base materials, viz. thiophenols and α -halogen ketones are, as a rule, easily obtainable.

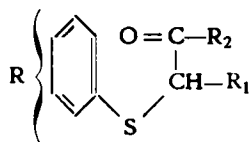
Results.

By reaction of thiophenols with α -halogen ketones in the presence of the calculated quantity of caustic solution, the arylketosulphides were obtained in very satisfactory yields.

⁵⁾ *W. Autenrieth*, *Ber.* **24**, 159 (1891).

⁶⁾ *A. Delisle* and *A. Schwalm*, *Ber.* **25**, 2980 (1892).

⁷⁾ *K. Fries*, *H. Heering*, *E. Hemmecke* and *G. Siebert*, *Ann.* **527**, 83 (1937).



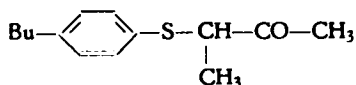
(Addition of too little caustic solution gave rise to formation of large quantities of aryldisulphides. Obviously these ketosulphides are not very stable with regard to hydrohalic acids, which is further shown e.g. when 3-phenylthio-2-butanone is heated with aniline hydrochloride: the reaction product contains diphenyldisulphide.)

Cyclization of the above ketosulphides was successful both with phosphorus pentoxide and zinc chloride. The yields were very satisfactory (85 to 95 % of the quantity calculated).

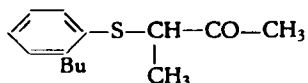
In this way we prepared:

- I. 3-methylbenzothiophene,
- II. 2,3-dimethylbenzothiophene,
- III. 2,3,5-trimethylbenzothiophene,
- IV. 2,3,7-trimethylbenzothiophene,
- V. 2,3-dimethylnaphtho (1',2' : 5,4)-thiophene, ("2,3-dimethyl- α -naphthothiophene"),
- IV. 2,3-dimethylnaphtho (1',2' : 4,5)-thiophene, ("2,3-dimethyl- β -naphthothiophene").

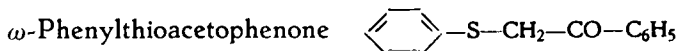
The presence of a butyl group in the benzene nucleus of ketosulphides in ortho or para position interfered with cyclization under the above conditions, as is shown by the fact that (4'-butylphenylthio)-propanone, 3-(4'-butylphenylthio)-2-butanone



and 3-(2'-butylphenylthio)-2-butanone



did not react with zinc chloride or phosphorus pentoxide. No such interference is caused by a methyl group in the same positions (compare III and IV).



did not form a benzothiophene either.

The above shows that the tendency of arylketosulphides to cyclodehydration is, after all, rather poor, so that it may be interfered with

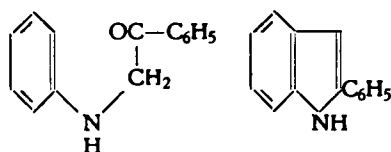
already by a slight inactivation of the ortho position in the benzene nucleus.

The structure of the benzothiophenes formed.

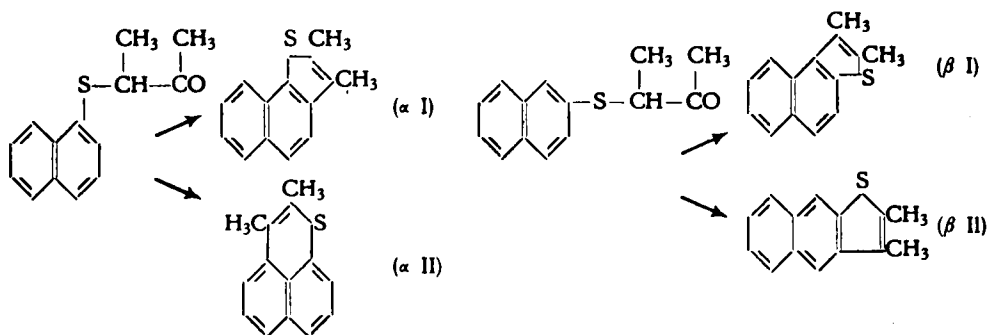
By comparison with 2-methylbenzothiophene synthesized by *Hansch and Blondon*⁸⁾ it could be indirectly demonstrated that the methylbenzothiophene obtained by cyclization of phenylthioacetone has the methyl group in the 3-position. This proof is necessary because it seems not impossible that ketosulphides are able to isomerize as has been shown for some ketoamines by *Julian et al.*⁹⁾ and recently confirmed by *Brown and Mann*¹⁰⁾, e.g.



