Formation of Benzo[*b*]thiophens and Related Compounds by a Rearrangement involving Ring Contraction

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Substituted 4-(naphthyl- and phenyl-thio)-4-methylpentan-2-ones (I)—(VI) undergo cyclodehydration by polyphosphoric acid at 100 °C to give thiochromens (VII)—(XII) which, under these conditions, rearrange with ring contraction to the corresponding fused thiophens (XIII)—(XVIII).

We have briefly described [1] products resulting from the action of polyphosphoric acid (PPA) at 100° on the keto-sulphide (I), the previously reported [2,3] thiochromen (VII) being accompanied by 2-isopropyl-3-methylbenzo[*b*]thiophen (XIII); under these conditions the thiochromen was shown to be capable of ring contraction to give the benzothiophen (XIII). The present paper, prompted by current interest in benzo[*b*]thiophens [4] and related compounds, reports an examination of the scope of this behaviour.

The keto-sulphides (I)—(VI) were readily prepared in good yield (Table 3) by piperidine-catalysed Michael addition of the appropriate arenethiols to mesityl oxide. Treatment of each of the six keto-sulphides with PPA at 100°, followed by appropriate work-up, gave product mixtures difficult to separate by conventional methods. Gel permeation chromatography proved of value here, however, and from the product mixture from the keto-sulphide (I), by employing a column of Sephadex LH-20 modified [5] with Nedox 1114 and eluting with methanol, we obtained the pure thiochromen (VII), the pure benzo[*b*]thiophen (XIII), and (eluted between these two compounds) an isomer $C_{12}H_{14}S$ (A). The structures of (VII) and (XIII) follow from their spectroscopic properties, and for (XIII) also from comparison with authentic 2-isopropyl-3-methylbenzo[*b*]thiophen. The isomer (A) has spectral properties consistent † with the structure (XIX): its ^{1}H n.m.r. spectrum [τ ($CDCl_3$)] comprises resonances at 8·64 (6H, s), 7·99 (3H, d, J 1·5 Hz), 4·53 (1H, q, J 1·5 Hz), and 2·5—3·0 (4H, m); and a significant positive nuclear Overhauser enhancement of the olefinic proton resonance is observed on irradiation at the frequency of the *gem*-dimethyl protons, excluding a similar isomeric structure with olefinic proton and methyl positions interchanged. This by-product (XIX), which is not formed in the rearrangement of the pure thiochromen (VII), may arise by interaction of benzenethiol and mesityl oxide formed by a retro-Michael reaction of the keto-sulphide (I); in

† This compound gave a satisfactory microanalysis, but it was never obtained completely free from minor, unidentified products which gave weak additional ^{1}H n.m.r. signals.

[1] D. D. MacNicol and J. J. McKendrick, *Tetrahedron Letters*, 1973, 2593.

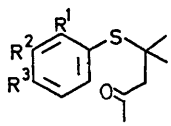
[2] B. D. Tilak, H. S. Desai, C. V. Deshpande, S. K. Jain, and V. M. Vaidya, *Tetrahedron*, 1966, **22**, 7.

[3] B. D. Tilak and V. M. Vaidya, *Tetrahedron Letters*, 1963, 487.

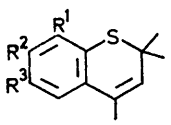
[4] See, for example, B. Iddon and R. M. Scrowston, *Adv. Heterocyclic Chem.*, 1970, **11**, 177.

[5] J. Ellingboe, E. Nystrom, and J. Sjovall, *Biochim. Biophys. Acta*, 1968, **152**, 803; *J. Lipid Res.*, 1970, **11**, 266.

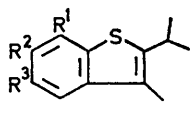
keeping with this view (XIX) is formed when equimolar proportions of benzenethiol and mesityl oxide are treated with PPA at 100°.



