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THIOPHENE CHEMISTRY – XXII*

SOME REACTIONS OF BENZO[b]THIOPHENE-2(3H)ONE

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Abstract—Benzo[b]thiophene-2(3H)one has been prepared from 2-t-butoxybenzo[b]thiophene by dealkylation. Alkylation of sodium, thallium and tetrabutylammonium salts of benzo[b]thiophene-2-(3H)one produces both C- and O-alkylation along with products due to ring-opening. At elevated temperatures benzo[b]thiophene-2(3H)one reacts with HMPA (hexamethylphosphorictriamide) to give 2-dimethylaminobenzo[b]thiophene. Other 2-aminobenzo[b]thiophenes are produced by refluxing benzo[b]thiophene-2(3H)one in HMPA in the presence of excess of the corresponding amine.

Recently Dickinson and Iddon[1] published the preparation and some reactions of benzo[b]thiophene-2(3H)one, 3. In 1964[2] 3 was prepared by first introducing the t-BuO group into the 2-position of 1 and then dealkylating of 2 by heating in the presence a catalytic amount of *p*-toluenesulphonic acid: A similar method has been applied to thiophenes.[3,4,5,6] In connection with our studies on alkylation of ambident ions,[6,7] derived from potential 2-hydroxythiophenes, we have investigated some salts of 3 and their reactions. Three different salts were studied, namely the sodium salt in HMPA,[8,9] the thallium salts,[10] and the tetrabutylammonium salt (the ion-extraction technique has been reviewed[11,12]).

The sodium salt of 3 was prepared from sodium hydride in HMPA, the alkylation reagent was then added and the mixture heated for 3½ h. The alkylation reagents were MeI, EtI and i-PrBr, the total and relative yields are given in Table 1

All product structures were assigned from spectroscopic evidence, analytical data, and by comparison with authentic samples (Tables 2–4). Compound **7b**, 3,3-diethylbenzo[b]thiophene-2(3H)one shows a special NMR pattern due to two different geminal hydrogens (=C(H^a)(H^b) in the Et groups. Fig 1 shows the 60 MHz spectrum of **7b** and Fig 2 a 100 MHz NMR spectrum of the methylene protons. The different δ- and *J*-values were calculated by use of the standard Laocoon 3 programme and gave the following values: $\delta_{Me} = 65{\cdot}48 \pm 0{\cdot}05$ Hz, $\delta_{H^a} = 176{\cdot}58 \pm 0{\cdot}06$ Hz, $\delta_{H^b} = 201{\cdot}65 \pm 0{\cdot}04$ Hz, $J_{H^aX_3} = 7{\cdot}39 \pm 0{\cdot}05$ Hz, $J_{H^bX_3} = 7{\cdot}45 \pm 0{\cdot}04$ Hz, $J_{gem} = -13{\cdot}61 \pm 0{\cdot}04$ Hz. Fig 3 shows the calculated spectrum based on the above data.

Inspection of the products-composition shows that the reaction mechanism, indicated in Scheme 1 is probably valid.

The first step involves reaction of the alkyl halide with ambident anion A, giving the O-alkylated product, 4, and the C-alkylated product, 6. The ambident anion can also react with benzo[b]-thiophene-2(3H)one, 3, to produce a ring-opened

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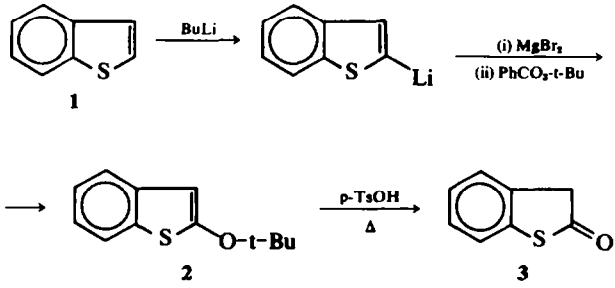
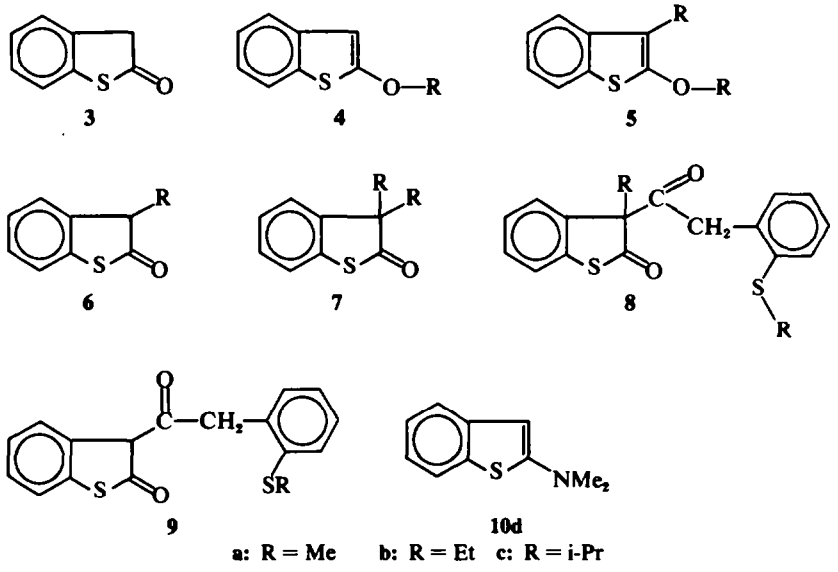