Another possibility is the occurrence of rearrangements as has been found by *Janetzky and Verkade*¹¹⁾ in a number of cyclizations of ketoamines to indols. Either phenomenon gives rise to formation of indols in which the substituents in the 2- and 3-positions seem to have changed places when compared to the compound one would expect to obtain, e.g.



In principle both 3-(α -naphthylthio)-2-butanone and 3-(β -naphthylthio)-2-butanone may cyclize in two ways:



⁸⁾ C. Hansch and W. A. Blondon, J. Am. Chem. Soc. **70**, 1561 (1948).

⁹⁾ P. L. Julian, E. W. Meyer, A. Nagnani and W. Cole, J. Am. Chem. Soc. **67**, 1203 (1945).

¹⁰⁾ F. Brown and F. G. Mann, J. Chem. Soc. **1948**, 847 and 858.

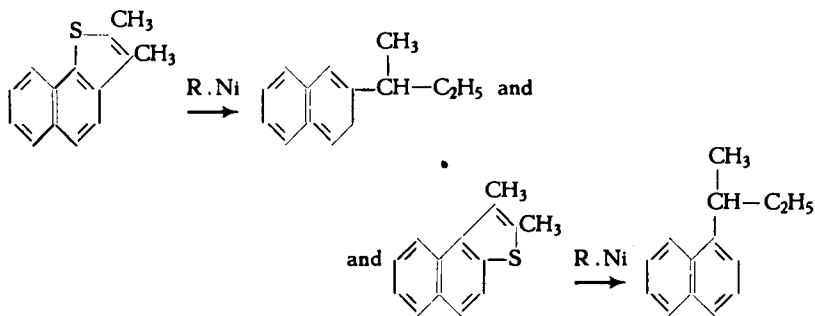
¹¹⁾ E. F. J. Janetzki, Diss. Delft (1943).

α I is more likely than α II on account of the greater resonance energy of the former which contains three aromatic rings.

On the other hand β I is in accordance with theoretical consideration and chemical evidences for electrophilic substitution of the naphthalene molecule showing a preference of the α -C atom over the β -C atom. To determine the configuration the cyclization products from α -thionaphthol and from β -thionaphthol were subjected to reductive desulphurization with Raney nickel.

By comparison of the picrates, styphnates and U.V. absorption spectra of the compounds formed from α -thionaphthol and from β -thionaphthol with those of 1-sec. butylnaphthalene obtained by synthesis from α -bromonaphthalene, the former compound was identified as 2-sec. butylnaphthalene, the latter as 1-sec. butylnaphthalene

This proves the correctness of structures (α I) and (β I):



Spectra.

The ultraviolet absorption spectra of the benzothiophenes, naphthothiophenes and the 1,1-dioxides prepared therefrom¹²⁾ were measured (see figures 1, 2, 3 and 4), to be used for the identification of benzothiophenes, in mixtures with other compounds.

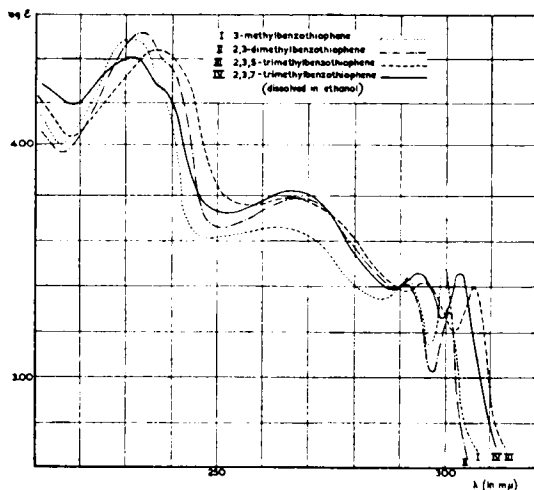


Fig. 1.

