Reactions of Thiocoumarin with Phenylmagnesium Bromide and with Bromine

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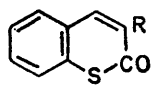
The original method of preparing thiocoumarin has been improved. Thiocoumarin reacts with phenylmagnesium bromide to give 2-phenyl-4*H*-thiochromen and thioflavone, and with bromine to yield 3,4-dibromo-3,4-dihydrothiocoumarin. Treatment of 3-bromocoumarin with alkali gives benzo[*b*]thiophen-2-carboxylic acid.

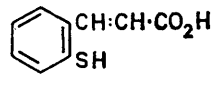
THE original method [1] of preparing thiocoumarin (Ia) from *o*-mercaptocinnamic acid (II) was improved by effecting the cyclisation with polyphosphoric acid. Application of the Perkin reaction [2] to *o*-mercaptobenzaldehyde (IIIa) gave thiocoumarin in very low yield. *o*-Mercaptobenzaldehyde (IIIa), obtained in ethereal solution by the reduction of *o*-mercapto-*N*-methylbenzanilide (IV) with lithium aluminium hydride,[3,4] was heated with acetic anhydride and potassium acetate. Attempts to isolate *o*-mercaptobenzaldehyde (IIIa) (as its sodium salt) following the reduction of *o*-thiocyanatobenzaldehyde (IIIb), prepared by the action of copper(I) thiocyanate on diazotised *o*-aminobenzaldehyde, with

[1] Ch. Chmelewsky and P. Friedländer, *Ber.*, 1913, **46**, 1903.
[2] J. R. Johnson, *Org. Reactions*, 1942, **1**, 210—265.
[3] D. Leaver, J. Smolicz, and W. H. Stafford, *J. Chem. Soc.*, 1962, 740.
[4] F. Weygand, G. Eberhardt, H. Linden, F. Schafer, and I. Eigen, *Angew. Chem.*, 1953, **65**, 525.

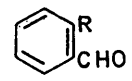
sodium sulphide were unsuccessful, though its presence in the reduction mixture was shown by the formation of benzo[*b*]thiophen-2-carboxylic acid (V) [5,6] on treatment with sodium chloroacetate.



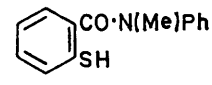
(I)
a; R = H
b; R = Br



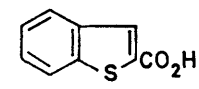
(II)



(III)
a; R = SH
b; R = CNS



(IV)



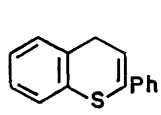
(V)

The reaction between thiocoumarin (Ia) and phenylmagnesium bromide gave 2-phenyl-4*H*-thiochromen (VI) and thioflavone (VII).[7] 2-Phenyl-4*H*-thiochromen (VI) was synthesised from 3,4-dihydrothiocoumarin (VIIIa), which was treated with 1 mol. equiv. of phenylmagnesium bromide to produce 2-phenylthiochroman-2-ol (IX). The alcohol (IX) was not isolated but was dehydrated directly by treatment with anhydrous copper sulphate in boiling benzene to give 2-phenyl-4*H*-thiochromen. 3,4-Dihydrothiocoumarin (VIIIa) was formed on boiling a mixture of *o*-mercapto-2,3-dihydrocinnamic acid [1] and concentrated hydrochloric acid.

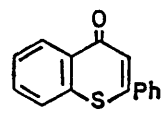
high nucleophilicity of sulphur.[9] The reactivity of the benzo[*b*]thiopyran-2-ol is analogous to that of the oxygen analogue; rapid rearrangement to benzo[*b*]thiopyran-4-ol takes place, followed by the intermolecular hydride transfer.

Attempts to separate and identify the products yielded by the reaction between thiocoumarin and methylmagnesium iodide were unsuccessful.

