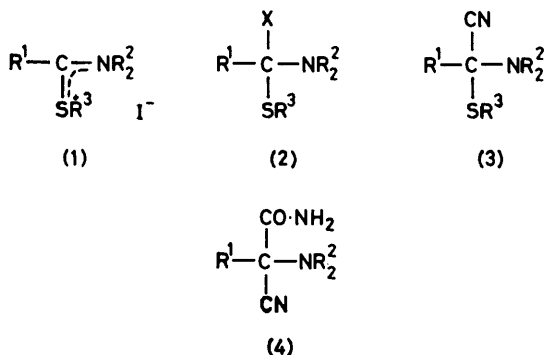


Reactions of S-Alkyl *NN*-Disubstituted Thioamide Salts. Part 2.¹ Orthothioamide Derivatives

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NN-Disubstituted thioamide salts (1) with aqueous potassium cyanide readily give quaternary cyanides (3) which sometimes react further, yielding cyano-amides (4) *via* aminomalononitriles, *e.g.* (6). 2-Methylthio-2-morpholino-2-phenylacetonitrile (3a) on heating with morpholine or primary amines undergoes disproportionation, probably by a free radical mechanism.

QUATERNARY salts (1) from *NN*-disubstituted thioamides are readily prepared, stable, crystalline compounds whose reactions with nucleophiles have been



widely investigated.^{1,2} The nucleophile first adds to give an orthothioamide derivative (2), but usually elimination of sulphur or nitrogen groups then occurs, giving a doubly bonded product. The group eliminated may depend on the experimental conditions.^{2a}

¹ S. I. Mathew and F. Stansfield, *J.C.S. Perkin I*, 1974, 540, is considered as Part 1.

Less commonly, the orthothioamide derivative (2) can be isolated, *e.g.* when the nucleophile is the azide ion,¹ though here the azido- and alkylthio-groups undergo cyclisation. The reaction of the salt (1; R¹ = Ph, R² = R³ = Me) with potassium cyanide in boiling benzene is reported^{2b} to give compound (3b) as an oil. We found that this compound can be prepared more easily, and as a crystalline solid, from the salt with potassium cyanide in aqueous solution at room temperature. The method is a general one and a series of quaternary cyanides have been prepared (Table). Their reactions are closely related to those of their oxygen analogues.³ Similarly the bismethylthio-salt (1; R¹ = SMe, R² = R³ = Me) gave compound (3k), whereas with mercury(II) cyanide in acetonitrile it is

² (a) D. A. Peak and F. Stansfield, *J. Chem. Soc.*, 1952, 4067; (b) T. Mukaiyama, T. Yamaguchi, and H. Nohira, *Bull. Chem. Soc. Japan*, 1965, **38**, 2107; (c) T. Mukaiyama and T. Yamaguchi, *ibid.*, 1966, **39**, 2005; (d) T. Yamaguchi, K. Inomata, and T. Mukaiyama, *ibid.*, 1968, **41**, 673; (e) R. Gompper and W. Elser, *Org. Synth.*, 1968, **48**, 97; (f) J. E. Oliver and J. B. Stokes, *Canad. J. Chem.*, 1971, **49**, 2898; (g) T. Yamaguchi, Y. Shimizu, and T. Suzuki, *Chem. and Ind.*, 1972, 380.

³ H. Bredereck, G. Simchen, and W. Kandlehner, *Chem. Ber.*, 1971, **104**, 924.

Quaternary cyanides (3) and cyanoamides (4)