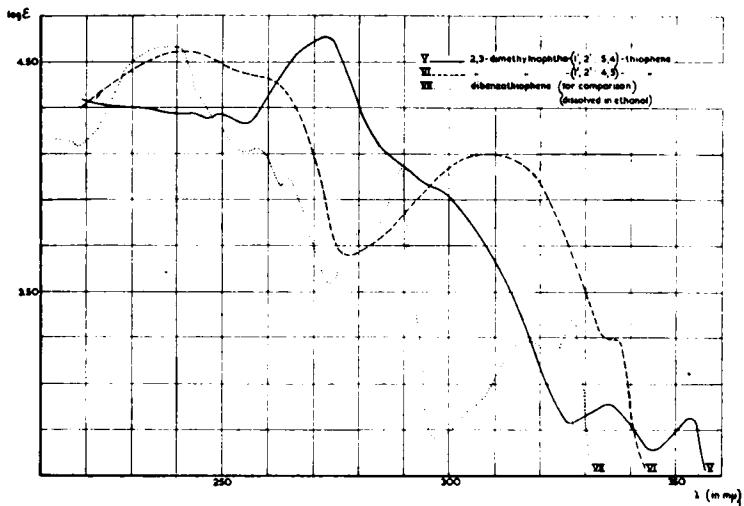


Fig. 2.

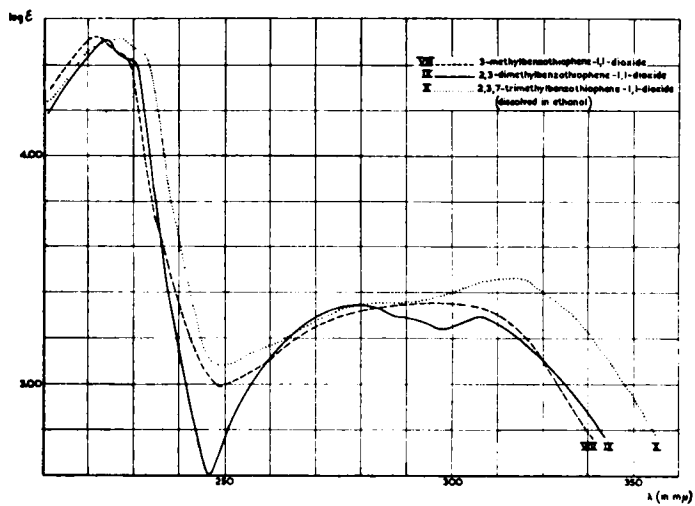


Fig. 3.

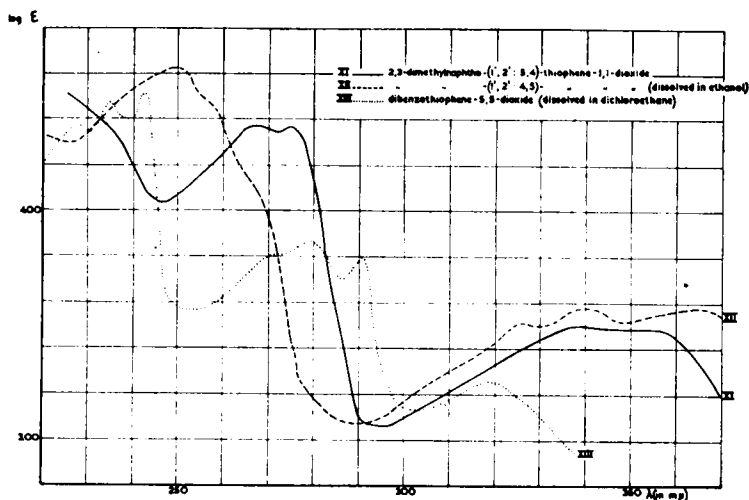


Fig. 4.

Experimental.

(in collaboration with *H. F. Eyhuisen* and *J. B. de Jonge*).

1. Preparation of ketosulphides.

1.00 mol. of a thiophenol or thionaphthol was dissolved in 1.00 mol. of a 30% sodium hydroxide solution in water. With cooling and stirring, 1.00 mol. of the α -halogen ketone was added dropwise in 30 minutes. The temperature was kept at 20–25° C. The reaction product was taken up in ether, washed with water, dried, and, after removal of the ether, subjected to distillation.

2. Cyclization of the ketosulphides.

The ketosulphide was mixed with an equal quantity by weight of anhydrous zinc chloride or with one third part of its weight of phosphorus pentoxide. The mixture was stirred and heated for 30–45 minutes at 160–180° C.

