Condensation of *o*-Thiocyanatoacetophenone with Hydroxylamine. Properties and *X*-Ray Crystal Structure Analysis of (*Z*)-2-Hydroxyimino-4-methyl-2*H*-1,3-benzo[*e*]thiazine

By **Tullo Vitali, Enrico Gaetani,** and **Ferdinando Ronchini,** Istituto di Chimica Farmaceutica e Tossicologica, **Mario Nardelli** * and **Giancarlo Pelizzi,** Istituto di Chimica Generale ed Inorganica, University of Parma, Centro di Studio per la Strutturistica Diffrattometrica del C.N.R., Parma, Italy

The i.r., u.v., n.m.r., and mass spectra, and *X*-ray crystal structure analysis of the title compound are given. Crystals are orthorhombic, with $a = 14.100(6)$, $b = 12.461(7)$, $c = 4.972(2)$ Å, space group $P2_12_12_1$, $Z = 4$. The structure was solved by the heavy-atom technique and refined by least-squares to R 0.051. The structural formula of the compound, assigned on the basis of the *X*-ray analysis, is helpful in devising syntheses of 3-substituted 1,2-benzisothiazoles

It is known that 3-methyl-1,2-benzisothiazole (IV) can be prepared [see Scheme 1, path (1)] from *o*-thiocyanatoacetophenone (I) by reaction with hydroxylamine, followed by hydrolysis with Na_2S and successive cyclization of the adduct with polyphosphoric acid.[1,2] It can then be a useful starting compound for the synthesis of biologically active substances (see refs. quoted in ref. 3) and, in particular, for the preparation of 1,2-benzisothiazol-3-ylacetic acid (IX).[4,5]

As a part of a research programme on benzisothiazole phytocides, we have recently re-examined the preparation of compound (IV) following this sequence. We have found that the product obtained by the reaction between *o*-thiocyanatoacetophenone and hydroxylamine, with the conditions quoted in the literature,[1,2] is not the oxime (II), but an isomeric substance (V), whose structure could not be determined by chemical and spectroscopic properties alone. In particular, it was found to be stable to hydrolysis with Na_2S, whereas it gave 3-methyl-1,2-benzisothiazole (IV) on reaction with polyphosphoric acid.

We now report the results of an *X*-ray crystal-structure analysis of compound (V). These results have clarified the structure, and enabled development of a corresponding synthesis (Scheme 1, path 2).

EXPERIMENTAL

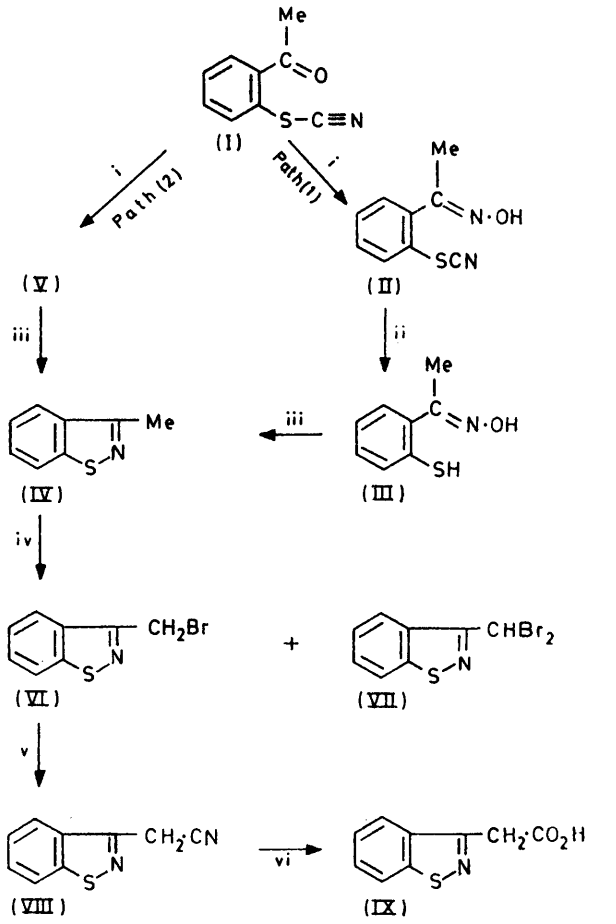
Physical Measurements.—M.p.s were determined on a Buchi apparatus (Tottoli).

