1,2-Benzisothiazoles. Part IV.[1] Preparation of the 3-Methyl Derivative from *o*-Mercaptoacetophenone Oxime: a Re-examination

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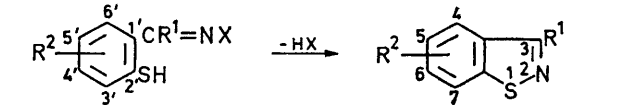
Treatment of *o*-mercaptoacetophenone oxime with polyphosphoric acid gives a mixture of 2-methylbenzothiazole, resulting from Beckmann rearrangement of the oxime prior to cyclisation, and 3-methyl-1,2-benzisothiazole. The former product always predominates, but the proportion depends upon the temperature of the cyclisation. Similar treatment of 4′-chloro-, 5′-chloro-, and 5′-nitro-2′-mercaptoacetophenone oxime gives mainly the substituted benzothiazole in each case. Italian workers had reported previously that the cyclisation of *o*-mercaptoacetophenone oxime and related compounds gave entirely the 3-methyl-1,2-benzisothiazole derivative. It seems probable that their starting material, which they believed to be *o*-mercaptoacetophenone oxime, was 2-imino-5-methyl-3,1,4-benzoxathiazepine (14). This compound is decomposed to 3-methyl-1,2-benzisothiazole and cyanic acid by heating either in polyphosphoric acid or in a suitable inert solvent.

In 1963 Ricci and Martani [2] claimed that the oximes, phenylhydrazones, and semicarbazones of *o*-mercaptobenzaldehydes and *o*-mercaptophenyl ketones could be cyclised by hot polyphosphoric acid to give substituted 1,2-benzisothiazoles (see Scheme; X = OH, NHPh, or NH·CO·NH_2). We used this potentially

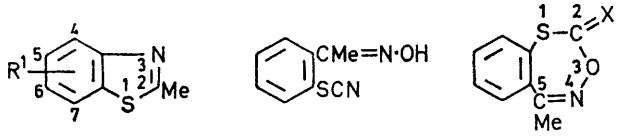


(1) R^2 = H
(2) R^2 = 5′-Cl
(3) R^2 = 5′-NO_2
(4) R^2 = 4′-Cl
} X = OH, R^1 = Me

(5) R^2 = H
(6) R^2 = 5-NO_2
(7) R^2 = 5-NH_2
(8) R^2 = 5-Cl
} R^1 = Me

Scheme

versatile method in an attempt to prepare 3-methyl-1,2-benzisothiazole (5) from *o*-mercaptoacetophenone oxime (1). However, the major product from the reaction differed † from 3-methyl-1,2-benzisothiazole prepared by the decarboxylation of (1,2-benzisothiazol-3-yl)acetic acid.[1] It was identified as the isomeric 2-methylbenzothiazole (9), which presumably had been formed by Beckmann rearrangement of the oxime (1) prior to cyclisation. Such cyclisations after rearrangement are not unusual and it is well known [3] that the analogous *o*-hydroxyphenyl ketone oximes cyclise preferentially to 2-substituted benzoxazoles under the conditions of the Beckmann rearrangement. Nevertheless the product obtained by Ricci and Martani [2] had characteristics corresponding with those reported for authentic 3-methyl-1,2-benzisothiazole obtained by various routes.[1,4-6] Further, the Italian workers [2] obtained, *inter alia*, crystalline 5-nitro- (6), 5-amino- (7), and 5-chloro-3-methyl-1,2-benzisothiazole (8) by cyclisation of the appropriately substituted *o*-mercaptoacetophenone oximes. Generally, the physical characteristics of these products excluded any possibility of their being the isomeric benzothiazoles. However, when we repeated the cyclisations of 5′-chloro-2′-mercaptoacetophenone oxime (2) and 2′-mercapto-5′-nitroacetophenone oxime (3) we obtained the benzothiazoles (10) and (11), respectively. A similar cyclisation of 4′-chloro-2′-mercaptoacetophenone oxime (4) gave 6-chloro-2-methylbenzothiazole (12) (70%).



