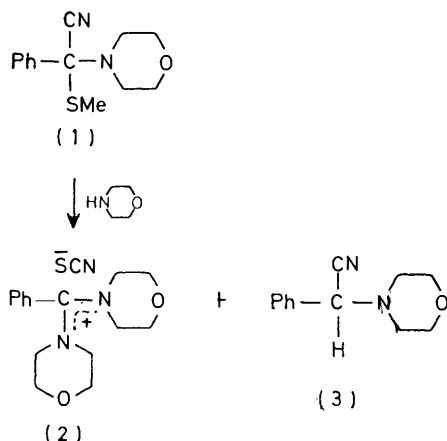


Reactions of *S*-Alkyl-*N,N*-disubstituted Thioamide Salts. Part 3.¹ Thiocarbamoyl Cyanide Derivatives

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Two tetrahedrally substituted thiocarbamoyl cyanide derivatives have been found to undergo rearrangement on heating with morpholine. Bis(methylthio)-4-morpholinoacetonitrile (7) and methylthio-4-morpholinomalononitrile (8) were synthesised from *SS'*-dimethyl-*N*-(3-oxapentamethylene)dithiocarbamidium iodide (4), and with morpholine gave tris-(3-oxapentamethylene)guanidinium thiocyanate (5; X = SCN) and reduction compounds. The salt (4) also reacted with morpholine to give the guanidinium iodide (5; X = I) and with hydrogen sulphide giving dimethyl trithiocarbonate.

PREVIOUSLY¹ we described the rearrangement of the quaternary cyanide (1) with morpholine, yielding the amidinium salt (2) and reduction product (3). A similar rearrangement has since been found to occur with the *S*-benzyl and piperidino analogues of the cyanide (1).² These reactions have now been extended to thiocarbamoyl derivatives.



RESULTS AND DISCUSSION

Methyl morpholine-4-dithiocarboxylate with iodomethane at room temperature slowly gave the quaternary iodide (4), which, on heating with morpholine, yielded the guanidinium iodide (5; X = I), whilst with hydrogen

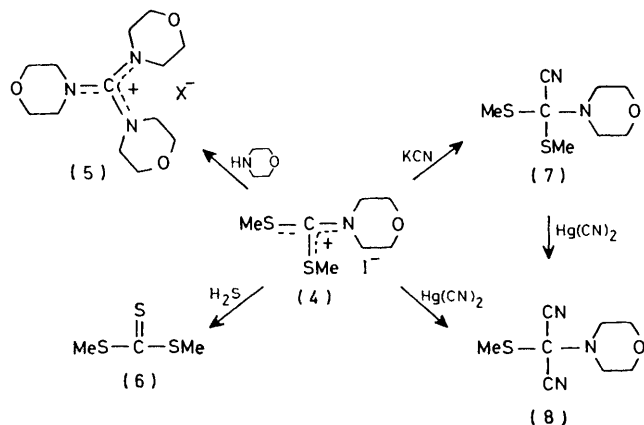
sulphide in methanol it gave dimethyl trithiocarbonate (6). As expected¹ the iodide (4) with aqueous potassium cyanide solution at room temperature gave the nitrile (7), and with mercury(II) cyanide in acetonitrile the bisnitrile (8) was formed. The dimethylamino-analogue of the latter has been obtained similarly.³ The bisnitrile (8) was also prepared from nitrile (7) with mercury(II) cyanide. In both these reactions the remaining methylthio-group is not replaced, presumably because the hypothetical intermediate carbonium ion would be destabilised by two cyano-groups.

When the nitrile (7) was heated with morpholine at 130–135 °C, methanethiol was liberated and, after cooling, the guanidinium thiocyanate (5; X = SCN) and dimorpholinoacetonitrile (9) were isolated as crystalline products. The thiocyanate, with potassium iodide in concentrated aqueous solution, gave an iodide identical with that described above.

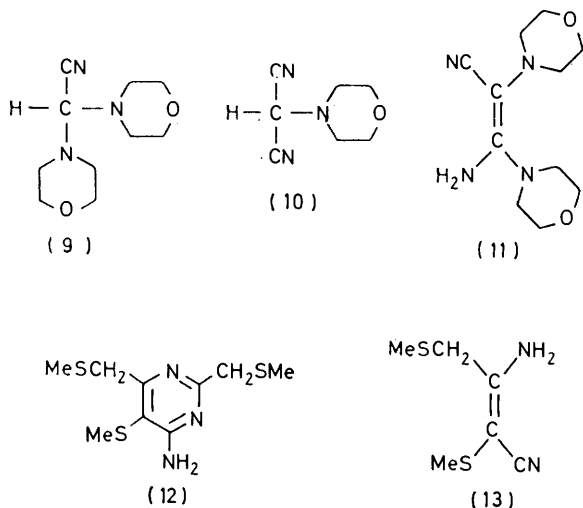
The bisnitrile (8) was partially decomposed on distillation at 3 mmHg, giving a colourless sublimate of morpholinomalononitrile (10), which was also obtained when the compound was heated in boiling toluene. When the bisnitrile (8) was heated with an excess of morpholine, a vigorous reaction occurred with evolution of methanethiol, and on cooling the dark red product, a crystalline solid was obtained, consisting of the guanidinium thiocyanate (5; X = SCN) and the enamino-nitrile [(11) or its *E*-isomer]. The latter almost certainly arises by addition of morpholine to morpholinomalononitrile (10), formed by thermal decomposition, and this was confirmed by heating compound (10) with morpholine, yielding the same enamino-nitrile. This compound is remarkable in crystallising from benzene or from carbon tetrachloride in large colourless crystals containing the solvent, which is lost with efflorescence on heating *in vacuo*.