Spectra were recorded on Beckman DK 2 (u.v.; conc. *ca.* 10^{-5} g ml^{-1}), Beckman IR 5 (i.r.; NaCl prism), Varian A 60 (n.m.r.; 60 MHz), and Varian MAT CH 5 (mass spectra; 70 eV) spectrometers.

Retention times, referred to phenanthrene (t_{rel}), were determined by means of a Fractovap P AID/f (C. Erba) gas chromatograph equipped with a flame ionization detector (H_2 0.40 kg cm^{-2}; air 1.0 kg cm^{-2}) under the following operational conditions: the steel column (100 × 0.25 cm) was filled with 4% Fluoroalkylsiloxane (QF 1; C. Erba) on Chromosorb W (silanized, 30—60 mesh; C. Erba), with temperatures for injector and column 235 and 173 °C, and carrier gas nitrogen (flow rate: 19 ml min^{-1}). Under these conditions t_{rel} was 5.8 min. For thin-layer chromatography (Kieselgel GF_{254}, Woelm, D.C.; 250 μm; not activated) the following solvents were used: (1) EtOH (95%) : benzene : ligroin (1 : 8 : 8); (2) benzene : ligroin (1 : 1). The R_F values (phenanthrene) were 0.93 and 0.85, respectively.

Elemental analyses were carried out by use of a Perkin-Elmer 240 analyser (C, H, N), and by the Schöniger method (S).

X-Ray intensity data were collected on an on-line Siemens A.E.D. single crystal diffractometer (ω—2θ scan technique).



SCHEME 1 Reagents: i, $NH_2OH·HCl$ and AcONa; ii, Na_2S; iii, polyphosphoric acid; iv, NBS and benzoyl peroxide; v NaCN; vi, hydrolysis

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[2] R. J. Crawford and Ch. Woo, *J. Org. Chem.*, 1969, **31**, 1655.
[3] T. Vitali and G. Bertaccini, *Il Farmaco (Ed. Sci.)*, 1974, **29**, 109.
[4] Ger.P. 1,950,370 (*Chem. Abs.*, 1970, **73**, 130, 991).
[5] T. Vitali, F. Mossini, M. R. Mingiardi, E. Gaetani, and V. Plazzi, *Ateneo Parmense (Acta Naturalia)*, 1971, **7**, 71.

Materials.—*o*-Thiocyanatoacetophenone (I) was prepared according to ref. 6; 3-methyl-1,2-benzisothiazole, 1,2-benzisothiazol-3-ylacetonitrile, and 1,2-benzisothiazol-3-ylacetic acid were obtained as previously described.[5]

Preparation and Chemical Properties of Compound (V).—*o*-Thiocyanatoacetophenone (0.10 mol), dissolved in EtOH (*ca.* 150 ml), was added to NH_2OH,HCl (0.11 mol) and AcONa (0.11 mol). After heating under reflux (30 min) the solution was concentrated to a small volume by distillation under reduced pressure. After dilution with water, the resulting precipitate was washed with water, and crystallized from EtOH (yield, based on ketone, 88%). The yellow crystals, m.p. (decomp.) 223—226 °C [lit.,[1,2] m.p. for (II) 222—223 °C], are soluble in EtOH, dioxan, $CHCl_3$, Me_2CO, Me_2SO, and hot glacial AcOH, slightly soluble in cold CCl_4 and benzene, and insoluble in water; R_F [solvent (1)] 0.17; for *o*-thiocyanatoacetophenone 0.67 (Found: C, 56.15; H, 4.3; N, 14.85. Calc. for $C_8H_8N_2OS$: C, 56.23; H, 4.2; N, 14.55%).