Table 1. Methylation, ethylation, and iso-propylation of the sodium salt of benzo[b]thiophene-2(3H)-one in HMPA

Alkylating agent	Temp.	Yield %	3	4	5	6	7	8	9	10d
MeI	105	total	3	—	1	1	2	65	1	—
		rel.	4	—	2	1	3	88	2	—
EtI	~ 140	total	—	4	4	—	42	—	—	19
		rel.	—	6	6	—	60	—	—	28
i-PrBr	~ 160	total	—	26	7	1	—	—	—	28
		rel.	—	41	11	2	—	—	—	46



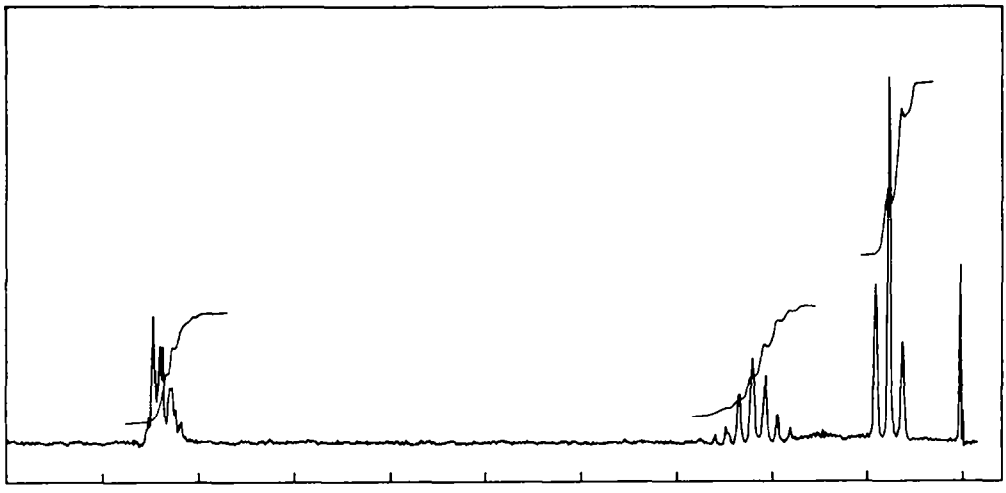


Fig 1.

product, which then can be alkylated to give 9. The second step involves attack on 6 of the ambident anion, A, giving a new ambident anion, B, which on alkylation gives 5 and/or 7. Reaction of B with 3 produces 8 in the same way as outlined for 9. This reaction mechanism also accounts for the unreacted benzo[b]thiophene-2(3H)one recovered. Formation of 8a is strongly temperature dependent as the yield decreases considerably when increasing the temperature from 105° to 130°. Besides spectro-