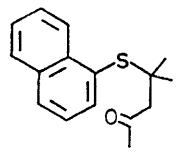
(I) $R^1=R^2=R^3=H$
(II) $R^1=Me, R^2=R^3=H$
(III) $R^1=R^3=H, R^2=Me$
(IV) $R^1=R^2=H, R^3=Me$



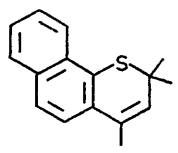
(VII) $R^1=R^2=R^3=H$
(VIII) $R^1=Me, R^2=R^3=H$
(IX) $R^1=R^3=H, R^2=Me$
(X) $R^1=R^2=H, R^3=Me$



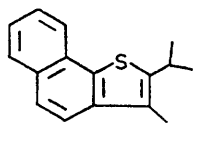
(XIII) $R^1=R^2=R^3=H$
(XIV) $R^1=Me, R^2=R^3=H$
(XV) $R^1=R^3=H, R^2=Me$
(XVI) $R^1=R^2=H, R^3=Me$



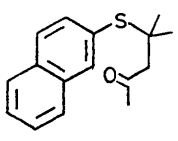
(V)



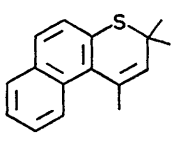
(XI)



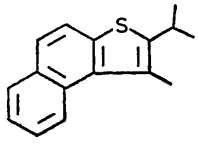
(XVII)



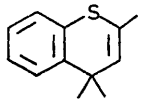
(VI)



(XII)



(XVIII)



(XIX)

The approximate relative percentages (±10%), estimated by ^1H n.m.r., of the major products from the keto-sulphides (I)—(VI) are given in Table 1; the product distribution has a marked dependence on the structure of the starting keto-sulphide. For the methyl-substituted keto-sulphides (II)—(IV), proton resonances in the spectra of the product mixtures were sufficiently close to those of known products from (I) to allow reliable line assignments; * for the naphthylthio-ketones (V) and (VI) the products were isolated and characterised, and (XVII) and (XVIII) were synthesised unambiguously.

The first indication [1] that thiochromens might be capable of undergoing ring contraction came from the variation in the ratio of the products (VII) and (XIII) with temperature, higher temperatures favouring and lower temperatures disfavouring the ring-contracted structure. We therefore treated the isolated thiochromens (VII), (IX), (XI), and (XII) (obtained by gel chromatography or crystallisation) with PPA at 100°, and found that they underwent ring contraction to the extents shown in Table 2.

TABLE 1

Percentages [a] of major products in material recovered from PPA treatment of the keto-sulphides (I)—(VI)

Compound number	Material recovered (%)	2*H*-Thiachromen	4*H*-Thiachromen	Ring-contracted product
(I)	23	15	15	70
(II)	22	60	*b*	40
(III)	29	60	5	35
(IV)	24	40	30	30
(V)	33	95	*b*	5
(VI)	38	20	*b*	80

[a] Percentages (±10%) obtained from integration of 60 or 100 MHz ^1H n.m.r. spectrum; other, minor products were detected in all cases. [b] <*ca.* 5%.

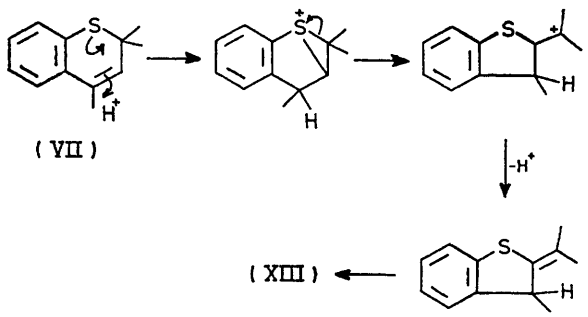
TABLE 2

Rearrangement of thiochromens with PPA

Compound	Weight of P_2O_5 (g per g reactant)	Reaction time (h)	% Rearranged [a]
(VII)	4	3	40
(IX)	4	3	17
(XI)	15	8	61
(XII)	4	3	91

[a] Obtained (±5%) from integration of 100 MHz ^1H n.m.r. spectrum.

