[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORIES, MONSANTO CHEMICAL COMPANY]

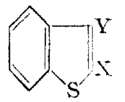
Benzothiophenes and their 1-Dioxides

BY ARTHUR H. SCHLESINGER AND DAVID T. MOWRY

The chlorination of benzothiophene has been studied and the chlorinated products and a number of other benzothiophene derivatives have been oxidized to benzothiophene 1-dioxides. Many of the latter compounds have phytotoxic activity, which is thought to be associated with the α,β-unsaturated sulfone group.

Since the phytotoxic activity of coumarin has been pointed out by Audus and Quastel,[1] it seemed desirable to investigate structurally related compounds. The sulfur analog of coumarin, *o*-hydroxystyrene-β-sulfonic acid sultone is not yet known but the related benzothiophene 1-dioxide is conveniently prepared by oxidation of benzothiophene with 30% hydrogen peroxide.[2] This compound did, in fact, possess herbicidal activity; consequently a number of related compounds were prepared for comparison.

Benzothiophene was chlorinated successively to give 3-chloro-[3] (Ib), 2,3-dichloro-[3] (Ic), 2,3,x,y-tetrachloro-[4] and 2,3,x,y,z-pentachlorobenzothiophenes. The first two compounds readily underwent oxidation to the corresponding dioxides but the latter two were inert to the action of hydrogen peroxide. The inert compounds probably have a chlorine atom in the 7-position and inactivation of the sulfur atom might reasonably be caused by steric factors similar to the *peri* effect frequently encountered in the isosteric naphthalene series.



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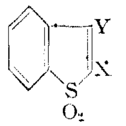

II

a, X = Y = H
b, X = H, Y = Cl
c, X = Y = Cl
d, X = Cl, Y = H
e, X = Br, Y = H
f, X = H, Y = OC_2H_5
g, X = Cl, Y = OCH_3
h, X = H, Y = CH_2Cl
i, X = H, Y = CH_2SCN
j, X = H, Y = CH_2OCH_3
k, X = H, Y = CH_2CN
l, X = H, Y = $COCH_3$
m, X = H, Y = CH_2COOH

2-Chlorobenzothiophene 1-dioxide (IId) was obtained by the action of pyridine on 2,3-dichloro-2,3-dihydrobenzothiophene 1-dioxide. The latter compound was prepared by the addition of chlorine to benzothiophene 1-dioxide (IIa). The corresponding bromo compounds have been reported by Bordwell, *et al.*[2b]

2-Bromobenzothiophene 1-dioxide (IIe) on treatment with sodium hydroxide in absolute ethanol was converted to an ethoxy derivative, assumed[2b] to be 3-ethoxybenzothiophene 1-dioxide (IIf). By a similar method, a compound was formed, believed to be 2-chloro-3-methoxybenzothiophene 1-dioxide (IIg), when 2,3-dichlorobenzothiophene 1-dioxide (IIc) was treated with sodium ethoxide.

3-Chloromethylbenzothiophene[5] (Ih) was converted to 3-thiocyanomethylbenzothiophene (Ii), in 89% yield by the action of potassium thiocyanate in ethanol. The use of potassium cyanide in dry methanol led to the formation of 3-methoxymethylbenzothiophene (Ij) in 68% yield rather than the 3-cyanomethyl derivative (Ik).[6] The latter compound was formed satisfactorily by refluxing with vigorous stirring in 50% acetone as a solvent.[5] Oxidation of 3-cyanomethyl- and 3-methoxymethylbenzothiophene to the corresponding sulfones using 30% hydrogen peroxide in acetic acid took place smoothly. Similar treatment of the 3-thiocyanomethyl- and 3-chloromethyl- compounds, however, led to tarry or indefinite products.

3-Acetylbenzothiophene[7] (Il) and benzothiophene-3-acetic acid[5] (Im) were also converted to the dioxides by 30% hydrogen peroxide. Dibenzothiophene, however, gave the 5-monoxide[8] under these conditions and it was necessary to use chromic acid to form the dioxide.[9]

The yields and physical properties of the cyclic sulfones mentioned above are listed in Table I.