Compound (V) is soluble in warm aqueous Na_2S, and the starting compound may be obtained from this solution, by heating.[1] Compound (V) (2.0 g) was slowly added to a stirred heated solution (boiling water-bath) containing Na_2S (2.5 g) previously crystallized from water (*ca.* 2.0 ml). After heating and stirring for *ca.* 1 h, the red solution was cooled, and acidified with SO_2 to give a precipitate which was washed with water and recrystallized from benzene as yellow crystals of compound (V) (1.85 g) (m.p. 220—221 °C).

From the reaction of compound (V) with polyphosphoric acid, compound (IV) was isolated, which corresponds to the 3-methyl-1,2-benzisothiazole obtained in a different way. Compound (V) (1.0 g) and polyphosphoric acid (5.0 g; 1.7 g H_3PO_4 and 3.3 g P_4O_{10}) were mixed and heated at 105—110 °C until foaming had ceased. The brown mass was then treated with cold water, extracted into diethyl ether, and the ethereal extract washed with sodium carbonate and water and dried (Na_2SO_4). Solvent was then removed by distillation under reduced pressure and the resulting oil, dissolved in a small amount of benzene–ligroin (1 : 1), chromatographed on a silica gel column (100 g SiO_2, Woelm) with (1 : 1) benzene : ligroin as eluant. Only the fractions of compound (IV) [R_F solvent (2) 0.20; t_{rel} 0.19] were collected. After removal of solvent from the eluate the resulting oil was distilled under reduced pressure (b.p. 80 °C at 1 mmHg; yield 0.55 g).

Bromination of 3-Methyl-1,2-benzisothiazole (IV).—3-Bromomethyl- (VI) and 3-dibromomethyl-1,2-benzisothiazole (VII) were obtained by bromination and separated by chromatography. Compound (IV) (1.00 g) in CCl_4 (15 ml), *N*-bromosuccinimide (1.45 g), and benzoyl peroxide (0.01 g) were heated under reflux with stirring overnight. The filtrate, obtained from the reaction adduct, was washed with $NaHSO_3$ and with saturated NaCl solution, then dried (Na_2SO_4). After solvent was distilled off the residue, dissolved in a small amount of benzene–ligroin, was chromatographed on a silica gel column (100 g SiO_2, Woelm) using benzene : ligroin (1 : 1) as eluant. Two fractions were collected, the first containing product (VII) {R_F [solvent (2)] 0.65; t_{rel} 0.81}, the second product (VI) {R_F [solvent (2)] 0.40; t_{rel} 0.54}. After evaporation of solvent and crystallization from light petroleum, yields were (VII) 0.20 g and (VI) 0.70 g.

3-*Bromomethyl*-1,2-*benzisothiazole* (VI) gave colourless needles; m.p. 63—64 °C (from light petroleum) (Found: C, 42.3; H, 2.8; N, 6.35. C_8H_6BrNS requires C, 42.1; H, 2.65; N, 6.15%); δ ($CDCl_3$) 8.3 (4 H, m) and 5.2 (2 H, s); *m/e* 229 (69), 227 (69, M^+), 185 (11), 183 (30), 150 (37), 149 (83), 148 (100), 123 (22), 122 (37), and 121 (65).

3-*Dibromomethyl*-1,2-*benzisothiazole* (VII) gave colourless needles; m.p. 87—88 °C (Found: C, 31.15; H, 1.7; N, 4.6. $C_8H_5Br_2NS$ requires C, 31.3; H, 1.65; N, 4.55%); δ ($CDCl_3$) 7.8 (4 H, m) and 7.0 (1 H, s); *m/e* 309 (5), 307 (10), 305 (5, M^+), 228 (100), 226 (100), 201 (5), 199 (5), 147 (71), 146 (41), and 120 (45).