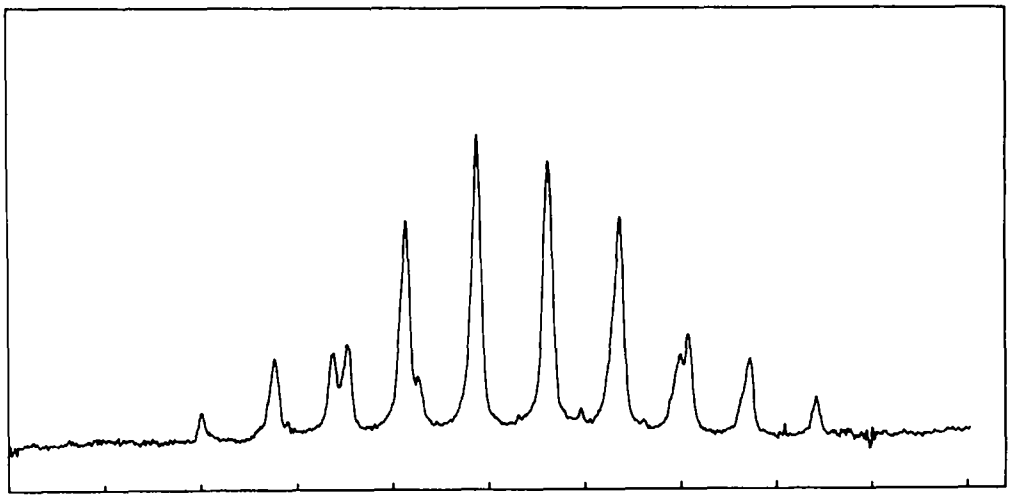


Fig 2.

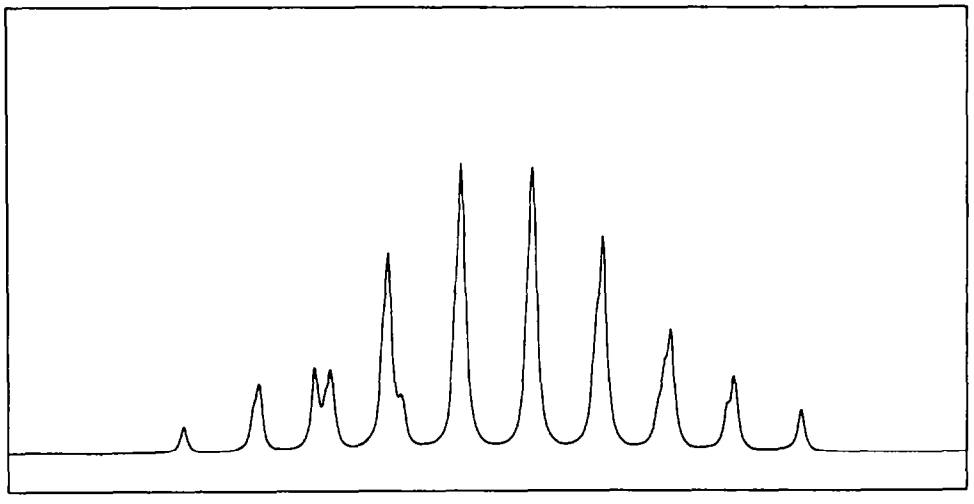
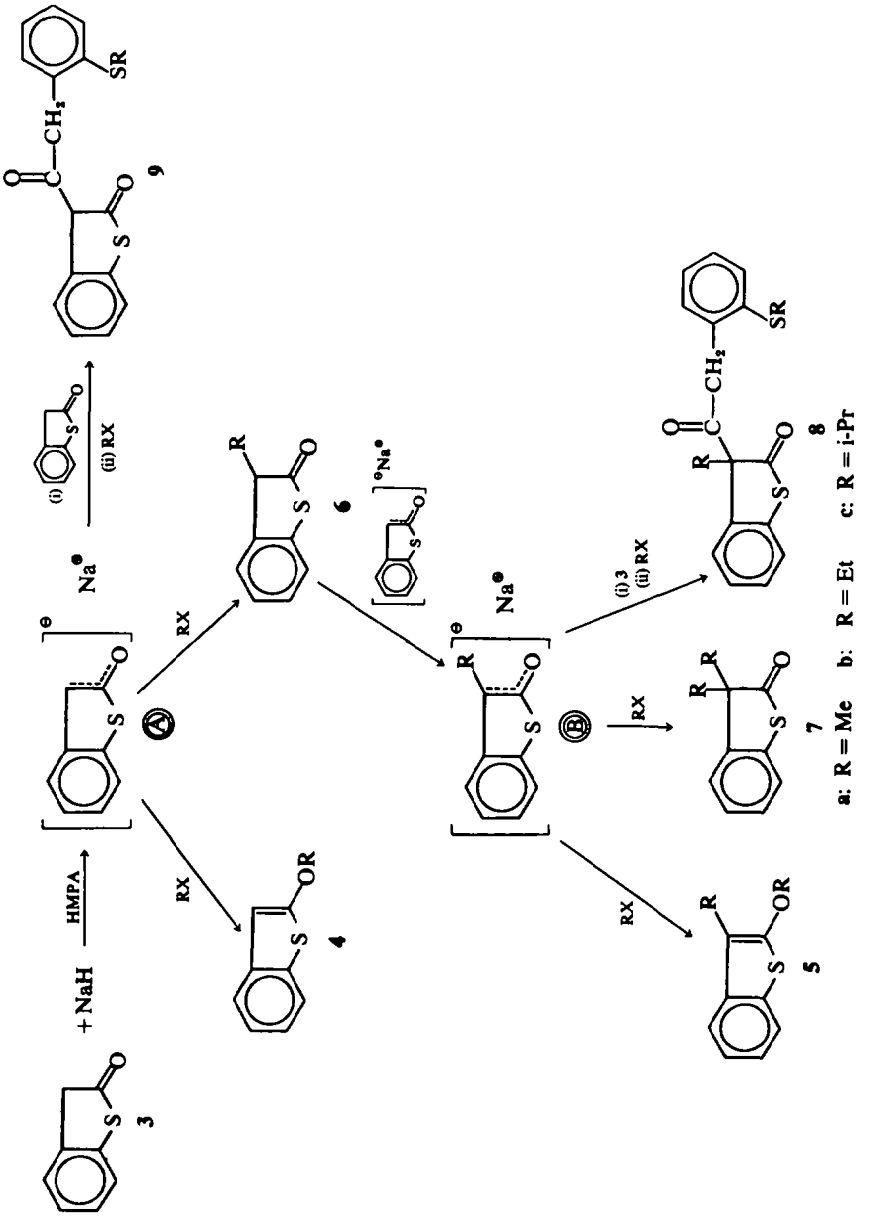