TABLE I

HYDROGEN PEROXIDE OXIDATIONS OF BENZOTHIOPHENES

Benzothiophene 1-dioxide	Yield, %	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Analyses, % Carbon Found	Analyses, % Hydrogen Calcd.	Analyses, % Hydrogen Found
3-Chloro-	38.5	158.5-160	$C_8H_5O_2SCl$	47.88	47.47	2.49	2.19
2,3-Dichloro-	65.0	160-161	$C_8H_4O_2SCl_2$	40.85	41.17	1.70	1.86
3-Acetyl-	56.0	148-149	$C_{10}H_8O_3S$	57.59	57.83	3.85	3.93
3-Cyanomethyl-	39.0	209-211	$C_{10}H_7O_2SN$	58.54	58.40	3.41	3.20
3-Methoxymethyl-	54.0	145-147	$C_{10}H_{10}O_3S$	57.14	56.98	4.76	4.60
3-Carboxymethyl-	60.0	268-269 (dec.)	$C_{10}H_8O_4S$	53.57	53.31	3.57	3.74

The above compounds and other related materials were assayed for phytotoxic activity by measuring the root growth of cucumber seedlings

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(1) L. J. Audus and J. H. Quastel, *Nature*, **159**, 320 (1947).

(2) (a) M. Lanfry, *Compt. rend.*, **154**, 519 (1912); (b) F. G. Bordwell, B. B. Lampert and W. H. McKellin, THIS JOURNAL, **71**, 1702 (1949).

(3) The structure of the 3-chloro compound was assigned by analogy to 3-bromobenzothiophene prepared by G. Komppa, *J. prakt. Chem.*, **122**, 319 (1929), who also prepared (Ic).

(4) In view of the indefinite m.p. of this compound, it may be a mixture of isomers.

(5) F. F. Blicke and D. G. Sheets, THIS JOURNAL, **70**, 3768 (1948).

(6) See R. Quelet, *Bull. soc. chim.*, [5] **7**, 205 (1940), for similar behavior.

(7) N. P. Buū-Hoi and P. Cagniant, *Ber.*, **76**, 1269 (1943).

(8) R. K. Brown, R. G. Christiansen and R. B. Sandin, THIS JOURNAL, **70**, 1748 (1948), prepared the 5-monoxide by the action of chlorine followed by water.

(9) J. Stenhouse, *Ann.*, **156**, 332 (1870); C. Graebe, *ibid.*, **174**, 177 (1874).

germinated in petri dishes.[10] The results, see Table II, are expressed as per cent. of normal growth (*i.e.*, in water) of the primary root of seedlings in the presence of aqueous solutions of the chemical at 10 and at 100 parts per million. In general, the cyclic sulfones show considerably greater toxicity than the sulfide precursors, with the exception of 3-acetylbenzothiophene and benzothiophene-3-acetic acid. The latter[11] undoubtedly has hormone-type activity similar to the isosteric naphthaleneacetic acid. The toxicity of benzothiophene 1-dioxide is not appreciably changed by halogen substituents in the heterocyclic ring. However, the other substituents examined caused marked inactivation. As indicated by the roughly equivalent phytotoxicity of several α,β-unsaturated aliphatic sulfones, the $>C{=}C{-}SO_2{-}$ group (or an easily dehydrohalogenated precursor) appears to be the essential moiety rather than the phenylsulfonyl or styryl residue.

TABLE II

PHYTOTOXICITY OF BENZOTHIOPHENES AND RELATED COMPOUNDS TO GERMINATING CUCUMBER SEEDS

	Per cent. root growth at	
	100 p.p.m.	10 p.p.m.
Benzothiophene[a]	86	91
3-Chlorobenzothiophene	58	56
2,3-Dichlorobenzothiophene	32	91
2,3,x,y-Tetrachlorobenzothiophene	65	78
2,3,x,y,z-Pentachlorobenzothiophene	52	86
3-Chloromethylbenzothiophene	23	74
3-Thiocyanomethylbenzothiophene	22	100
3-Cyanomethylbenzothiophene	11	17
3-Methoxymethylbenzothiophene	46	66
Benzothiophene-3-carboxylic acid[b]	16	77
Benzothiophene-3-acetic acid[c]	3	8
3-Acetylbenzothiophene[a]	7	59
3-Nitrobenzothiophene[a]	18	73
Dibenzothiophene 5-monoxide	59	97
Dibenzothiophene 5-dioxide[d]	94	92
Benzothiophene 1-dioxide	3	46
2-Chlorobenzothiophene 1-dioxide	2	102
2-Bromobenzothiophene 1-dioxide[e]	3	79
3-Chlorobenzothiophene 1-dioxide	2	88
2,3-Dichlorobenzothiophene 1-dioxide	5	33
3-Hydroxybenzothiophene 1-dioxide[f]	101	108
3-Ethoxybenzothiophene 1-dioxide	68	89
2-Chloro-3-methoxybenzothiophene 1-dioxide	71	93
6-Nitrobenzothiophene 1-dioxide[g]	1	89
3-Acetylbenzothiophene 1-dioxide	44	80
3-Cyanomethylbenzothiophene 1-dioxide	21	34
3-Methoxymethylbenzothiophene 1-dioxide	45	74
Benzothiophene-3-carboxylic acid 1-dioxide[h]	104	111
Benzothiophene-3-acetic acid 1-dioxide	31	53
2,3-Dichloro-2,3-dihydrobenzothiophene 1-dioxide	3	80
2,3-Dibromo-2,3-dihydrobenzothiophene 1-dioxide	5	96
Methyl vinyl sulfone[i]	3	88
Octyl vinyl sulfone[j]	12	102
Divinyl sulfone[k]	2	7
Diphenyl sulfone	59	93
Coumarin	15	58
2,4-Dichlorophenoxyacetic acid	6	9