1,2-*Benzisothiazol*-3-*ylacetonitrile* (VIII) *and* 1,2-*Benzisothiazol*-3-*ylacetic Acid* (IX).—Compound (VI) (0.83 g), dissolved in acetone (3 ml) and ethanol (2 ml), was added to NaCN (0.2 g) in H_2O (4 ml). After heating under reflux for 30 min the solution was evaporated to dryness and the residue recrystallized from benzene–light petroleum as white needles (m.p. 56—57 °C) with properties corresponding to those reported [4,5] for 1,2-benzisothiazol-3-ylacetonitrile (yield 60%).

Hydrolysis of compound (VIII) gave 1,2-benzisothiazol-3-ylacetic acid (IX).[5,7]

Crystal Structure Analysis of Compound (V)

Crysta lData.—M = 192.3. Orthorhombic, a = 14.100 (6), b = 12.461(7), c = 4.972(2) Å, U = 873.6 Å^3, Z = 4, D_c = 1.46 g cm^{-3}, $F(000)$ = 400. Cu-K_α radiation, λ = 1.541 78 Å, μ(Cu-K_α) = 28.6 cm^{-1}. Space group $P2_12_12_1$ (from systematic absences and structural analysis).

Preliminary unit-cell dimensions and space group were determined from rotation and Weissenberg photographs. More precise cell parameters were obtained, together with the orientation matrix for the diffractometer, by least-squares fit for 13 accurately measured values of θ,χ,ϕ.

Data Collection.—Intensity data were collected for a sample mounted with the c axis coincident with the ϕ axis of the diffractometer, by use of Cu-K_α radiation. Reflections with $l > 5$ were rejected being affected by spurious diffraction effects due to the goniometer head metal. 982 independent reflections were measured in the range $0° < 2\theta < 140°$; of which 50 were judged to be below background, having $I < 2\sigma(I)$. The intensity of a standard reflection re-measured every twenty reflections was essentially constant during data collection. Corrections to the structure amplitudes were applied for Lorentz and polarization factors, while the absorption effects were disregarded in view of the low absorbance of the sample (μr 0.23). Data were placed on an absolute scale by correlating observed and calculated values.

Structure Analysis.—The structure was solved by the heavy-atom technique, with an initial set of co-ordinates for sulphur obtained from a three-dimensional Patterson map; a successive electron-density synthesis gave the position of all remaining non-hydrogen atoms. Refinement by block-diagonal least-squares calculations gave a conventional R index of 7.0%. Isotropic refinement of the hydrogen atoms, located unambiguously at this stage in a difference-Fourier synthesis, improved R to 5.1%.

Atomic scattering factors were taken from ref. 8 for sulphur, oxygen, nitrogen, and carbon, and from ref. 9 for hydrogen. Final atomic and isotropic thermal parameters,

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[8] D. T. Cromer and J. B. Mann, *Acta Cryst.*, 1968, **A24**, 321.
[9] R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.

with their estimated standard deviations, are quoted in Table 1. Observed and calculated structure factors and anisotropic thermal parameters are listed in Supplementary Publication No. SUP 21915 (6 pp., 1 microfiche).*

TABLE 1

Fractional atomic co-ordinates ($\times 10^4$, $\times 10^3$ for H) with estimated standard deviations in parentheses, and isotropic thermal parameters for H atoms