The reaction product was treated with water and taken up in ether. The ether layer was washed with water and dried with sodium sulphate. After removal of the solvent the residue was distilled.

The picrates were prepared by mixing solutions of the benzothiophenes and picric acid in ethanol.

The 1,1-dioxides were obtained by stirring the benzothiophenes for one hour at about 70° C with a slight excess of a mixture of hydrogen peroxide of 30% and acetic acid. The yields were almost quantitative.

¹²⁾ The spectra were measured by *Dr. J. Beintema* with a Beckman Quartz Spectrophotometer.

Table I.
Arylketosulphides.

Sulphide	Prepared from and		Boiling pt in °C/mmHg	Melting pt in °C	n_D^{20}
butanone	C_6H_5-SH	$ClCH_2-CO-CH_3$	142°/17	34—35°	
-butanone	"	$CH_3-CHBr-CO-CH_3$	132—133°/13		1.5563
(phenylthio)-2-butanone	$p-CH_3-C_6H_4-SH$	"	150—152°/13		1.5515
(phenylthio)-2-butanone	$o-CH_3-C_6H_4-SH$	"	146—147°/13		1.5565
(phenylthio)-2-butanone	$p-C_4H_9-C_6H_4-SH$ ¹³⁾	"	111—112°/0.03		1.5354
(phenylthio)-2-butanone	$o-C_4H_9-C_6H_4-SH$	"	103—105°/0.01		1.5378
(phenylthio)-propanone	$p-C_4H_9-C_6H_4-SH$	$ClCH_2-CO-CH_3$	116—118°/0.1		1.5430
acetophenone	C_6H_5-SH	$BrCH_2-CO-C_6H_5$		51—52°	1.6270 *)
(phenylthio)-2-butanone	$\alpha-C_{10}H_7-SH$	$CH_3-CHBr-CO-CH_3$	ca. 147°/0.03		1.6260
(phenylthio)-2-butanone	$\beta-C_{10}H_7-SH$	"	ca. 150°/0.06		1.6293

ylthiophenol were prepared under the direction of Prof. Dr. J. P. Wibaut at the Laboratory for organic chemistry, University of Groningen, Groningen, The Netherlands.

Table II.
Analyses of the ketosulphides.

Empirical formula	Calculated		Found	
	% C	% H	% C	% H
a $C_9H_{10}OS$ (166)	65.06	6.02	65.1	6.1
b $C_{10}H_{12}OS$ (180)	66.66	6.06	66.5	6.8
c $C_{11}H_{14}OS$ (194)	68.04	7.21	67.9	7.2
d "	"	"	67.8	7.3
e $C_{14}H_{20}OS$ (236)	71.10	8.48	70.9	8.5
f "	"	"	70.3	8.5
g $C_{13}H_{18}OS$ (222)	70.27	8.11	70.0	8.2
h $C_{14}H_{12}OS$ (228)	73.69	5.26	73.8	5.3
i $C_{14}H_{14}OS$ (230)	73.04	6.09	72.8	6.2
j "	"	"	72.5	6.1

3. Hydrodesulphurization of the naphthothiophenes with Raney nickel.

2,3-Dimethyl- α -naphthothiophene and 2,3-dimethyl- β -naphthothiophene were dissolved in ethanol and boiled for eight hours with Raney nickel (2 g per mmol. of naphthothiophene) prepared according to *Mozingo et al.*¹⁴).

The sec. butylnaphthalene thus formed was purified via the picrate and finally distilled.

2,3-Dimethyl- α -naphthothiophene gave a sec. butylnaphthalene with b.pt. 142—144° C/17 mm; $n_D^{20} = 1.5756$; picrate, m.p. 62—63° C. Neither with ethanol nor with benzene could a styphnate be obtained.

Analysis:

Found: C = 90.9 %, H = 8.8 %.

Calculated for $C_{14}H_{16}$ (184): C = 91.30 %, H = 8.70 %.

2,3-Dimethyl- β -naphthothiophene gave a sec. butylnaphthalene with b.pt. 96—97° C/0.1 mm; $n_D^{20} = 1.5795$; picrate m.pt. 82—83° C; styphnate m.pt. 114—115° C.