(9) R^1 = H
(10) R^1 = 5-Cl
(11) R^1 = 5-NO_2
(12) R^1 = 6-Cl

(13)

(14) X = NH
(15) X = O

At first we thought that the amount of substituted benzothiazole formed might be a function of the temperature at which the cyclisation was carried out. We therefore cyclised *o*-mercaptoacetophenone oxime (1) with polyphosphoric acid at various temperatures and obtained a mixture of 2-methylbenzothiazole and 3-methyl-1,2-benzisothiazole in each case. The former was always the major component, but its proportion decreased as the temperature was raised (3·9 : 1 at 80°, 1·75 : 1 at 120°, and 1·3 : 1 at 200°). We confirmed that 3-methyl-1,2-benzisothiazole was recovered unchanged after treatment with hot polyphosphoric acid, thereby excluding the possibility of its formation and subsequent isomerisation under the conditions of the reaction. Next we treated *o*-mercaptoacetophenone semicarbazone with hot polyphosphoric acid, and, unlike the Italian workers [2] obtained a mixture which contained *o*-mercaptoacetophenone as the only identifiable product; neither 3-methyl-1,2-benzisothiazole nor 2-methylbenzothiazole was present.

We then considered the possibility that we and the Italian workers [2] had used different starting materials for our cyclisation studies. Like Ricci and Martani,[2] we prepared 2′-mercapto-5′-nitroacetophenone oxime (3) from 2′-chloro-5′-nitroacetophenone oxime by nucleophilic replacement of the activated halogen atom, and our products were identical. By cyclisation of the oxime (3) at 120—130° in polyphosphoric acid and

† We thank Dr. D. E. L. Carrington for this observation.

[1] Part III, D. E. L. Carrington, K. Clarke, C. G. Hughes, and R. M. Scrowston, *J.C.S. Perkin I*, 1972, 3006.
[2] A. Ricci and A. Martani, *Ann. Chim. (Italy)*, 1963, **53**, 577.
[3] L. G. Donaruma and W. Z. Heldt, *Org. Reactions*, 1960, **11**, 1.
[4] M. Giannella, F. Gualtieri, and C. Melchiorre, *Phytochem.*, 1971, **10**, 539.
[5] E. Haddock, P. Kirby, and A. W. Johnson, *J. Chem. Soc. (C)*, 1971, 3994.
[6] R. J. Crawford and C. Woo, *J. Org. Chem.*, 1966, **31**, 1655.

repeated crystallisation of the product, we obtained pure 2-methyl-5-nitrobenzothiazole (11) (30%). The Italians,[2] however, cyclised the oxime at 105—110° and obtained 3-methyl-5-nitro-1,2-benzisothiazole (6) in unspecified yield. This difference in results may be due to a temperature effect, but it seems more probable that their supposed 3-methyl-5-nitro-1,2-benzisothiazole (6) was a mixture of isomers, since the reported m.p.[2] was *ca.* 20° lower than that of authentic material prepared by another route.[5]

In all the other cases we prepared our mercapto-ketone oximes (1)—(4) by more convenient routes than those used by Ricci and Martani.[2] We obtained *o*-mercaptoacetophenone in high yield by debenzylation of (*o*-benzylthio)acetophenone [1] with aluminium chloride in benzene. We converted 5-chloro-2-mercaptobenzoic acid by standard procedures into 2-benzylthio-5-chlorobenzoyl chloride, treatment of which with diethyl ethoxymagnesiomalonate, followed by acidic hydrolysis, gave 2′-benzylthio-5′-chloroacetophenone. This then gave 5′-chloro-2′-mercaptoacetophenone when debenzylated with aluminium chloride in benzene. Similarly, 4-chloro-2-mercaptobenzoic acid gave 4′-chloro-2′-mercaptoacetophenone. The ketones were then converted into the required oximes, (1), (2), and (4), the structures of which were confirmed spectroscopically (see Experimental section). The m.p.s of these mercapto-ketone oximes were much lower than those reported by the Italians,[2] and we thought at first that their products might have become oxidised to the corresponding disulphides during work-up. We therefore repeated their synthesis of one of the mercapto-ketone oximes to check this point.