	x/a	*y/b*	*z/c*	*B*/Å²
S	−278(1)	1 557(1)	1 781(4)	
O	−1 938(3)	940(3)	−248(10)	
N(1)	−593(3)	−317(4)	4 798(11)	
N(2)	−1 701(3)	175(4)	1 754(13)	
C(1)	740(4)	1 479(4)	3 813(13)	
C(2)	1 397(4)	2 312(5)	3 507(16)	
C(3)	2 196(4)	2 336(5)	5 079(18)	
C(4)	2 359(4)	1 547(6)	7 003(15)	
C(5)	1 718(4)	692(5)	7 246(15)	
C(6)	896(4)	657(5)	5 694(13)	
C(7)	195(4)	−229(4)	6 032(12)	
C(8)	419(5)	−1 114(5)	7 992(15)	
C(9)	−903(4)	397(4)	2 882(14)	
H(1)	254(5)	62(5)	−81(16)	6(2)
H(2)	134(5)	272(5)	161(17)	7(2)
H(3)	277(4)	288(5)	452(15)	5(2)
H(4)	297(4)	149(5)	757(13)	4(2)
H(5)	187(4)	3(5)	876(15)	6(2)
H(6)	−24(4)	−150(5)	771(15)	5(2)
H(7)	62(4)	−87(5)	994(14)	5(2)
H(8)	113(4)	−154(5)	759(13)	5(2)

All calculations were carried out on a Cyber 76 computer at the Centro di Calcolo Elettronico Interuniversitario dell'Italia Nord-Orientale.

RESULT AND DISCUSSION

Properties of Compound (V).—*U.v. spectrum.* The electronic spectrum, registered in ethanol solution, shows three absorption bands at 212 (log ε 4.22), 254 (4.48), and 390 (3.27) nm. The relevant features with respect to the thiocyanatoacetophenone (I) spectrum are the hyperchromic modification of the second band and the bathochromic shift of the third band.

I.r. spectrum. The main features of the i.r. spectrum (KBr disc) are the absence of the nitrile and carbonyl stretching absorption at *ca.* 2 150 and 1 660 cm^{-1} respectively, the presence of a very broad band in the range 3 410—2 700 cm^{-1}, and the appearance of a band at 1 615 cm^{-1}, which can be attributed to the C=N bond vibration.

N.m.r. spectrum. The spectrum ([$^2H_6$]dimethyl sulphoxide solution) shows signals characteristic of four aromatic (δ 7.5, m) and three methyl (δ 2.5, s) hydrogen atoms.

Mass spectrum. The molecular ion peak is very intense [192 M^+ (91), 174(16), 163(24), 162(100), 135(98), 134(43), 121(18), 91(91), 77(17), 69(16)]. Moreover the metastable transitions are in agreement with the following scheme:

$$[C_9H_8N_2OS]^{+\cdot} \xrightarrow{-NO} [C_9H_8NS]^+ \xrightarrow{-HCN} [C_8H_7S]^+ \xrightarrow{-CS} [C_7H_7]$$

m/e 192 → 162 → 135 → 91

X-*Ray Analysis.*—Table 2 gives interatomic distances and angles with their estimated standard deviations, and the molecular structure is illustrated in Figure 1.

TABLE 2

Bond distances (Å) and angles (°)

(*a*) Distances			
S–C(1)	1.757(6)	C(7)–C(6)	1.491(8)
S–C(9)	1.779(6)	C(6)–C(1)	1.404(8)
C(9)–N(2)	1.287(7)	C(1)–C(2)	1.399(8)
N(2)–O	1.417(7)	C(2)–C(3)	1.371(10)
C(9)–N(1)	1.374(8)	C(3)–C(4)	1.390(11)
N(1)–C(7)	1.273(7)	C(4)–C(5)	1.402(9)
C(7)–C(8)	1.505(9)	C(5)–C(6)	1.392(9)
(*b*) Angles			
C(1)–S–C(9)	100.5(3)	C(5)–C(6)–C(1)	118.4(5)
S–C(9)–N(2)	118.3(5)	C(7)–C(6)–C(5)	120.8(5)
C(9)–N(2)–O	115.5(5)	C(6)–C(1)–S	123.4(4)
S–C(9)–N(1)	125.6(4)	C(6)–C(1)–C(2)	120.7(5)
N(2)–C(9)–N(1)	116.1(5)	S–C(1)–C(2)	115.9(5)
C(9)–N(1)–C(7)	123.7(5)	C(1)–C(2)–C(3)	119.9(6)
N(1)–C(7)–C(8)	115.6(5)	C(2)–C(3)–C(4)	120.8(6)
N(1)–C(7)–C(6)	126.0(5)	C(3)–C(4)–C(5)	119.3(6)
C(8)–C(7)–C(6)	118.5(5)	C(4)–C(5)–C(6)	120.8(6)
C(7)–C(6)–C(1)	120.8(5)		