No evidence for free radicals as intermediates was obtained † by carrying out the reaction of (I) with PPA at 100° in the probe of a Decca X3 e.s.r. spectrometer. This finding is consistent with the possible general ring contraction mechanism given in the Scheme for (VII) ⟶ (XIII).



(VII) (XIII)

SCHEME

EXPERIMENTAL

^1H N.m.r. spectra were recorded on Varian T-60 and HA-100 instruments with $CDCl_3$ as solvent, and Me_4Si as internal standard. U.v. and i.r. spectra were measured on Unicam SP 800A and Perkin-Elmer 225 spectrometers, respectively. Mass spectra were run on an A.E.I.-G.E.C. MS 12 spectrometer. M.p.s were determined on a Kofler hot-stage apparatus.

* Available as Supplementary Publication No. SUP 21139; for details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1973, Index issue.

† We thank Dr. A. L. Porte for this measurement.

Preparation of the Keto-sulphides (I)—(VI).—Piperidine-catalysed Michael addition of the appropriate thiol to mesityl oxide (1·2 mol. equiv.) as reported by Tilak *et al.*,[2,3] with various reflux times [*e.g.* 5 h for (II), overnight for (VI)], gave the compounds described in Table 3. The reactions were monitored by n.m.r.

Reaction of the Keto-sulphides (I)—(VI) *with Polyphosphoric Acid.*—Polyphosphoric acid was prepared by heating P_2O_5 (80 g) and orthophosphoric acid (50 ml; *d* 1·75) at 150 °C for 1 h, with exclusion of moisture. The keto-sulphides (20 g) were added to the PPA at room temperature and the mixtures were stirred mechanically at 99 ± 1° (thermostatic control). After cooling, the viscous products were poured into iced water (750 ml) and extracted with ether (3 × 500 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (1 × 300 ml) and then water (4 × 400 ml) (to pH *ca.* 7), dried (Na_2SO_4), and evaporated to leave viscous brown oils which were distilled. The boiling ranges were 65—114° at 0·02, 63—110° at 0·06, 38—91° at 0·04, 71—85° at 0·03, 70—100° at 0·005, and 108—154° at 0·005 mmHg for the products from (I)—(VI), respectively. The compositions of the various reaction mixtures are set out in Table 1. In the case of (I), the product ratio was temperature-dependent; the formation of (VII) was favoured by temperatures below 100 °C and the proportion of (XIII) rose with increasing temperature; however at higher temperatures the percentage of volatile material recovered was lower.

Separation of the Products from PPA Treatment of the Keto-sulphides (I)—(VI).—Complete separation of the products proved impossible by repeated distillation, t.l.c., or preparative g.l.c. (although analytical g.l.c. separation was achieved on a 4 ft column of 1% OV-17 at 100 °C). Consequently gel permeation chromatography was used: elution of a column (200 × 2·5 cm) of Sephadex LH-20 modified [5] with Nedox 1114 with methanol allowed separation of pure (VII), (IX), (X), and (XII). The first three were oils, and recrystallisation of (XII) from light petroleum gave white crystals, m.p. 73—74°. The product from (V) slowly solidified; recrystallisation (light petroleum) gave white crystals (XI), m.p. 104—106°. Analyses and u.v. data are given in Table 4. Compound (XIX) and 2,4,4,6-tetramethyl-4*H*-thiochromen were eluted just after (VII) and (X), respectively; neither was obtained completely pure but enough data were recorded to allow identification. Nuclear Overhauser enhancements of the olefinic proton resonance of (XIX), measured by employing a degassed solution in CS_2, were 10% on irradiation at the olefinic methyl frequency, and 28% on irradiation at that of the *gem*-dimethyl group.