Ricci and Martani [2] prepared what they believed to be *o*-mercaptoacetophenone oxime from the relatively inaccessible *o*-aminoacetophenone. This was converted *via* the diazonium salt into *o*-thiocyanatoacetophenone and thence into the oxime (13). Finally, the thiocyanato-compound was treated with sodium sulphide [7a] to give the required thiol (1). Related oximes were prepared analogously. When we repeated this work, we were unable to reduce the thiocyanato-group to give the required thiol. It seems probable that the Italian workers also failed at this stage, for the m.p. of their alleged mercapto-oxime was in most cases only a few degrees lower than that of the thiocyanate precursor. Also, no proof of structure, either analytical or spectroscopic, was presented for any of their mercapto-oximes.

We had followed Ricci and Martani's [2] route for the preparation of *o*-thiocyanatoacetophenone, and analytical data and spectroscopic evidence confirmed its structure. The product of the reaction of this ketone with hydroxylamine had the recorded [2] m.p., but its i.r. spectrum lacked the characteristic SCN absorption expected for (13) and showed =NH absorption ($\nu_{max.}$ 3200 cm^{-1}). Attempts to regenerate the ketone from the supposed oxime were unsuccessful. These observations suggested that the *o*-thiocyanatoacetophenone oxime (13), once formed, had cyclised spontaneously to 2-imino-5-methyl-3,1,4-benzoxathiazepine (14). Analogous cyclisations of certain *ortho*-substituted phenyl thiocyanates are known,[7b] but the 3,1,4-benzoxathiazepine system is novel. Structure (14) was supported by the mass spectrum, which showed strong peaks due to M — NO and M — NO — HCN; such a fragmentation pattern is much less readily accommodated by the alternative structure (13). We confirmed that the oxathiazepine (14) cyclised on treatment with hot polyphosphoric acid to give 3-methyl-1,2-benzisothiazole (80%), with no trace of 2-methylbenzothiazole. (The spontaneous formation of this benzoxathiazepine from *o*-thiocyanatoacetophenone oxime would explain why no Beckmann rearrangement occurs, and why attempts to reduce it to the corresponding thiol failed.)

We believe that the reaction proceeds by hydrolysis of the imine (14) to 5-methyl-3,1,4-benzoxathiazepin-2-one (15), followed by extrusion of carbon dioxide to give the observed product. We confirmed that carbon dioxide (*ca.* 1 mol. equiv.) was liberated during the reaction. We then argued that it should be possible to form 3-methyl-1,2-benzisothiazole from the oxathiazepine (14) by the thermal extrusion of cyanic acid, and thus avoid the need to use polyphosphoric acid. 2-Imino-5-methyl-3,1,4-benzoxathiazepine (14) decomposed at 210° and 3-methyl-1,2-benzisothiazole was detected in the residue. The decomposition proceeded more smoothly either in bis-(2-methoxyethyl) ether at 210° or in boiling diethylene glycol, to give 3-methyl-1,2-benzisothiazole (86 and 75% respectively) and cyanic acid. The decomposition in bis-(2-methoxyethyl) ether was repeated in the presence of a calculated amount of cyclohexanol. The isolation of cyclohexyl allophanate proved that cyanic acid had been liberated. As well as being of synthetic importance, this reaction is of mechanistic interest because the extrusion of cyanic acid is only rarely encountered.[8]

It appears that all the ' mercapto-oximes ' prepared by Ricci and Martini [2] from substituted *o*-thiocyanatobenzaldehydes or acetophenones may be analogues of the oxathiazepine (14). The decomposition of such compounds either in the presence of polyphosphoric acid, or by heat alone in a suitable solvent, should then proceed as already described to provide the pure 1,2-benzoisothiazole derivative in high yield. It is unfortunate that no yields were quoted in the original work.[2]

EXPERIMENTAL

General experimental directions are given in Part I.[9] Molecular weights determined by mass spectrometry for

[7] *Cf.* ' Methoden der Organischen Chemie (Houben-Weyl),' Thieme Verlag, Stuttgart, 1955, 4th edn., Band 9, (*a*) p. 17; (*b*) p. 866.