Fig 3.

Table 2. Analyses, NMR- and IR-spectra of **6** and **7**

Compound	Analyses						NMR δ ($CDCl_3$)[a]						C=O
	Calc. (%)			Found (%)									
	C	H	S	C	H	S	$C^{\alpha}H$	$C^{\beta}H$	H^{3}	aromatic	$J_{H^3C^{\alpha}H}$	$J_{C\alpha_{HC}\beta_H}$	cm^{-1}
6a[1]	65·81	4·88	19·53	65·63	4·76	19·82	1·41 d		3·34 q	7·05–7·25	7·5 Hz		1705
6c	68·73	6·29	16·64	68·61	6·25	16·71	3·15 m	1·37 d	3·79 d	6·72–7·44	8·0 Hz	6·5 Hz	1710
7a[16]	67·05	6·14	17·89	67·13	6·02	17·97	1·45 s			7·16–7·35			1725
7b	69·88	6·84	15·50	69·82	6·79	15·56	1·83 m	0·64 t		6·71–7·18	~7·5 Hz[b]		1710

[a] α and β refer to the side-chain in the 3-position.
[b] ABX_3 system.



SCHEME 1

Table 3. Analyses, NMR- and IR-spectra of 4 and 5

Compound	Analyses Calc. (%) C	H	S	Found C	H	S	NMR δ ($CDCl_3$)[a] $C^{\alpha}H$	$C^{\beta}H$	$C^{\alpha'}H$	$C^{\beta'}H$	H^3	aromatic	$J_{C\alpha_{HC}\beta_H}$	$J_{C\alpha'_{HC}\beta'_H}$
4a[1]	63·20	5·26	21·07	63·06	5·34	21·13			3·96 s		6·31 s	7·10–7·39		
4b	67·45	5·62	17·98	67·23	5·49	18·12			2·95 q	1·05 t	6·07 s	6·84–7·41		7·0 Hz
4c[b]	68·73	6·29	16·64	68·53	6·18	16·81			4·28 h	1·28 d	6·08 s	6·67–7·38		6·0 Hz
5a[21]	67·45	5·62	17·98	67·58	5·71	17·42	2·10 s		3·84 s			6·92–7·58		
5b	69·87	4·75	15·54	69·95	4·83	15·32	2·64 q	1·18 t	4·01 q	1·37 t		6·81–7·41	7·5 Hz	7·0 Hz
5c[c]	71·77	7·74	13·66	71·62	7·69	13·72	3·22 h	1·33 d	4·21 h	1·32 d		6·71–7·42	6·5 Hz	6·0 Hz

[a] α and β refer to the side-chain in the 3-position, and α' and β' to the oxygen side-chain.
[b] In IR a symmetrical doublet at 1390 cm^{-1}.
[c] In IR a symmetrical doublet at 1385 cm^{-1}.