[a] Obtained from Jefferson Chemical Company. [b] M.p. 179–180°, prepared by sodium hypochlorite oxidation of 3-acetylbenzothiophene. G. Komppa, ref. 3, reported m.p. 174–175°. [c] Obtained from Dr. F. F. Blicke, ref. 5. [d] Ref. 9. [e] Ref. 2b. [f] 2,3-Dihydrobenzothiophene-3-one 1-dioxide, A. W. Weston and C. M. Suter, THIS JOURNAL, **61**, 389 (1939); F. G. Bordwell and C. J. Albisetti, *ibid.*, **70**, 1558 (1948). [g] F. Challenger and P. H. Clapham, *J. Chem. Soc.*, 1615 (1948). [h] Ref. 11. [i] Obtained from Monomer-Polymer Corporation. [j] Courtesy of Mr. John Fincke of these laboratories. [k] Obtained from Naugatuck Chemical Division, U. S. Rubber Company.

Experimental[12]

3-Chlorobenzothiophene (Ib).—A solution of 14 g. (0.20 m.) of chlorine in 300 ml. of carbon tetrachloride was added to a solution of 27 g. (0.20 m.) of benzothiophene[13] (Ia) in 100 ml. of carbon tetrachloride. The solution was allowed to stand overnight during which time hydrogen chloride was evolved. The solvent was removed *in vacuo* and distillation gave 6 g. of starting material (Ia), b.p. 78–84° at 5 mm., and 8 g. (24% conversion, 32% yield) of (Ib), b.p. 96–101° at 5 mm., n^{25}D 1.6390.

Anal. Calcd. for C_8H_5SCl: Cl, 21.07. Found: Cl, 21.38, 21.42, 21.38.

2,3-Dichlorobenzothiophene (Ic) was prepared in 83.5% yield, m.p. 55.5–56.5°, by passing chlorine into a carbon tetrachloride solution of benzothiophene according to Komppa.[3]

2,3,x,y-Tetrachloro- and 2,3,x,y,z-Pentachlorobenzothiophenes.—Chlorine was passed into 320 g. (2.4 m.) of fused benzothiophene containing a few iron tacks. The rate of addition was adjusted so that the exothermic reaction maintained itself at 135–150°. After five hours the increase in weight was 345 g. A 300-g. portion of the black tarry product was distilled to give 85 g. (13%) of the waxy tetrachloride,[4] b.p. 175–179° at 5 mm., and 85 g. (11.5%) of the pentachloride, b.p. 202–208° at 5 mm., m.p. 111–112°.

Anal. Calcd. for $C_8H_2SCl_4$: Cl, 52.1. Found: Cl, 51.6. Calcd. for C_8HSCl_5: Cl, 57.8. Found: Cl, 57.1.

2,3-Dichloro-2,3-dihydrobenzothiophene 1-Dioxide.—A stirred suspension of 41.5 g. (0.25 m.) of benzothiophene 1-dioxide[2] (IIa) in 500 ml. of carbon tetrachloride was irradiated with a 4-watt G.E. Germicide lamp. A slow stream of chlorine gas was passed in over a 7.5-hour period, at the end of which time all the dioxide had dissolved. The solution was allowed to stand overnight and the precipitated solid was collected by filtration. The yield of air-dried crystals, m.p. 101.5–103.0° was 14.5 g. By concentration of the liquors in an air stream, there was obtained an additional 12.5 g., m.p. 100–102° after crystallization from ethanol. The total yield was 45%.