[8] B. P. Stark and A. J. Duke, ' Extrusion Reactions,' Pergamon, Oxford, 1967, p. 165.

[9] D. E. L. Carrington, K. Clarke, and R. M. Scrowston, *J. Chem. Soc.* (*C*), 1971, 3262.

chlorine-containing compounds refer to the ^{35}Cl isotope. Light petroleum had b.p. 60—80°.

2-(*Benzylthio*)-5-*chlorobenzoic Acid*.—Benzyl chloride (29·5 ml) was added dropwise under nitrogen to a cooled (0°), stirred solution of 5-chloro-2-mercaptobenzoic acid [10] (47·1 g, 0·25 mol) in water (20 ml) and ethanol (250 ml) containing sodium hydroxide (24 g). The mixture was heated under reflux for 5 h, then stirred overnight at room temperature, and poured into water. A small amount of solid material (probably disulphide) was filtered off, the filtrate was acidified with hydrochloric acid, and the product was collected. It formed *prisms* (50 g, 73%), m.p. 165—167° (from ethanol) (Found: C, 60·45; H, 4·1%; *M*, 278. $C_{14}H_{11}ClO_2S$ requires C, 60·3; H, 3·95%; *M*, 278), $\nu_{max.}$ 1680 (C=O) cm^{-1}.

Prepared similarly from 4-chloro-2-mercaptobenzoic acid,[10] 2-(*benzylthio*)-4-*chlorobenzoic acid* (70%) had m.p. 185—186° (needles from ethanol) (Found: C, 60·35; H, 3·8%; M, 278), $\nu_{max.}$ 1685 (C=O) cm^{-1}.

2′-(*Benzylthio*)-5′-*chloroacetophenone*.— 2-(Benzylthio)-5-chlorobenzoyl chloride was prepared by treatment of the corresponding acid with thionyl chloride in benzene, and was used without purification. A solution of the acid chloride (30 g, 0·1 mol) in dry tetrahydrofuran (250 ml) was added slowly to a stirred solution of diethyl ethoxymagnesiomalonate [11] [from magnesium (2·7 g), dry ethanol (13 ml), and diethyl malonate (17·5 g)] and carbon tetrachloride (0·5 ml) in boiling ether (100 ml). The mixture was heated under reflux for 2 h, then cooled and treated with dilute sulphuric acid (120 ml). The organic layer was separated, washed, dried, and evaporated under reduced pressure. The residue was heated under reflux for 6 h with a mixture of acetic acid (30 ml), concentrated sulphuric acid (3·7 ml), and water (20 ml), then basified with concentrated aqueous sodium carbonate. Extraction with ether gave the *ketone* (21 g, 76%) as needles, m.p. 114—115° (from ethanol) (Found: C, 64·9; H, 4·55%; *M*, 276. $C_{15}H_{13}ClOS$ requires C, 65·1; H, 4·75%; *M*, 276), $\nu_{max.}$ 1670 (C=O) cm^{-1}.

Prepared similarly, 2′-(*benzylthio*)-4′-*chloroacetophenone* (75%) had m.p. 120—123° (needles from ethanol) (Found: C, 65·2; H, 4·85%; *M*, 276), $\nu_{max.}$ 1670 (C=O) cm^{-1}.