R ¹	NR ₂ ^{2*}	R ³	M.p. (°C) [B.p.; mmHg]	Yield (%) ^a	Formula	Found (Reqd.) (%)			δ(CDCl ₃) ^{b,c}		
						C	H	N	R ¹	R ²	R ³
(3a) Ph	Morph	Me	74—75	99	C ₁₃ H ₁₆ N ₂ OS	62.8 (62.9)	6.4 (6.5)	11.2 (11.3)	7.5 ^d	2.6 ^e 3.6 ^f	1.97
(3b) Ph	NMe ₂	Me	40	99	C ₁₁ H ₁₄ N ₂ S	64.0 (64.1)	6.8 (6.8)	13.4 (13.6)	7.5 ^d	2.37 ^h	1.97 ^g
(3c) 4-ClC ₆ H ₄	Morph	Me	55—56	99	C ₁₃ H ₁₅ ClN ₂ OS	55.3 (55.2)	5.4 (5.3)	9.8 (9.9)	7.3, 7.6 ^j	2.6 ^e	1.97 ^g
(3d) 4-MeO·C ₆ H ₄	Morph	Me	40—41	50	C ₁₄ H ₁₈ N ₂ O ₂ S	60.4 (60.4)	6.6 (6.5)	10.1 (10.1)	6.8, 7.6, 3.80 ^k	2.7 ^e	2.00 ^g
(3e) 4-Me ₂ N·C ₆ H ₄	Morph	Pr ⁱ	68—69		C ₁₇ H ₂₅ N ₃ OS	63.9 (64.0)	7.8 (7.8)	13.2 (13.2)	6.6, 7.5 ^j	2.7 ^e	1.0 ^m
(3f) PhCH ₂	Morph	Me	44—45	69	C ₁₄ H ₁₈ N ₂ OS	64.3 (64.1)	6.8 (6.9)	10.7 (10.7)	2.99 ^l 7.33 ^{b,d}	3.6 ^f 2.9 ^{b,e}	1.3 ^{m,n} 2.09 ^{b,g}
(3g) Me ₂ CH	Morph	Me	55	98	C ₁₀ H ₁₆ N ₂ OS	56.1 (56.1)	8.5 (8.4)	12.9 (13.1)	1.1, 1.3 ^p	2.8 ^e 3.7 ^f	2.40 ^g
(3h) Me	NMe ₂	Me	[58—60; 2]	22	C ₆ H ₁₂ N ₂ S	49.5 (50.0)	8.4 (8.3)	19.4 (19.5)	1.70 ^r	2.40 ^h	2.27 ^g
(3j) H	NMe ₂	Me	[102; 15]	50	C ₅ H ₁₀ N ₂ S	46.1 (46.2)	7.9 (7.7)	21.0 (21.5)	4.70 ^q	2.40 ^h	2.27 ^g
(3k) MeS	NMe ₂	Me	[58—60; 0.8]	98	C ₆ H ₁₂ N ₂ S ₂	41.0 (40.9)	7.1 (6.8)	16.1 (15.9)	2.33 ^{e,t}	2.60 ^{u,v}	See R ¹
(4f) PhCH ₂	Morph		204—205	11	C ₁₄ H ₁₇ N ₃ O ₂	64.6 (64.9)	6.6 (6.6)	16.2 (16.3)			
(4h) Me	NMe ₂		149—151	21	C ₆ H ₁₁ N ₃ O	51.0 (51.1)	7.9 (7.8)	29.8 (29.8)	1.67 ^r	2.40 ^h	u
(4m) Me	Morph		159—160	38	C ₈ H ₁₃ N ₃ O ₂	52.4 (52.5)	7.1 (7.1)	22.7 (23.0)	1.70 ^r	2.7 ^e 3.8 ^f	u

^a Yield of crude material; product then crystallised from ethanol or light petroleum. ^{b,c} Except where indicated ^b CCl₄ or ^c neat liquid. ^d 5 H, m, ArH. ^e 4 H, m, CH₂NCH₂. ^f 4 H, t, CH₂OCH₂. ^g 3 H, s, MeS. ^h 6 H, s, Me₂N. ⁱ Each 2 H, d, J 8 Hz, ArH. ^k 3 H, s, MeO. ^l 6 H, s, Me₂N. ^m 3 H, d, MeC. ⁿ The CH multiplet is under the multiplet at δ 2.7. ^p Each 3 H, d, J 4 Hz, MeC. ^q 1 H, m, CH. ^r 3 H, s, MeC. ^s 1 H, s, CH. ^t 6 H, s, (MeS)₂. ^u Also 6.50br (2 H, s, CONH₂).

* Morph = morpholino.

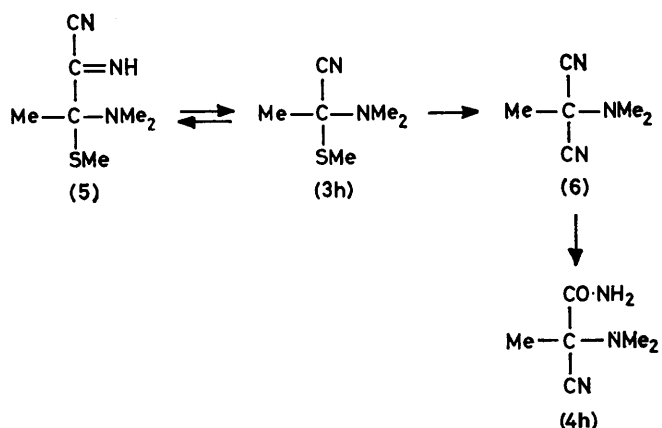
reported^{2d} to give α-dimethylamino-α-methylthiomalononitrile.