Anal. Calcd. for $C_8H_6O_2SCl_2$: Cl, 29.9. Found: Cl, 29.5.

2-Chlorobenzothiophene 1-Dioxide (IId).—To 7 g. (0.030 m.) of the dichloro-dihydro compound in 70 ml. of hot benzene there was added 2.5 g. (0.032 m.) of pyridine. After refluxing two hours, the pyridine hydrochloride was removed by washing with water and the benzene phase was concentrated *in vacuo*. Chilling, filtration and crystallization from dilute ethanol gave 4.2 g. (70%) of (IId), m.p. 142–143°.

Anal. Calcd. for $C_8H_5SO_2Cl$: Cl, 17.31. Found: Cl, 17.42.

3-Ethoxybenzothiophene 1-Dioxide (IIf).—A solution of 5 g. (0.02 m.) of 2-bromobenzothiophene 1-dioxide[2b] (IIe) and 0.8 g. (0.02 m.) of sodium hydroxide in 60 ml. of absolute ethanol was heated under reflux for four hours. After standing at room temperature, crystals were filtered off and recrystallized from methanol to yield 3.4 g. (77%) of the 3-ethoxy compound, m.p. 165.5–166.5°.

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[10] The method used was Test A described by H. E. Thompson, C. P. Swanson and A. G. Norman, *Bot. Gaz.*, **107**, 476 (1946), except that cucumber was substituted for corn.

[11] E. M. Crook and W. Davies, *J. Chem. Soc.*, 1697 (1937).

[12] All melting points listed are corrected.

[13] Courtesy of the Jefferson Chemical Company.

Anal. Calcd. for $C_{10}H_{10}O_3S$: C, 57.14; H, 4.76. Found: C, 56.97; H, 4.58.

2-Chloro-3-methoxybenzothiophene 1-Dioxide Methanolate (IIg).—To a solution of 12.5 g. (0.053 m.) of 2,3-dichlorobenzothiophene 1-dioxide in 200 ml. of methanol there was added 3 g. (0.055 m.) of sodium methoxide. After refluxing 2.5 hours, sodium chloride was filtered off the hot solution and the filtrate was allowed to stand overnight at room temperature. The solid was filtered off and recrystallized from methanol to yield 10 g. (81.5%) of the product (IIg), m.p. 152–153°.

Anal. Calcd. for $C_9H_7O_2ClS \cdot CH_3OH$: C, 45.71; H, 4.18; Cl, 13.48. Found: C, 45.82; H, 4.03. Cl, 13.14.

3-Thiocyanomethylbenzothiophene (Ii).—3-Chloromethylbenzothiophene (Ih) was prepared from benzothiophene (Ia), formalin and hydrogen chloride according to Blicke and Sheets.[5] To a solution of 35 g. (0.192 m.) of (Ih) in 600 ml. of absolute ethanol there was added 19.4 g. (0.20 m.) of potassium thiocyanate. After a 30-minute period of refluxing, the solution was filtered hot and the filtrate concentrated *in vacuo*. Water was added, the oil separated and the aqueous phase was washed with chloroform. The oil and chloroform extract were combined and the solvent removed *in vacuo*. Distillation gave 8 g. of starting chloride (Ih), b.p. 121–137° at 2.5–3 mm., and 27 g. (69% conversion, 89% yield) of the thiocyanate (Ii), b.p. 172–176° at 2–2.5 mm., n^{25}_D 1.6790.

Anal. Calcd. for $C_{10}H_7NS_2$: C, 58.54; H, 3.42. Found: C, 58.99; H, 3.40.

3-Methoxymethylbenzothiophene (Ij).—To a refluxing suspension of 70 g. (1.08 m.) of potassium cyanide in 1.5 l. of methanol there was added 166 g. (0.91 m.) of 3-chloromethylbenzothiophene[5] (Ih). After 30 minutes the theoretical amount of potassium chloride was removed by filtration, water was added to the filtrate and the oil separated. A benzene extract of the aqueous phase was combined with the oil and the solution was dried over sodium sulfate. The benzene was removed *in vacuo* and the oil distilled. There was obtained 111 g. (68.5%) of the ether (Ij), b.p. 118–120° at 4 mm., n^{25}_D 1.6120.

Anal. Calcd. for $C_{10}H_{10}OS$: C, 67.47; H, 5.62. Found: C, 65.66, 65.59; H, 5.00, 5.16.