o-*Mercaptoacetophenone Oxime and Related Compounds*.—A solution of *o*-(benzylthio)acetophenone [1] (30 g) in dry benzene (500 ml) was added dropwise to a stirred suspension of aluminium chloride (29 g) in benzene (200 ml) at 5—10° under oxygen-free nitrogen. Stirring was continued for 24 h, then water was added and the thiol was extracted from the organic layer with aqueous 5% sodium hydroxide. Acidification of the combined alkaline extracts and extraction with ether gave the product as an *oil* (16·5 g, 89%) (Found: *M*, 152. C_8H_8OS requires *M*, 152), $\nu_{max.}$ 2520 (SH) and 1665 (C=O) cm^{-1}, δ 2·6 (Me) and 3·95 (SH) p.p.m. The *semicarbazone* had m.p. 178—179° (from ethanol) (Found: C, 51·65; H, 5·15; N, 20·0%; *M*, 209. $C_9H_{11}N_3OS$ requires C, 51·65; H, 5·3; N, 20·1%; *M*, 209); the *oxime* (1) had m.p. 154—156° (white needles from benzene–light petroleum) (Found: C, 57·4; H, 5·35; N, 8·2%; *M*, 167. C_8H_9NOS requires C, 57·45; H, 5·4; N, 8·35%; *M*, 167), δ 2·2 (Me), 3·0 (SH), and 10·74 (OH) p.p.m., *m/e* 150 (*M* — OH) and 149 (*M* — H_2O).

Prepared similarly were: (a) 5′-*chloro*-2′-*mercaptoacetophenone* (90%), m.p. 86—87° (Found: *M*, 186. C_8H_7ClOS requires *M*, 186), $\nu_{max.}$ 2555 (SH) and 1670 (C=O) cm^{-1}, δ 2·56 (Me) and 3·82 (SH) p.p.m.; *oxime* (2), m.p. 122—124° (needles from benzene–light petroleum) (Found: C, 47·5; H, 3·8; N, 6·7%; *M*, 201. C_8H_8ClNOS requires C, 47·65; H, 4·0; N, 6·95%; *M*, 201), $\nu_{max.}$ 2560 (SH) and 3300 (OH) cm^{-1}, δ 2·3 (Me), 3·2 (SH), and 10·0 (OH) p.p.m., *m/e* 184 (*M* — OH) and 183 (*M* — H_2O); (b) 4′-*chloro*-2′-*mercaptoacetophenone* (4) (90%), m.p. 95—97° (Found: C, 51·8; H, 4·0; Cl, 18·8%; *M*, 186. C_8H_7ClOS requires C, 51·5; H, 3·8; Cl, 19·0%; *M*, 186), $\nu_{max.}$ 2525 (SH) and 1660 (C=O) cm^{-1}, δ 2·6 (Me) and 3·9 (SH) p.p.m.; *oxime*, needles, m.p. 133—134° (from benzene–light petroleum) (Found: C, 47·6; H, 3·8; N, 6·85%; *M*, 201), $\nu_{max.}$ 2575 (SH) and 3220 (OH) cm^{-1}, δ 2·4 (Me), 3·7 (SH), and 9·8 (OH) p.p.m., *m/e* 184 (*M* — OH) and 183 (*M* — H_2O).

The ketones and oximes just described decomposed easily with loss of hydrogen sulphide and, except for small samples taken for analysis, were therefore used without purification.

2′-*Mercapto*-5′-*nitroacetophenone Oxime* (3).—2′-Chloro-5′-nitroacetophenone [12] was converted into the oxime, m.p. 163—165° (lit.,[2] 164—165°). A solution of the oxime (10 g) in boiling ethanol (60 ml) was treated dropwise during 15 min with aqueous ethanolic sodium disulphide [13] [from sodium sulphide (8·2 g), sulphur (1·1 g), water (6 ml), and ethanol (75 ml)]. A solution of sodium hydroxide (1·8 g) in water (3 ml) and ethanol (30 ml) was then added dropwise, and the mixture was poured on ice, and filtered. The filtrate was acidified, and the crude product was filtered off. It was then dissolved in aqueous 3% sodium hydroxide and reprecipitated with concentrated hydrochloric acid to give yellow needles, (6·1 g, 60%), m.p. 157—158° (lit.,[2] 157—158°) (from ethanol), $\nu_{max.}$ 2450 (SH) cm^{-1}.