The arrangement of the non-hydrogen atoms can be considered as a whole to be almost planar, the largest displacement of any atom from the mean least-squares plane being only 0.06 Å [C(8)]. The two rings in the molecule are strictly planar and nearly coplanar, the dihedral angle between their planes being 177.7°. In the thiazine ring the bond length with the highest double-bond character is N(1)–C(7) which is only slightly longer than the usually accepted value (1.255 Å) for a C–N double bond. This shortening is accompanied by a

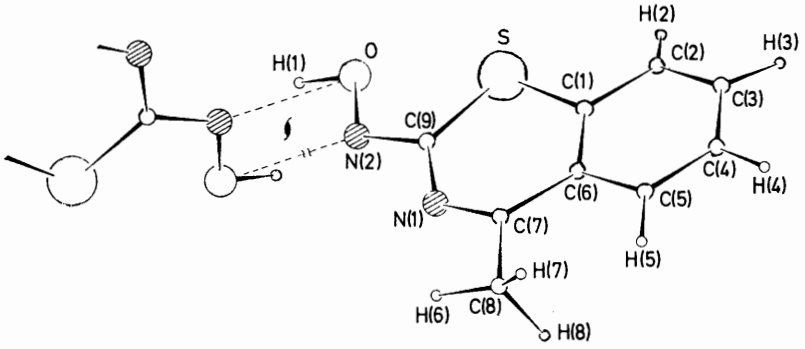


FIGURE 1 Clinographic projection of the structure

* See Notice to Authors No. 6 in *J.C.S. Perkin II*, 1976, Index issue.

sensible lengthening of the C(6)–C(7) bond, whose value (1.491 Å) agrees fairly well with that for a single C(sp^2)–C(sp^2) bond (1.48 Å). The two S–C bonds are slightly different: S–C(9) (1.779 Å) is very close to a S–C(sp^2) single bond (1.78 Å), while S–C(1) (1.757 Å) shows some double-bond character. Some π-delocalization seems to involve also N(1)–C(9) as this distance (1.374 Å) is significantly shorter than a C(sp^2)–N(sp^2) single bond (1.47 Å). The angle at sulphur (100.5°) is in the range usually found for thiazine derivatives (*e.g.* 99.6 in phenothiazine,[10] 102.2 in 4*H*-1,4-benzothiazine 1,1-dioxide,[11] and 102.3° in 3-methyl-4-oxo-1,3-thiazine-2-thione [12]). Although the structures of several phenothiazines have been studied, only a few benzothiazines, hydrogenated or not, have been considered.[11–14]

Bond distances in the benzene rings are as expected and the strain caused by the fusion of the two six-membered rings is shown by the angles at C(1)·C(6)–C(1)–S is increased to 123.4° and, conversely, C(2)–C(1)–S is reduced to 115.9°, while the bonds formed by C(1) maintain their planarity. The C(7)–C(8) distance (1.505 Å) corresponds to a normal C(sp^2)–C(sp^3) single bond (1.51 Å).