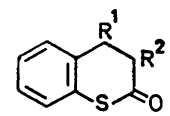
Treatment of thiocoumarin (Ia) with 1 mol. equiv. of bromine in chloroform afforded 3,4-dibromo-3,4-dihydrothiocoumarin (VIIIb), which readily eliminated hydrogen bromide on treatment with pyridine to yield



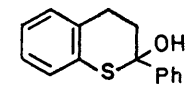
(VI)



(VII)



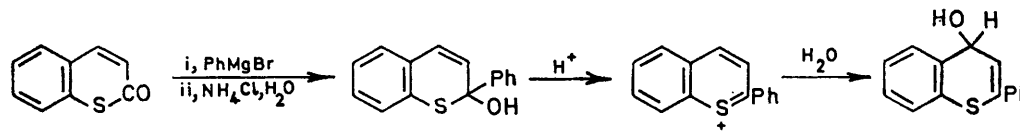
(VIII)
a; $R^1 = R^2 = H$
b; $R^1 = R^2 = Br$

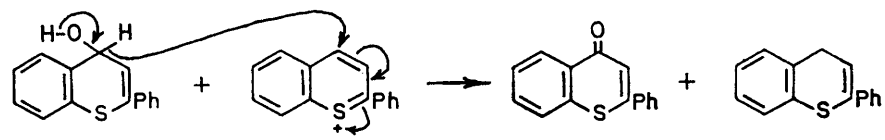


(IX)

The formation of 2-phenyl-4*H*-thiochromen (VI) and thioflavone (VII) in the reaction between thiocoumarin and phenylmagnesium bromide may be explained by the process involving an intermolecular hydride shift from benzo[*b*]thiopyran-4-ol to the thiobenzopyrylium cation.

3-bromothiocoumarin (Ib). Benzo[*b*]thiophen-2-carboxylic acid (V) [6] was formed on heating 3-bromothiocoumarin (Ib) with aqueous alkali. The foregoing reactions are analogous to those of Perkin's synthesis of benzo[*b*]furan-2-carboxylic acid from coumarin.[10]





(VII) (VI)

Phenylmagnesium bromide reacts with thiocoumarin to give a complex which when decomposed yields benzo[*b*]-thiopyran-2-ol initially. Benzo[*b*]pyran-2-ol is unstable under acid conditions,[8] and yields *via* the intermediacy of the benzopyrylium cation, benzo[*b*]pyran-4-ol, which cannot be isolated owing to its susceptibility to oxidation. The ring–chain tautomeric equilibrium between benzo-[*b*]thiopyran-2-ol and thiochalcone favours the cyclic compound rather than the open chain, owing to the

EXPERIMENTAL

N.m.r. spectra were obtained with a Varian A60A spectrometer for *ca.* 10% solutions in deuteriochloroform. M.p.s were determined with a Kofler hot-stage apparatus.

[5] P. Friedländer and E. Lenk, *Ber.*, 1912, **45**, 2083.
[6] R. Weissenberger and O. Kruber, *Ber.*, 1920, **53**, 1551; W. D. Cotterill, C. J. France, R. Livingstone, J. R. Atkinson, and J. Cottom, *J. C. S. Perkin I*, 1972, 787.
[7] S. Ruhemann, *Ber.*, 1913, **46**, 2188.
[8] D. W. Hill and R. R. Melhuish, *J. Chem. Soc.*, 1935, 1161.
[9] J. F. Bunnett and W. D. Merritt, *J. Amer. Chem. Soc.*, 1957, **79**, 5967.
[10] W. H. Perkin, *J. Chem. Soc.*, 1870, **23**, 368; 1871 **24** 37.