Cyclisation of the Oximes (1)—(4).—The oxime (10 g) was added in portions with stirring to hot (120—130°) polyphosphoric acid (50 g). The mixture was stirred at this temperature for 1·5 h, then cooled, and poured into water. The products were isolated by steam distillation [for (3)] or by ether extraction.

The cyclisation of *o*-mercaptoacetophenone oxime (1) was repeated at 80° and at 200° and the mixture of products in each case was analysed by g.l.c., to give the results described in the text.

Cyclisation of 5′-chloro-2′-mercaptoacetophenone oxime (2) gave 5-chloro-2-methylbenzothiazole (10) (70%), which crystallised from light petroleum as needles, m.p. 63—65° (lit.,[14] 69°); 4′-chloro-2′-mercaptoacetophenone oxime (4) gave 6-chloro-2-methylbenzothiazole (12) (70%), m.p. 80—82° (lit.,[15] 82—83°) (from light petroleum); 2′-mercapto-5′-nitroacetophenone oxime (3) gave 5-nitro-2-methylbenzothiazole (11) (30%), m.p. 135—137° (lit.,[16] 137°) (yellow needles from ethanol).

2-*Imino*-5-*methyl*-3,1,4-*benzoxathiazepine* (14).—*o*-Thiocyanatoacetophenone,[17] m.p. 59—60° (lit.,[17] 60—61°), was

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[12] N. B. Chapman, K. Clarke, and S. N. Sawhney, *J. Chem. Soc.* (*C*), 1968, 518.
[13] *Cf.* C. C. Price and G. W. Stacy, *J. Amer. Chem. Soc.*, 1946, **68**, 498.
[14] R. Klink, J. Augl, and R. Kirchmayr, *Monatsh.*, 1961, **92**, 96.
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[17] F. Arndt, A. Kirsch, and P. Nachtwey, *Ber.*, 1926, **59**, 1074.

treated with hydroxylamine hydrochloride in aqueous ethanol under the usual conditions for oxime formation. The product separated as golden-yellow *needles* (80%), m.p. 208—210° (decomp.) (from ethanol) (Found: C, 56·1; H, 4·25; N, 14·6%; *M*, 192·0326. $C_9H_8N_2OS$ requires C, 56·2; H, 4·2; N, 14·55%; *M*, 192·0357), $\nu_{max.}$ 3200 (=NH) cm^{-1} (no SCN band), δ [$(CD_3)_2SO$] 2·61 (Me) and 11·64 (NH) p.p.m., *m/e* 162·0428 (C_9H_8NS, *M* — NO, *m** 136·8) and 135·0260 (C_8H_7S, 162 — HCN, *m** 112·5).

3-*Methyl*-1,2-*benzisothiazole*.—(*a*) The benzoxathiazepine (14) was treated with polyphosphoric acid at 120° for 1 h as already described, to give 3-methyl-1,2-benzisothiazole (80%), b.p. 80—83° at 0·6 mmHg (lit.,[1] b.p. 66—70° at 0·2 mmHg). It was identical with authentic[1] material, and was not contaminated (g.l.c.) with 2-methylbenzothiazole. The carbon dioxide evolved during the reaction was collected as barium carbonate (0·94 mol. equiv.).

(*b*) A solution of the benzoxathiazepine (14) (0·96 g, 0·005 mol) and cyclohexanol (0·25 g. 0·0025 mol) in dry bis-(2-methoxyethyl) ether (10 ml) was kept at 210° in a sealed tube for 0·5 h. Water was then added, and the precipitate was filtered off, dried, washed thoroughly with benzene, and crystallised from ethanol, to give cyclohexyl allophanate[18] (0·235 g, 51%), m.p. and mixed m.p. 174—175°. The aqueous solution was extracted with ether, to give 3-methyl-1,2-benzisothiazole (0·65 g, 86%), identical with that obtained in (*a*).

When the reaction was repeated in boiling diethylene glycol in the absence of cyclohexanol, 3-methyl-1,2-benzisothiazole was obtained in 75% yield.

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