Reaction of the Thiochromens (VII), (IX), (XI), *and* (XII) *with PPA.*—The thiochromens were treated with PPA as above, the scale being reduced by a factor of *ca.* 100. In the case of (XI) both the weight of polyphosphoric acid and the reaction time were increased in view of the low percentage of (XVII) formed during the PPA treatment of (V). On mixing with PPA each thiochromen assumed a bright, persistent colour, *viz.* blue, violet, green, and red for (VII), (IX), (XI), and (XII), respectively. After work-up, ^{1}H n.m.r. spectra of the products were recorded, thus allowing the percentage rearrangement to be calculated (Table 2). Almost quantitative recoveries were achieved, the only compounds present being the starting thiochromens and the ring-contracted analogues.

TABLE 3

Physical and ^{1}H n.m.r. data of 4-(naphthyl- and phenyl-thio)pentan-2-ones

			Analysis (%)				^{1}H N.m.r. (τ)				
			Found		Required						
Compound	B.p. (°C) [mmHg]	Yield (%) [a]	C	H	C	H	Aromatic H	CH_2	Aromatic Me	CH_2CO	CMe_2
(I)	94—95 [0·01]	75	69·25	7·7	69·2	7·75	2·3—2·9	7·35		7·90	8·63
(II)	89—91 [0·01]	54	70·4	8·3	70·25	8·15	2·4—3·1	7·29	7·50	7·87	8·63
(III)	79—80 [0·01]	77	70·4	8·2	70·25	8·15	2·4—3·0	7·35	7·67	7·90	8·62
(IV)	91—92 [0·06]	56	70·15	8·2	70·25	8·15	2·4—3·0	7·35	7·65	7·88	8·63
(V)	135—136 [0·04]	69	74·35	6·9	74·4	7·0	1·9—2·7	7·28		7·91	8·60
(VI)	146—147 [0·25]	58	74·2	7·05	74·4	7·0	1·8—2·7	7·28		7·87	8·55

[a] Yields are not optimised.

TABLE 4

Analytical and u.v. data for isolated thiochromens

	Analysis (%) Found		Required		
Compound	C	H	C	H	$\lambda_{max.}$(EtOH) (log ε)
(VII)	75·95	7·45	75·75	7·4	323 (3·13), *ca.* 281sh, 244 (4·29)
(IX)	76·55	7·9	76·45	7·9	322 (3·07), *ca.* 284sh, 248 (4·27)
(X)	76·55	7·9	76·45	7·9	328 (3·11), *ca.* 280sh, 244 (4·22)
(XI)	79·95	6·85	79·95	6·7	*ca.* 354sh, *ca.* 343sh, 330 (3·28), *ca.* 320sh, 279 (4·07), *ca.* 274sh, 252 (3·90), 232 (4·03)
(XII)	79·9	6·85	79·95	6·7	352 (3·41), 325 (3·66), 313 (3·70), 276 (4·26), 260 (4·52), 234 (4·41)

2-*Isopropyl*-3-*methylbenzo*[b]*thiophen* (XIII).—3-Bromo-4-methylpentan-2-one, prepared by bromination of isobutyl methyl ketone [6] and purified by distillation, was added dropwise to a solution of sodium benzenethiolate in methanol. The mixture was refluxed for 30 min then stirred overnight at room temperature. Sodium bromide was filtered off and the solvent was removed, leaving an oil; distillation gave 4-*methyl*-3-*phenylthiopentan*-2-*one* as a liquid, b.p. 68—70° at 0·02 mmHg, *m/e* 208 (M^+), $\nu_{max.}$ (film) 1705, 1482, 1468, 1440, 1355, 750, 740, and 692 cm^{-1}; τ ($CDCl_3$) 2·5—2·9 (5H, m), 6·65 (1H, d, *J* 9 Hz), 7·81 (3H, s), *ca.* 7·9 (1H, m), 8·80 (3H, d, *J* 6 Hz), and 9·00 (3H, d, *J* 6 Hz) (Found: C, 69·4; H, 7·8. $C_{12}H_{16}OS$ requires C, 69·2; H, 7·7%). The keto-sulphide was cyclised with PPA (3 h at 100 °C; work-up as before) giving (XIII)

[6] H. M. E. Cardwell and A. E. H. Kilner, *J. Chem. Soc.*, 1951, 2430.

as a *liquid* (72%), b.p. 147° at 12 mmHg, *m/e* 190 (M^+), $\nu_{max.}$ (film) 1462, 1436, 752, and 728 cm^{-1}; $\lambda_{max.}$ (EtOH) 233 (log ε 4·54), 268 (3·78), 290 (3·43), and 299 nm (3·27) (Found: C, 75·9; H, 7·5. $C_{12}H_{14}S$ requires C, 75·75; H, 7·4%).