o-*Mercaptocinnamic Acid* (II).—*o*-Nitrocinnamic acid (7·5 g) dissolved in the minimum of hot dilute ammonium hydroxide solution was poured slowly into a vigorously stirred, boiling solution of iron(II) sulphate heptahydrate (800 g) in water (1600 ml).[11] Small portions of concentrated ammonium hydroxide were added until the boiling solution was alkaline (litmus). After being boiled for a further 5 min, the hot mixture was filtered and the filtrate made acid (litmus) with acetic acid. Cooling gave *o*-aminocinnamic acid (48·8 g, 76%) as bright yellow plates, m.p. 149—155° (decomp.) [lit.,[11] 158—159° (decomp.)]. Concentrated hydrochloric acid (60 ml) was added to a stirred suspension of *o*-aminocinnamic acid (47·8 g) in water (250 ml) and the mixture was cooled in an ice-bath. Sodium nitrite (20·7 g) in water (100 ml) was added dropwise to the stirred mixture and the temperature was kept $<5°$ by the addition of ice. The cold solution was added to a stirred alkaline solution of sodium disulphide [prepared by dissolving sodium sulphide nonahydrate (78·1 g) and powdered sulphur (10 g) in water (100 ml) by stirring and heating, and then adding sodium hydroxide (12 g) in water (30 ml)] and and the temperature was kept $<5°$ by the addition of ice. The mixture was allowed to warm to room temperature. When the evolution of nitrogen had ceased the mixture was acidified (Congo Red) with concentrated hydrochloric acid to precipitate crude dithiocinnamic acid (*cf.* dithiosalicylic acid),[12] which was separated by filtration and washed with water. The crude acid was freed from sulphur by dissolving in hot sodium carbonate solution and filtering. Acidification (Congo Red) of the filtrate with concentrated hydrochloric acid afforded dithiocinnamic acid (42·8 g) as a sandy coloured powder. A solution of dithiocinnamic acid (42·8 g), anhydrous sodium carbonate (100 g), and sodium dithionite (75 g) in water (600 ml) was boiled for 1 h, cooled, treated with charcoal, filtered, and acidified (Congo Red) with concentrated hydrochloric acid. Filtration and thorough washing with water afforded *o*-mercaptocinnamic acid (35·9 g, 68%), as a pale yellow powder, m.p. 148—156° (lit.,[1] *ca.* 156°; varies with rate of heating).

Thiocoumarin (Ia).—(*a*) Removal of the solvent in a stream of nitrogen from a solution of *o*-mercaptobenzaldehyde prepared in ether from *o*-mercapto-*N*-methylbenzanilide (30 g) [3,4] afforded a gum, which was heated with acetic anhydride (16 ml) and potassium acetate (5·0 g) at 140—150° for 12 h. The residue obtained after pouring into water and isolation with ether was dissolved in hot light petroleum (b.p. 60—80°). Cooling and decantation yielded an oil from which a solid eventually separated. Filtration and recrystallisation from light petroleum (b.p. 40—60°) gave thiocoumarin (0·2 g) as small flakes, m.p. and mixed m.p. 78—81° (lit.,[1] 80—80·5°).

(*b*) *o*-Mercaptocinnamic acid (5·0 g), sodium acetate (10·0 g), and acetic anhydride (25 ml) were heated at 140—150° for 1 h. Pouring into water and isolation with ether yielded a gum which was extracted with hot light petroleum (b.p. 60—80°). The light petroleum solution on cooling yielded a solid, which was recrystallised from light petroleum (b.p. 40—60°) to give thiocoumarin (0·25 g, 6%), m.p. and mixed m.p. 79—81°.

(*c*) *o*-Mercaptocinnamic acid (10·0 g) was stirred with polyphosphoric acid (*d* 2·1; 250 g) at 100—105° for 35 min. Pouring on ice afforded a gummy solid which was extracted with ether. The ether layer was washed successively with water, 5% sodium carbonate solution, and 10% sodium chloride solution, dried ($MgSO_4$), and evaporated to give a dark red gum, which rapidly solidified on cooling. Extraction of the solid with hot light petroleum (b.p. 60—80°) (carbon) yielded thiocoumarin (1·8 g, 20%) as pale yellow flakes, m.p. and mixed m.p. 79—81°.