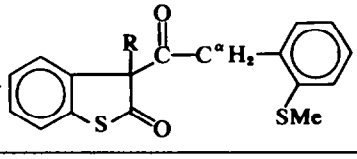
scopic evidence, the structure of **8a** was also confirmed by chemical means: cleavage of **8a** with pyrrolidine in HMPA gave **6a** and N,N-tetramethylene *o*-methylthiophenylacetamide.

MeI as alkylation agent gave **8a** as the main product, no **4a** was detected. Dickinson and Iddon,[1] however, using dimethylsulphate as alkylation agent, obtained **4a**. With respect to the O-alkylated products, the yields follow the normal sequence MeI < EtI < i-PrBr according to the alkylation agents (Table 1).[19]

A quite unexpected result was observed when EtI and i-PrBr were used; 2-dimethylaminobenzo[b]thiophene **10d** was isolated in high yield. In the latter case **10d** was surprisingly the main product. This prompted us to find out if **3**, when heated with HMPA, would also give 2-dimethylaminobenzo[b]thiophene; a 55% yield of the expected product was isolated. However would it be possible to prepare other 2-amino-benzo[b]thiophenes when refluxing **3** in HMPA in the presence of an added amine.

Different amines have been investigated with pK_b-values varying from 2·79 to 9·42 and in all cases 2-amino-benzo[b]thiophenes were isolated (Table 5). It is also noted that when an aromatic amine (anilin) is used, the yield of 2-anilinobenzo[b]thiophene is extremely low. The reason is that aromatic amines and HMPA produce 1,3,2,4-diazadiphosphetidines[18] in high yields. In this connection it should be stressed that the temperature is quite crucial for the successful preparation of 2-amino-benzo[b]thiophenes by this new method. If the reaction temperature is too low, no reaction occurs. This also accounts for the fact that the yield of **10d** increased with temperature in the alkylation reactions (Table 1). The importance of HMPA as solvent and reaction agent was shown

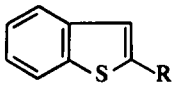
Table 4. Analyses, NMR- and IR-spectra for

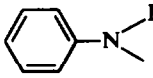


Compound	Analyses Calc. (%) C	H	S	Found C	H	S	NMR δ ($CDCl_3$) C^{α}—R	S—Me	—$C^{\alpha}H_2$—	Aromatic	J_{gem}	C=O cm^{-1}
8a	65·85	4·91	19·52	65·80	4·94	19·62	1·68[a]	2·26	3·83[c]	6·75–7·50	17 Hz	1705 and 1740
9a	63·82	4·61	21·05	63·75	4·62	21·01	3·51[b]	2·29	3·78[c]	6·75–7·50	17 Hz	1710 and 1740

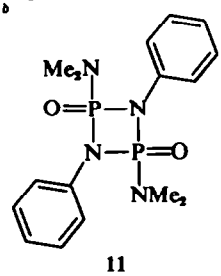
[a] R = Me.
[b] R = H.
[c] AB-system.

Table 5. Reaction of benzo[b]thiophene-2(3H)one in HMPA with amines

(RH) giving 

R	Product	Reflux-time (h)	Reflux-temp	Yield (%)	m.p.
Me_2N—	**10d**	3·5	230	55	35–36[a]
	**10e**[13,14]	23	183	40	175
	**10f**	24	172	63	94–95
	**10g**[14,15] **11**[b,18]	7	248	3 76	123–26 255–58

[a] b.p. 94°/0·4 mm.