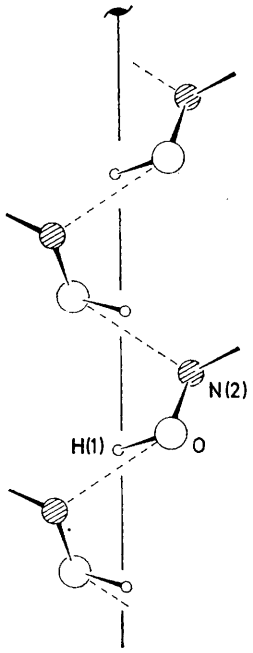
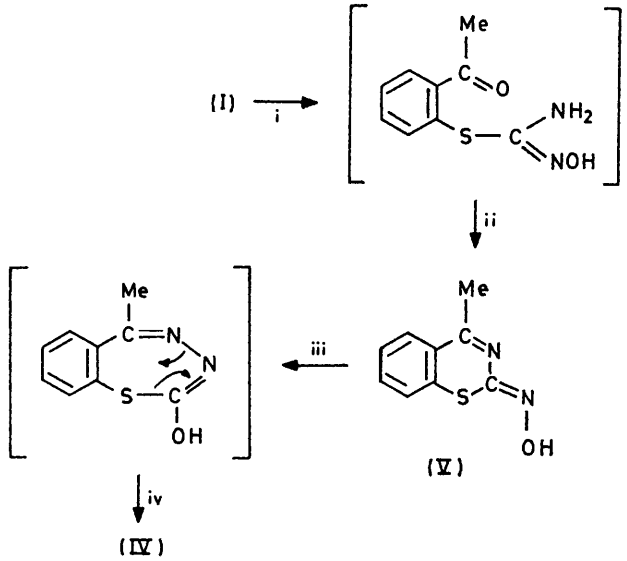


FIGURE 2 A chain of hydrogen-bonded molecules

* o-*Thiocyanatoacetophenone 2,4-dinitrophenylhydrazone*, from 2,4-dinitrophenylhydrazine and compound (I), in MeOH–H_2SO_4 (yield 85%) gave yellow–orange needles, m.p. 214—215 °C (from $CHCl_3$); $\nu_{max.}$ (KBr) 3 410 (w, NH), 2 180 (w, CN), 1 385, and 1 310 cm^{-1} (s, NO_2); *m/e* 357 (M^+) (Found: C, 50.35; H, 3.1; N, 19.45. $C_{15}H_{11}N_5O_4S$ requires C, 50.4; H, 3.1; N, 19.6%).

[10] J. D. Bell, J. F. Blount, O. V. Briscoe, and H. C. Freeman, *Chem. Comm.*, 1968, 1656.

In the oxime moiety the values of the C–N and N–O bond lengths, which are in agreement with those found in similar compounds,[15] indicate the >C=N–O– structure to prevail, with only a small contribution from ⩾C–N=O. The hydroxy-group of the oxime is *trans* with respect to the methyl group, so that it can be involved in a hydrogen-bonding system with an adjacent molecule related by a 2_1 axis. Hydrogen bonded chains are thus formed running along [001] (Figure 2). This hydrogen bonding association explains the features observed in the i.r. spectrum.



SCHEME 2 Reagents: i, $+NH_2OH$; ii, $-H_2O$; iii, polyphosphoric acid, 110 °C; iv, —HCNO

Conclusions.—All the chemical and physicochemical properties reported here confirm that hydroxylamine, in contrast with 2,4-dinitrophenylhydrazine * and probably other carbonyl-group reagents, condenses with *o*-thiocyanatoacetophenone (I) to give, through probable primary addition to the triple bond (see Scheme 2), a bicyclic compound which is (*Z*)-2-hydroxyimino-4-methyl-2*H*-1,3-benzo[*e*]thiazine (V). This compound has the correct configuration to give, through a Beckmann rearrangement, polyphosphoric acid, and successive elimination of HCNO, 3-methyl-1,2-benzisothiazole (IV). The yield is fairly good and the method simpler than that of the traditional synthesis.

[6/920 *Received*, 14*th May*, 1976]

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[14] A. Griffiths, *J. Cryst. Mol. Struct.*, 1973, **3**, 357.
[15] F. Bachechi and L. Zambonelli, *Acta Cryst.*, 1972, **B28**, 2489, and references therein.