2-*Isopropyl*-3-*methylnaphtho*[1,2-b]*thiophen* (XVII).—Repeating the above route with naphthalene-1-thiol instead of benzenethiol gave 4-*methyl*-3-(1-*naphthylthio*)*pentan*-2-*one* as a brown solid (74%). Sublimation (*ca.* 40° at 0·02 mmHg) and recrystallisation (light petroleum) gave white needles, m.p. 41—43°, *m/e* 258 (M^+), $\nu_{max.}$ (KBr) 1696, 1504, 1355, 1230, 805, 770, and 738 cm^{-1}; τ ($CDCl_3$) 1·4—1·6 (1H, m), 2·0—2·8 (6H, m), 6·54 (1H, d, *J* 9 Hz), *ca.* 7·8 (1H, m), 7·85 (3H, s), 8·67 (3H, d, *J* 6 Hz), and 8·94 (3H, d, *J* 6 Hz) (Found: C, 74·6; H, 7·15. $C_{16}H_{18}OS$ requires C, 74·4; H, 7·0%). Cyclisation of the keto-sulphide with PPA (3 h at 100 °C) gave a brick-red solid (86%) which on recrystallisation (light petroleum) yielded white *crystals* of (XVII), m.p. 72—73 °C, *m/e* 240 (M^+), $\nu_{max.}$ (KBr) 1378, 1252, 855, 805, 745, and 742 cm^{-1}; $\lambda_{max.}$ (EtOH) 230 (log ε 4·21), 240 (4·19), 249 (4·27), 272 (4·56), 331 (2·91), and 347 nm (2·81) (Found: C, 79·8; H, 6·9. $C_{16}H_{16}S$ requires C, 79·95; H, 6·7%).

2-*Isopropyl*-1-*methylnaphtho*[2,1-b]*thiophen* (XVIII).—A similar route from naphthalene-2-thiol gave 4-*methyl*-3-(2-*naphthylthio*)*pentan*-2-*one*, as a yellow, viscous liquid (47%), b.p. 134—136° at 0·05 mmHg, *m/e* 258 (M^+), $\nu_{max.}$ (film) 1702, 1502, 1355, 815, 745, and 475 cm^{-1}; τ ($CDCl_3$) 2·1—2·8 (7H, m), 6·53 (1H, d, *J* 9 Hz), 7·81 (3H, s), *ca.* 7·9 (1H, m), 8·77 (3H, d, *J* 6 Hz), and 8·99 (3H, d, *J* 6 Hz) (Found: C, 74·5; H, 7·1%). Cyclisation of the keto-sulphide with PPA (3 h at 100 °C) yielded a pale yellow solid (87%) which on two recrystallisations (light petroleum) gave (XVIII) as white *crystals*, m.p. 72—74°, *m/e* 240 (M^+), $\nu_{max.}$ (KBr) 1455, 1360, 1318, 900, 802, 780, 748, and 742 cm^{-1}; $\lambda_{max.}$ (EtOH) 232 (log ε 4·56), 243 (4·58), 257 (4·45), 302 (4·15), and 334 nm (3·19) (Found: C, 80·1; H, 6·65%).

^1H N.m.r. parameters for (XIII), (XVII), and (XVIII) were identical with those for the corresponding materials obtained by rearrangement. Mixtures of samples from the two sources also gave identical proton spectra, and mixed m.p.s for (XVII) and (XVIII) showed no depression.

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