[b] 

11

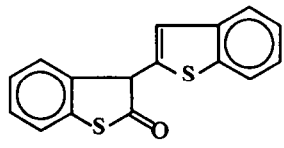
Table 6. Analyses, NMR- and UV-spectra of 2-amino-benzo[b]thiophenes

	Analyses								NMR δ ($CDCl_3$)			UV nm (EtOH)			
Com-	Calc. (%)				Found (%)										
pound	C	H	N	S	C	H	N	S	aromatic	H^5		ν_{max}	log ε	ν_{max}	log ε
10d	67·78	6·26	7·91	18·06	67·84	6·29	7·82	17·96	6·52–7·37	5·69 s	3·81 s	233	4·19	283	4·12
10e	65·78	5·94	6·39	14·59	65·64	6·02	6·23	14·71	7·05–7·75	6·18 s	3·06–3·94 m	227	4·54	284	4·33
10f	71·89	6·96	6·45	14·72	71·52	6·77	6·32	14·93	6·82–7·64	6·09 s	1·58 and 3·19	232	4·03	292	4·91
10g	74·71	4·89	6·22	14·21	74·93	4·16	6·02	14·45	6·91 7·63	6·38 s	3·88 s	231	4·62	311	4·47

when heating **3** with an added amine in *o*-dichlorobenzene (b.p. = 179°) with no observed reaction.

As for attempts to react **10d** with other amines, RH (Table 5) gave only starting material. This route for the formation of the 2-aminobenzo[b]-thiophene is thus discarded.

Thallium salts of potential 2-hydroxythiophenes have recently been prepared and found to be quite stable[6,7]. These salts offer some advantages over other salts as they do not undergo condensation reactions etc. It was therefore thought that the thallium salt of **3** should be the salt of choice in our investigations and it was readily prepared in quantitative yields by adding thallium(I)ethoxide to **3** in an inert solvent. For other reasons we suspected the product actually to be a salt mixture. Acidification gave about 90% of **3** and 8% of a condensation product **12**, only was charac-



12

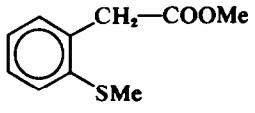
SCHEME 2

terized by NMR and IR data (δ 7·05, 8H; δ 5·08, 1H; δ 3·70, 1H; >C=O at 1710 cm^{-1}) and 2% of unidentified material which indicated that more than one salt had been formed. This forced us to run only one alkylation experiment as a rather complex reaction-mixture was foreseen. The methylation of the thallium salt of 3 was carried out by using a Soxhlet extraction apparatus[6,7] and the product distribution and yields are given in Table 7.

The main product (13) was quite unexpected and

Table 7. Alkylation of the thallium(I) salt of 3

	Yields (%)	3	4	5	6	7	8	9	13
MeI	Total	7	—	1	2	1	16	3	28
	Relative	12	—	2	3	2	28	5	48



13[20]

must have been formed after a ring-opening reaction and a subsequent S- and O-methylation. This single experiment on alkylation of thallium salts of 3 did not inspire further work and research in this field was not continued.

The advantage of working with a tetrabutylammonium salt of 3 is that the salt can be extracted into an organic phase ($CHCl_3$, CH_2Cl_2) and the alkylation be run in a homogeneous and anhydrous medium. The alkylation was carried out by adding the alkylating agent to the organic phase and after the reaction had ceased (1 h), the organic phase was removed. The tetrabutylammonium halide was precipitated by adding ether to the residue and the products found in the ether phase. This alkylation method gave also a complex product-mixture (Table 8) but the separation of the products seems to be simpler than in the two other methods.

Table 8. Alkylation of the tetrabutylammonium salt of 3

	Yields (%)	3	4	5	6	7	8	9
MeI	Total	16	4	3	13	20	27	2
	Relative	19	5	4	15	23	32	2

Table 8 also shows that the yield of 7 is greater than that of 6, which is not as expected as the tetrabutylammonium ion is rather bulky. It is also seen that two O-alkylated compounds, 4 and 5, are formed which shows that O-alkylation is no hindrance, when using the ion pair extraction technique.

No further experiments were conducted as the method offered no significant new findings about syntheses or mechanisms.

EXPERIMENTAL

BNR spectra were recorded in $CDCl_3$ at 60 MHz on a Varian A-60 (15–20% w/w, solns at 33° ± 1°). TMS was used as internal standard and the chemical shifts are expressed in δ-values (ppm) downfield from TMS and are believed correct to ±0·002 ppm. Coupling constants were measured with an accuracy of ±0·2 Hz on the 50 Hz scale. IR spectra were recorded as 5% solns in $CHCl_3$ on a Beckman A 18. UV spectra were measured on a Perkin-Elmer 402 in EtOH. The mixture of alkylated products were separated by unidimensional multiple chromatography (UMC).[22] UMC (*j*; *k*:*l*) was carried out on Kiselgel $PF_{254+366}$ (Merck) support (20 × 40 cm and 0·3 cm thick) and eluted; *j* times with ether-light petroleum in ratio *k*:*l*. The light petroleum (b.p. 37–50°) was distilled before use. Analyses were made by NOVO Industri A/S, Copenhagen.