Since these analyses indicated the material to be impure, a derivative, the 1-dioxide, was prepared by hydrogen peroxide oxidation. This product gave analytical data in excellent agreement with the indicated structure (see Table I).

3-Cyanomethylbenzothiophene (Ik).—This material was prepared in 58.5% yield from the chloromethyl compound (Ih) and potassium cyanide in 50% acetone by the method of Blicke and Sheets.[5] However, it is essential that vigorous stirring be employed, no product being isolated when the reagents were merely refluxed.

Dibenzothiophene 5-Monoxide.[8]—To 20 g. (0.012 m.) of dibenzothiophene in 75 ml. of glacial acetic acid there was added 62 ml. (0.60 m.) of 30% hydrogen peroxide. The mixture was slowly warmed to 106° and heated at this temperature for ten minutes when it became homogeneous. The solution was cooled and poured into 200 ml. of water. The precipitate was collected by filtration and crystallized twice from absolute ethanol to give 13.2 g. (55.5%) of the 5-monoxide, m.p. 183.5–184.5°. No dioxide was detected even after refluxing for one hour.

Oxidation of Substituted Benzothiophenes to Dioxides.—The benzothiophene 1-dioxides listed in Table I were prepared by oxidation of the corresponding benzothiophene in a fashion similar to the procedure given for dibenzothiophene 5-monoxide.

In each case a sixfold excess of 30% hydrogen peroxide was used in glacial acetic acid. The reagents were always slowly and carefully heated to 106–108°, allowing for any exothermic reaction which might occur before that temperature was reached. The period of reflux at 106–108° was usually about 30 minutes.

In the case of 3-chloromethylbenzothiophene a violent oxidation occurred at about 65°. However, the product was always a sirup that could not be characterized.

Oxidation of 3-thiocyanomethylbenzothiophene in the usual fashion with 30% hydrogen peroxide produced in good yield, a solid, m.p. 124.0–125.0° (dec. with evolution of gas). Analyses gave no clue as to its structure.

Procedure for Herbicidal Assay.—The method is substantially that described by Thompson, *et al.*,[10] with the modifications noted below. For each compound tested, twenty-five cucumber seeds (variety, Early Fortune) were placed on a filter paper in each of three covered petri dishes. Twenty ml. of the solution at the dilution desired was then placed on the paper. The seeds were allowed to germinate for four days at 76°F. The average length of the primary root of the seventy-five seeds was then determined and compared to the average length of the controls germinated in water alone (arbitrarily designated 100).

The data obtained are listed in Table II.

Acknowledgment.—The authors wish to express their gratitude to Dr. R. M. Hedrick and Messrs. Richard Martin and Norman Phillips for the herbicidal evaluation data and to Miss Mary Neal and Messrs. Paul Adams and Donald Stoltz for the microanalyses.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

Alpha-oxygenated Pyridines. I. The Synthesis of an Isomer of 4-Desoxypyridoxin

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An α-oxygenated isomer of 4-desoxypyridoxin, 3-hydroxymethyl-4,6-dimethyl-2-pyridol, and several related compounds were prepared. None of these compounds possesses any B_6 or anti-B_6 activity.

As a continuation of our studies of compounds related to pyridoxin,[3] we are investigating the effect of the presence of oxygen attached to the α position of the pyridine ring on vitamin B_6 and anti-B_6 activity. All the known compounds possessing B_6 or anti-B_6 activity have one α-position open. In this work, several new substances, all of which possess one oxygen atom in some form in the α-position, have been prepared. These compounds are related to the natural vitamin in that the oxygen atom, normally present in the β-position, is now in the α-position on the other side of the ring. In this regard, IX is an isomer of 4-desoxypyridoxin, a compound of known anti-B_6 activity.

Compounds IV, V and IX, and two previously reported compounds, 4,6-dimethyl-2-pyridol (VI) and 4,6-dimethyl-3-carbethoxy-2-pyridol (VIIIb), exhibited no B_6 or anti-B_6 activity when tested against *Neurospora Sitophila*.[4]

Attempts to reduce 4,6-dimethyl-3-cyano-2-methoxypyridine (III) in the presence of a strong

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(1) Eli Lilly and Co. Fellow, 1949–1951.

(2) Taken in part from the Ph.D. Thesis of E. P. Belcher.

(3) For the previous paper in this series see R. P. Mariella and J. L. Leech, THIS JOURNAL, **71**, 331 (1949).

(4) Tests conducted by the biochemical group at the Eli Lilly Research Laboratories, Indianapolis, Indiana.