Analysis:

Found: C = 91.2 %, H = 8.7 %.

Calculated for $C_{14}H_{16}$ (184): C = 91.30 %, H = 8.70 %.

For identification purposes 1-sec. butylnaphthalene was synthesized from 1-bromonaphthalene (b. pt. 147—148° C/21 mm), which was converted into 1-cyanonaphthalene¹⁵; after reaction with methylmagnesium iodide this product gave 1-acetylnaphthalene¹⁶ (b.pt. 166—167° C/18 mm) which, after reaction with ethyl-

¹⁴ R. *Mozingo*, D. E. *Wolf*, S. A. *Harris* and K. *Folkers*, J. Am. Chem. Soc. **65**, 1013 (1943).

¹⁵ M. S. *Newman*, Org. Synth. **21**, 89 (1941).

¹⁶ Cf. L. G. *Nunn* and H. R. *Henze*, J. Org. Chem. **12**, 540 (1947).

Tabel III.
Benzothiophenes.

Benzothiophene	Boiling pt in C/mm Hg	Melting pt in °C	n_D^{20}	d_4^{20}	Yield in %	Picrate		1,1-dioxyde melting pt in °C
						Colour	Melting pt in °C	
benzothiophene	125—127°/25		1.6229	1.1190	85	yellow	119—120	146—146.5
thylbenzo-	122--124°/13		1.6170	1.1054	85	orange	101—102	149—150
thylbenzo-	144—146°/13	56—57	1.6022		70—75	..	124,5-- 125.5	
thylbenzo-	143—144°/13	51—52	1.6080		85—90	..	110— 110.5	190—191
ynaphtho- (,4)-thiophene	ca. 200°/0.03	108.5—109			95	red	143—144	257—258
ynaphtho- (5)-thiophene	ca 200°/0.03	106—107				..	143—144	207—208

Synthesis of benzothiophenes.

Tabel IV.
Analyses of the benzothiophenes.

	Emperical formula	Calculated			Found		
		% C	% H	% N	% C	% H	% N
picrate dioxide	I C ₉ H ₈ S (148) C ₁₅ H ₁₁ N ₃ O ₇ S (387) C ₉ H ₈ O ₂ S (180)	72.97	5.41	11.34	72.9	5.5	11.3
		60.00	4.45		59.8	4.5	
picrate dioxide	II C ₁₀ H ₁₀ S (162) C ₁₆ H ₁₃ N ₃ O ₇ S (391) C ₁₀ H ₁₀ O ₂ S (194)	74.07	6.17	10.73	74.1	6.2	10.3
		61.86	5.16		62.0	5.3	
picrate	III C ₁₁ H ₁₂ S (176) C ₁₇ H ₁₅ N ₃ O ₇ S (405)	75.00	6.82	10.37	74.6	6.9	10.0
picrate	IV C ₁₁ H ₁₂ S (176) C ₁₇ H ₁₅ N ₃ O ₇ S (405)	75.00	6.82	10.37	74.6	6.7	10.3
dioxide	V C ₁₄ H ₁₂ S (212) C ₁₄ H ₁₂ O ₂ S (244)	79.25	5.66		79.1	5.6	
		68.85	4.92		68.9	5.1	
picrate dioxide	VI C ₁₈ H ₁₂ S (212) C ₂₀ H ₁₅ N ₃ O ₇ S (441) C ₁₄ H ₁₂ O ₂ S (244)	79.25	5.66	9.52	78.8	5.6	9.4
		68.85	4.92		68.8	4.9	

magnesium bromide followed by dehydration with potassium bisulphate, gave 1-sec. butylnaphthalene ¹⁷⁾ (b.pt. 145—146° C/18 mm).

Hydrogenation of this substance with Raney nickel gave 1-sec. butylnaphthalene, b.p.t 96—97° C/0.1 mm; $n_D^{20} = 1.5790$; picrate m.pt. 82—83° C; styphnate m.pt. 113—114° C (mixed m.pt. of the corresponding derivatives from sec. butyl-naphthalene prepared from 2,3-dimethyl- β -naphthothiophene: 82—83° C and 113—114° C, respectively).

(Received April 4th 1949).

¹⁷⁾ Cf. F. Bergmann and A. Weizmann, J. Org. Chem. 9, 352 (1944).