In two cases, a mixture of the quaternary cyanide (3f or h) and the α-cyano-amide (4f or h) was obtained, the latter being readily separated because of their sparing solubility in boiling light petroleum. With other cyanides, no cyano-amide was obtained even on prolonged stirring with aqueous alkali metal cyanide. The cyanides (3f and h) are precursors of the cyano-amides: when the reactions are prolonged they are transformed into the latter. Ease of cyano-amide formation appears to depend on the size of the group R¹; it does not occur when R¹ is aryl or isopropyl, is slow when R¹ is benzyl, and is very rapid when R¹ is methyl. Exceptionally, it does not occur when R¹ is H.

In the case of the cyanide (3h), a third compound, the α-imino-nitrile (5) was also isolated. This was considered as a possible intermediate in the reaction, since no more cyanide would then be required to give the cyano-amide (4h), which was indeed formed in low yield when the imino-nitrile was stirred with aqueous potassium hydrogen carbonate at room temperature.

That the imino-nitrile is not an intermediate, however, was shown by ¹³C n.m.r. spectroscopy with use of potassium [¹³C]cyanide. The spectrum of the cyano-amide (4h) containing natural abundance of ¹³C showed signals at δ_C 174.6 (CONH₂), 120.0 (CN), 74.1 (quaternary C), 43.6 (NMe₂), and 27.8 (Me attached to C). Unlabelled cyanide (3h) and imino-nitrile (5) were then stirred, separately, with potassium [¹³C]cyanide solution,

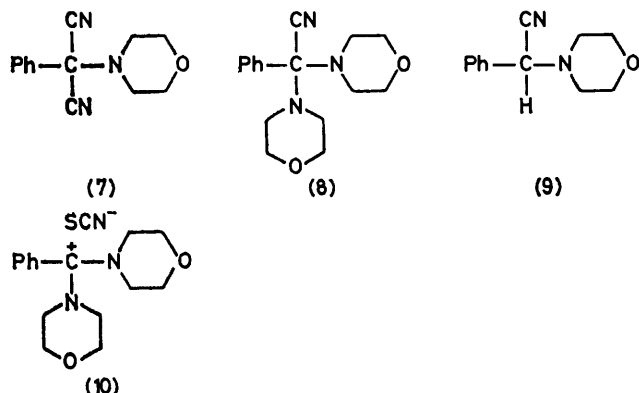
and the cyano-amide was isolated from each reaction. In both cases this was strongly and equally labelled at both cyanide and amide carbon atoms. These results show that the imino-nitrile is the product of a reversible side-reaction, and that the intermediate is symmetrical, probably the malononitrile derivative (6). This was synthesised by Yamaguchi's method^{2c} and gave the cyano-amide (4h) with aqueous potassium cyanide.



The quaternary cyanide (3a), with mercury(II) cyanide in acetonitrile at room temperature, gave almost quantitatively the aminomalononitrile (7), analogues of which have been prepared^{2d} from thioamide salts (1) with mercury(II) cyanide.

When a solution of the cyanide (3a) in an excess of

morpholine was boiled under reflux, three crystalline products, (8)—(10), were obtained, methanethiol was evolved, and formation of *N*-methylmorpholine was shown by comparison of the g.l.c. retention times with those of an authentic morpholine-*N*-methylmorpholine mixture.



The covalent cyanide (8) and the thiocyanate (10), which appears from its physical properties to be an ion pair, were identical with those synthesised from the corresponding amidinium iodide with aqueous potassium cyanide or thiocyanate, respectively. The reduction product (9) was also obtained by treatment of the cyanide (3a) with hydrogen over Raney nickel or with borohydride.

The cyanide (8) may arise from compound (3a) by simple ionic or radical replacement of a methylthio- by a morpholino-group with elimination of methanethiol. However, the reduction product (9) and the thiocyanate (10) are probably formed by a radical disproportionation mechanism. A similar reaction occurs when the cyanide (3a) is heated with a primary amine (*n*-butylamine, 1,2-diaminoethane, or 1,3-diaminopropane), the reduction product (9) being obtained in yields of 28, 65, and 63%, respectively. In the case of diaminoethane, formation of thiocyanate was shown by its i.r. absorption and colour with iron(III) chloride, and 2-phenyl- Δ^1 -imidazoline was also isolated.

Quaternary cyanides (3) show little or no $C\equiv N$ stretching absorption in their i.r. spectra, thus resembling basically substituted malononitriles.⁴

EXPERIMENTAL

I.r. and ¹H and ¹³C n.m.r. spectra were recorded with Unicam SP 1200, Varian T 60, and Varian XL 100 FT instruments, respectively. Light petroleum used had b.p. 60–80 °C.