Reaction between Phenylmagnesium Bromide and Thiocoumarin.—Thiocoumarin (1·62 g) dissolved in ether (50 ml) was added dropwise to a stirred ethereal solution of phenylmagnesium bromide [from bromobenzene (4·7 g), magnesium (0·73 g), and ether (50 ml)]. The solution was boiled gently for 1 h and then set aside overnight. Decomposition of the Grignard complex with 22% ammonium chloride solution and isolation with ether gave a gum, which was dissolved in the minimum of benzene and chromatographed on alumina. Elution with light petroleum (b.p. $<40°$) gave biphenyl (0·22 g); elution with light petroleum (b.p. 40—60°) then gave a solid (0·395 g), m.p. 57—61°, which afforded 2-*phenyl*-4H-*thiochromen* (VI) (0·19 g, 8·5%), m.p. and mixed m.p. 60—61·5° [from light petroleum (b.p. $<40°$)]. Further elution, with benzene–light petroleum (b.p. 40—60°) and benzene yielded gums (0·5 g), and finally elution with ether afforded a solid (0·32 g), which gave thioflavone (VII) (0·215 g, 9%), m.p. and mixed m.p. 123—124·5° [from light petroleum (b.p. 100—120°)], $\nu_{max.}$ (Nujol) 1610 cm^{-1} (C=O); δ 8·66—8·68 (1H, m) and 7·43—7·81 (8H, m) (aromatic protons), and 7·25 p.p.m. (1H, s, vinylic proton).

3,4-*Dihydrothiocoumarin* (VIIIa).—*o*-Mercapto-2,3-dihydrocinnamic acid (5·15 g) [1] and concentrated hydrochloric acid (25 ml) were boiled for 0·5 h. The cooled mixture was extracted with ether and the ether layer washed with 5% sodium carbonate solution and then water and dried ($MgSO_4$). Removal of the solvent and distillation afforded 3,4-*dihydrothiocoumarin* (2·5 g, 55%) as a pale yellow liquid, b.p. 112—114° at 1·5 mmHg, n_D^{20} 1·606 (Found: C, 65·6; H, 5·0; S, 19·25. C_9H_8OS requires C, 65·85; H, 4·9; S, 19·5%).

2-*Phenyl*-4H-*thiochromen* (VI).—3,4-Dihydrothiocoumarin (2·0 g) in ether (10 ml) was added dropwise to a stirred ethereal solution of phenylmagnesium bromide [from bromobenzene (1·9 g), magnesium (0·3 g), and ether (20 ml)]. The solution was boiled gently for 0·5 h and allowed to cool. After decomposition with a mixture of ice and 22% ammonium chloride solution, the ether layer was separated, washed with water, and dried ($MgSO_4$). Removal of the solvent afforded a yellow viscous oil, which was dissolved in benzene (100 ml) and boiled with anhydrous copper sulphate (1·5 g) for 12 h under Dean–Stark head. The mixture was cooled, filtered, and evaporated to yield a dark brown oil, which was dissolved in the minimum of benzene and chromatographed on alumina [light petroleum (b.p. $<40°$) as eluant]. Recrystallisation from light petroleum (b.p. $<40°$) afforded 2-*phenyl*-4H-*thiochromen* (0·49 g, 18%) as needles, m.p. 60—61°, δ 6·88—7·45 (9H, complex, m, aromatic), 6·0 (1H, t, vinylic proton, *J* 4·9 Hz), and 3·4 p.p.m. (2H, d, CH_2, *J* 4·9 Hz) (Found: C, 79·9; H, 5·3; S, 14·45. $C_{15}H_{12}S$ requires C, 80·35; H, 5·35; S, 14·3%).

3,4-*Dibromo*-3,4-*dihydrothiocoumarin* (VIIIb).—Bromine (10% v/v solution) in chloroform (1·6 ml) was added dropwise to thiocoumarin (1·26 g) in chloroform (10 ml) cooled in an ice-bath, and the mixture was left overnight. Removal of the solvent gave a red gum which on trituration with light petroleum (b.p. 40—60°) gave a yellow solid. Recrystallisation from light petroleum (b.p. 60—80°) (carbon) afforded

[11] W. A. Jacobs and M. Heidelberger, *J. Amer Chem. Soc.*, 1917, **39**, 1435.
[12] C. F. H. Allen and D. D. Mackay, *Org. Synth.*, 1932, **12**, 76.

3,4-*dibromo*-3,4-*dihydrothiocoumarin* (1·15 g, 46%), as plates, m.p. 91—93° (Found: C, 33·7; H, 2·0; Br, 50·1; S, 10·2. $C_9H_6Br_2OS$ requires C, 33·55; H, 1·85; Br, 49·7; S, 9·9%).