2-t-Butoxybenzo[b]thiophene, 2. To a soln of 55·2 g (0·4 mol) benzo[b]thiophene in 200 ml anhydrous ether were added 285 ml 15% n-BuLi in hexane for 30 min at 25°. The mixture was stirred and refluxed for 3 h. An ether soln of anhydrous magnesium bromide, prepared from 25·5 ml (0·5 mol) of bromine and 13·3 (0·55 mol) of magnesium suspended in 225 ml of dry ether, were added to the lithium compound. 0·36 mol of t-butylperbenzoate in 200 ml anhydrous ether was then added dropwise to the Grignard reagent at room temp for 1 h. The soln was stirred overnight, 50 ml of H_2O added and ether decanted. The ether was extracted several times with water, dried (Na_2SO_4), the ether removed, and the remainder distilled giving 2 53·2 g (79%). B.p. 74–79°/0·15 mm, recrystallized from pet. ether (b.p. 40–60°) m.p. 33–34°. (Found: C, 69·81; H, 6·80; S,. 15·50. $C_{12}H_{14}S$ requires: C, 69·88; H, 6·84; S, 15·52%.)

Benzo[b]thiophene-2[3H]one.[1,17] 6·2 g ether (2) and 0·1 g *p*-TSOH were heated on an oil bath at 150–160° till all isobutylene had been eliminated. The yield was quantitative (5·0 g). The solid compound was recrystallized from EtOH, m.p. 43–45°. (Found: C, 64·0; H, 4·1; S, 21·4. C_8H_6S requires: C, 54·0; H, 4·0; S, 21·3%.)

Alkylation of the sodium salt of benzo[b]thiophene-2[3H]one in HMPA. A cold (0°) soln of benzo[b]thiophene-2[3H]one (5·0 g) in HMPA (25 ml) was added to a stirred suspension of NaH (1·0 g) in HMPA (25 ml) at 0° at such a rate that the evolution of hydrogen was not too vigorous, and then the mixture stirred at 0° for 30 min. MeI (8 ml), EtI (12 ml) or i-PrI (14 ml) was then added and the mixture kept for 3½ h at the temp indicated in Table 1. The mixture was poured onto ice-water, ether extracted, the combined ether phases dried (Na_2SO_4) and the ether removed. The remainder was separated by UMC (2; 5:95) and gave the products (Table 1). In the methylation experiment compound **8a** immediately precipitated, when the oil was dissolved in EtOH and cooled to −70°.

Preparation of 2-aminobenzo[b]thiophenes. 1 g benzo[b]thiophene-2[3H]one was dissolved in 25 ml HMPA and the corresponding amine added. The resulting mixture was refluxed at 160–240° until the C=O absorption disappeared in IR. The resulting soln was poured on ice-water and ether extracted (HMPA remains in the water phase). After drying (Na_2SO_4) the ether was evaporated and the remaining oil recrystallized (EtOH).

Methylation of the thallium salt (15). 6·7 g of $(TlOEt)_4$ were added at once to 4 g of 3, dissolved in 75 ml C_6H_6. The thallium salt (15) precipitated immediately in quantitative yield, was washed with light petroleum and air dried. 8 g of freshly prepared 15 were extracted for 22 h

with 12 ml MeI in 150 ml light petroleum in a Soxhlet extraction apparatus. The solvent was removed to give a yellow oil, 2·8 g. UMC (2; 5:95) gave the products listed in Table 7.

Methylation of the tetrabutylammonium salt of 3. 6·8 g of tetrabutylammonium hydrogen sulphate were added to a soln of 20 ml 2 M NaOH, and 3·0 g of benzo[b]thiophene-2[3H]one in 50 ml $CHCl_3$ were added. The mixture was stirred for 30 min. The two layers were separated and 6 ml MeI were added to the dried $CHCl_3$ phase which was stirred for 2 h. $CHCl_3$ was removed and the tetrabutylammonium iodide precipitated by adding ether. The ether phase was dried ($MgSO_4$), the ether removed giving 3·5 g of crude products. Separation by UMC (2; 5:95) gave the products listed in Table 8.

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