Preparation of Thioamides and Quaternary Salts.—Thioamides were prepared^{2a} by the Willgerodt–Kindler procedure or by reaction of the amide with phosphorus pentasulphide.

By the former method, *thioisobutyromorpholide* was obtained (78%) as leaflets (from light petroleum), m.p. 41–42° (Found: C, 55.6; H, 8.8; N, 7.9. C₈H₁₅NOS requires C, 55.5; H, 8.7; N, 8.1%).

The thioamides with alkyl iodides in boiling acetone gave the quaternary salts.^{2a}

Preparation of Quaternary Cyanides (3) and Cyano-amides (4) (Table).—(a) Thiobenzomorpholide methiodide (3.0 g, 0.0086 mol) was dissolved by shaking with potassium cyanide (9.0 g, 0.14 mol) in water (75 ml). The mixture was set aside overnight in a refrigerator, and the crystalline solid was filtered off, washed with water, and dried (2.1 g). 2-Methylthio-2-morpholino-2-phenylacetone nitrile (3a) formed large prisms from ethanol.

In the same way, the cyanides (3b–k, except f and h) were obtained.

(b) Phenylthioacetomorpholide methiodide (12.5 g, 0.034 mol) was stirred with potassium cyanide (36.0 g, 0.55 mol) in water (300 ml) for 70 h. The resulting oil was extracted four times with dichloromethane (500 ml total), and the extract was washed with water (300 ml), dried, and evaporated. The gummy residue was boiled with light petroleum (120 ml) and the insoluble material filtered off, dried (1.1 g), and crystallised from ethanol, forming crystals of 2-cyano-2-morpholino-3-phenylpropionamide (4f). The light petroleum filtrate was evaporated and the residue cooled in a refrigerator for 3 days; the crystals were filtered off, dried (6.3 g), and recrystallised from light petroleum, forming 2-methylthio-2-morpholino-3-phenylpropionitrile (3f).

(c) *NN*-Dimethylthioacetamide methiodide (36.0 g, 0.15 mol) was stirred for 30 min with sodium cyanide (80.0 g, 1.23 mol) in water (480 ml). The product was extracted four times with dichloromethane (500 ml total), and the extract was washed with water (150 ml), dried, and evaporated. The residue was boiled with light petroleum (100 ml) and the insoluble material filtered off while hot and dried (3.0 g). Crystallisation from ethanol gave 2-cyano-2-dimethylaminopropionamide (4h).

The light petroleum filtrate, on cooling, gave an oil which crystallised at low temperature (–5 °C). The product was filtered off, dried (7.1 g), and recrystallised from light petroleum, forming large prisms of 3-dimethylamino-2-imino-3-methylthiobutyronitrile (5), m.p. 54–55° (Found: C, 49.1; H, 7.8; N, 24.4. C₇H₁₃N₃S requires C, 49.1; H, 7.6; N, 24.6%), ν_{\max} (Nujol) 3 240w, 2 220w, and 1 600s cm⁻¹, λ_{\max} (EtOH) 235 nm (ϵ 4 500).

The light petroleum filtrate from the imino-nitrile was evaporated and the residue distilled *in vacuo* giving 2-dimethylamino-2-methylthiopropionitrile (3h) as an oil (4.6 g), n_D^{22} 1.4816.

Reactions of the Imino-nitrile (5) and the Cyanide (3h).—

(a) The imino-nitrile (1.0 g) was stirred at room temperature for 18 h with potassium hydrogen carbonate (1.0 g) in water (50 ml). The product was extracted with dichloromethane (200 ml total), and the extract washed with water, dried, and evaporated. The residue was boiled with light petroleum, and the insoluble cyano-amide (4h) (0.1 g), identical with an authentic sample, was filtered off.

(b) A similar reaction of the imino-nitrile (0.5 g) in 1,2-dimethoxyethane (0.3 ml), mixed with potassium cyanide (0.5 g) in water (1 ml) and shaken for 48 h, gave the cyano-amide (0.025 g). Repetition of this with potassium [¹³C]cyanide (37% labelled) gave the labelled cyano-amide.

(c) The cyanide (3h) (0.5 g) with potassium cyanide (0.5 g) in water (1 ml), when shaken for 72 h, likewise gave the cyano-amide, which was labelled when the [¹³C]cyanide was used.

⁴ H. Gold and O. Bayer, *Chem. Ber.*, 1961, **94**, 2594.