3-*Bromothiocoumarin* (Ib).—3,4-Dibromo-3,4-dihydrothiocoumarin (1·15 g) was dissolved in pyridine (5 ml) and the solution was set aside for 0·5 h. Pouring into water afforded a pale yellow solid, which was filtered off, air-dried, and recrystallised from light petroleum (b.p. 100—120°) to give 3-*bromothiocoumarin* (0·62 g, 74%), as pale yellow plates, m.p. 129—131° (Found: C, 44·75; H, 2·3; Br, 32·9; S, 13·45. C_9H_5BrOS requires C, 44·8; H, 2·1; Br, 33·2; S, 13·3%).

Benzo[b]*thiophen-2-carboxylic Acid.*—(*a*) *o*-Thiocyanatobenzaldehyde (8·0 g) was added in small portions to a stirred warm solution of sodium sulphide nonahydrate (25·0 g) in water (10 ml). After being stirred for 0·5 h the deep red solution was filtered and then heated on a water-bath for 0·5 h with a solution of chloroacetic acid (5·0 g) previously neutralised with sodium carbonate. On cooling, the solution was acidified (Congo Red) with concentrated hydrochloric acid and the resulting yellow solid was filtered off. The solid was dissolved in sodium carbonate solution; the solution was treated with charcoal, filtered, and acidified with 2N-hydrochloric acid. Filtration and recrystallisation from ethanol afforded benzo[*b*]thiophen-2-carboxylic acid (3·3 g, 28%) as stout needles, m.p. 232—240° (lit.,[6] 236°); acid chloride, m.p. 86—87° (lit.,[6] 88—89°); methyl ester, m.p. 70—71° (lit.,[6] 72—73°).

(*b*) 3-Bromothiocoumarin (0·4 g) was heated with 30% potassium hydroxide solution (20 ml) until all the solid had dissolved. On cooling the resulting pale green solution was acidified (Congo Red) with concentrated hydrochloric acid to give a solid, which was filtered off and recrystallised from water to give benzo[*b*]thiophen-2-carboxylic acid (0·155 g, 53%), m.p. and mixed m.p. 232—238°; methyl ester, m.p. and mixed m.p. [with a sample prepared by method (*a*)] 70—71°.

o-Thiocyanatobenzaldehyde.—An ice-cold solution of *o*-aminobenzaldehyde (10·0 g) [13] in ethanol (100 ml) containing water (25 ml) and sodium nitrite (6·7 g) was added dropwise to a vigorously stirred solution of concentrated sulphuric acid (9·0 ml) and water (20 ml) cooled in an ice-bath maintaining the temperature below 5°. The mixture was then stirred for 15 min at 0—5°.

Meanwhile copper(I) thiocyanate was prepared by warming copper sulphate pentahydrate (50·0 g) dissolved in water (200 ml) to 50—60° and adding a solution of sodium disulphite (13·5 g) in water (50 ml) with stirring. Potassium thiocyanate (19·5 g) dissolved in water (50 ml) was added with vigorous stirring, giving a precipitate of copper(I) thiocyanate. After 10 min the product was filtered off, washed thoroughly with water, and dissolved in saturated potassium thiocyanate solution (60·0 g KSCN).

The cold diazotised solution of *o*-aminobenzaldehyde was added to the stirred ' copper(I) thiocyanate solution ' with the temperature kept below 5°. A chocolate-brown solution was produced, which was allowed to warm to room temperature and then warmed to 40—50° to complete the reaction. The mixture was diluted with an equal volume of water and set aside overnight. Filtration and drying ($CaCl_2$ desiccator) afforded a light brown powder which was extracted (Soxhlet) with light petroleum (b.p. 60—80°). Cooling the light petroleum (b.p. 60—80°) extract (ethyl acetate was added to prevent the product separating as an oil) afforded *o*-thiocyanatobenzaldehyde (6·5 g, 48%) as needles, m.p. 73—75° (lit.,[5] 76°).

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[13] L. I. Smith and J. W. Opie, *Org. Synth.*, 1948, **28**, 11.