Reaction of the Cyanide (3a) with Mercury(II) Cyanide.—Mercury(II) cyanide (5.06 g, 0.02 mol) was added in portions to a stirred solution of the cyanide (3a) (4.96 g, 0.02 mol) in acetonitrile (60 ml). Stirring was continued for 7 h more, the yellow mercury(II) salt was filtered off, and the filtrate was evaporated leaving a solid which was dried (4.5 g) and crystallised from ethanol, giving α -morpholino- α -phenylmalononitrile (7), m.p. 109–110° (Found: C, 68.6; H, 5.7; N, 18.6. $C_{13}H_{13}N_3O$ requires C, 68.7; H, 5.7; N, 18.5%), δ ($CDCl_3$) 7.6 (5 H, m, ArH), 3.8 (4 H, t, CH_2OCH_2), and 2.7 (4 H, t, CH_2NCH_2).

Reaction of the Cyanide (3a) with Morpholine.—The cyanide (4.96 g, 0.02 mol) in morpholine (6.09 g, 0.07 mol) was boiled under reflux for 3.5 h. During this time crystals of the thiocyanate were formed and methanethiol was liberated (odour and reaction to lead acetate paper). The mixture was cooled, ether (40 ml) added, and the solid filtered off, washed with ether, and dried (2.14 g). It crystallised from ethanol giving $\alpha\alpha$ -dimorpholinobenzylum thiocyanate (10), m.p. 254–255° (Found: C, 60.1; H, 6.6; N, 13.0. $C_{16}H_{21}N_3O_2S$ requires C, 60.2; H, 6.6; N, 13.1%), ν_{max} (Nujol) 2 040vs (SCN), 1 600vs, 1 280vs, and 1 130vs cm^{-1} . An identical product was obtained (65%) when the corresponding amidinium iodide^{2a} was stirred with an excess of concentrated aqueous potassium thiocyanate at room temperature for 22 h.

The combined ether filtrate and washings were shaken out with water (5 × 30 ml), dried, and evaporated, leaving a pale yellow oil which crystallised on scratching. It was triturated with ethanol (5 ml) with cooling (ice), and the solid was filtered off, washed twice with cold ethanol (2 × 1.5 ml), and dried (1.82 g). Crystallisation from a little ethanol gave flattened needles of 2,2-dimorpholino-2-phenylacetonitrile (8), m.p. 164–167° (Found: C, 66.9; H, 7.3; N, 14.5. $C_{16}H_{21}N_3O_2$ requires C, 66.9; H, 7.3; N, 14.6%), δ ($CDCl_3$) 7.43 (5 H, s, ArH), 3.7 (8 H, t, 4 × CH_2O), and 2.6 (8 H, t, 4 × CH_2N). An identical product was obtained, quantitatively, from the amidinium iodide and potassium cyanide solution.

The ethanolic filtrate and washings were evaporated; the residue deposited large crystals (0.80 g), which, re-crystallised from light petroleum, yielded rods of 2-morpholino-2-phenylacetonitrile (9), m.p. 66–67° (lit.,⁵ 67–68°), identical with the product from reduction (Raney nickel or borohydride) of the starting material.

In a duplicate experiment, using morpholine pure to g.l.c., a sample of the crude product showed an additional, faster-running peak, whose retention time, under the same conditions (3% PEGA column at 100 °C) was identical with that of authentic *N*-methylmorpholine.

Reaction of the Cyanide (3a) with Primary Amines.—The cyanide (4.96 g), 1,2-diaminoethane (13.5 g), and benzene (30 ml), were boiled under reflux for 6 h, and the benzene and volatile amines were removed *in vacuo*. Water (15 ml) was added, the mixture cooled in ice, and the crystalline solid filtered off, washed with water, and dried (2.65 g, 65%). It had m.p. 66–67° and i.r. spectrum identical with that of compound (9).

The aqueous mother liquor and washings were evaporated to dryness *in vacuo*. The partly crystalline residue showed strong thiocyanate i.r. absorption at 2 070 cm^{-1} (film), and gave a blood-red colour with aqueous iron(III) chloride. Crystallisation of the residue from boiling light petroleum gave needles of 2-phenyl- Δ^1 -imidazoline, m.p. 100° (lit.,^{2b} 100–101°) (Found: C, 73.8; H, 6.9; N, 19.2. Calc. for $C_9H_{10}N_2$: C, 74.0; H, 6.9; N, 19.2%).

Repetition of the experiment with 1,3-diaminopropane or *n*-butylamine gave compound (9) in yields of 63 or 28%, respectively.

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⁵ R. A. Henry and W. M. Dehn, *J. Amer. Chem. Soc.*, 1950, **72**, 2804