N-Methylmorpholine was previously detected in the product from reaction of morpholine with the thioamide derivative (1)¹ and is almost certainly produced similarly with morpholine and the nitriles (7) and (8). All these rearrangements therefore involve formation of an amidinium or guanidinium thiocyanate, interchange of hydrogen and an alkyl group between morpholine and the substrate, and evolution of methanethiol.

The driving force is probably relief of overcrowding



around the central carbon atom, both by formation of the cation and by replacement of a bulky alkylthio-group by hydrogen. The uncrowded methylthioacetoneitrile gave no thiocyanate when heated with morpholine and with ethanolic sodium ethoxide it gave a mixture of the pyrimidine (12) and enamionitrile (13 or its geometrical isomer) by the Frankland-Kolbe reaction.⁴



The relatively high melting points and ease of crystallisation of the morpholino-compounds (9)—(11) are probably due to intramolecular hydrogen bonding involving the ring oxygen atom, as shown by weak C-H stretching absorptions at low wavenumber.

EXPERIMENTAL

I.r., u.v., and ¹H n.m.r. spectra were recorded with Unicam SP 1 000, Unicam SP 800, and Varian T 60 instruments, respectively. Elemental analyses were by Scandinavian Microanalytical Laboratories.

Methyl Morpholine-4-dithiocarboxylate and its Methiodide (4).—Carbon disulphide (19.0 g, 0.25 mol) was added dropwise with stirring over 1 h to a solution of sodium hydroxide (7.5 g, 0.19 mol) and morpholine (21.75 g, 0.25 mol) in water (90 ml) at 20–25 °C. Dimethyl sulphate (31.5 g, 0.25 mol) was then added dropwise with continued stirring over 1 h, the temperature rising to 40 °C. After stirring for a further 0.5 h, the colourless solid was filtered off, washed well with water, and dried (33.6 g, 85%). A sample, crystallised from methanol had m.p. 81–83 °C (lit.,⁵ m.p. 82.5–83.5 °C); δ(CDCl₃) 4.2 (4 H, t, CH₂OCH₂), 3.8 (4 H, t, CH₂NCH₂), and 2.70 (3 H, s, SMe).

The crude product (17.7 g, 0.1 mol) and iodomethane (42.6 g, 0.3 mol) were set aside together in a stoppered flask at room temperature for 48 h; acetone (10 ml) was added, and the product filtered off, washed with a small amount of acetone, and dried (26.0 g, 81%), giving SS'-dimethyl-N-(3-oxapentamethylene)dithiocarbamidium iodide (4) as large golden-yellow crystals, m.p. 105–106 °C (Found: C, 26.3; H, 4.4; N, 4.3. C₇H₁₄INOS₂ requires C, 26.3; H, 4.4; N, 4.4%).

Reactions of the Methiodide (4).—(a) A mixture of the methiodide (1.59 g, 5 mmol) and morpholine (1.30 g, 15 mmol) was heated at 120–130 °C for 2 h. Methanethiol was evolved, and the product was cooled, triturated with

ether, filtered off, and dried (1.61 g, 80%), forming colourless crystals (from water) of *tris*-(3-oxapentamethylene)guanidinium iodide (5; X = I), m.p. 300 °C (Found: C, 39.2; H, 6.1; N, 10.6. C₁₃H₂₄IN₃O₃ requires C, 39.3; H, 6.0; N, 10.6%); ν_{max.} (Nujol) 1 565vs, 1 280vs, and 1 105vs cm⁻¹.

(b) The methiodide (10.0 g) was added to a saturated solution of hydrogen sulphide in methanol (100 ml), and the gas passed through it for a further 2 h. The solution was set aside overnight, the methanol evaporated, the residue dissolved in ether (80 ml), filtered, and the solvent evaporated off, leaving dimethyl trithiocarbonate (6) as a yellow oil (2.30 g, 53%), b.p. 118 °C at 28 mmHg (lit.,⁶ b.p. 92 °C at 11 mmHg); δ(CDCl₃) 2.75 (6 H, s, 2 MeS).

(c) The methiodide (63.8 g, 0.2 mol) was added to a solution of potassium cyanide (65.0 g, 1.0 mol) in water (850 ml). An oil was immediately precipitated and after stirring for 10 min the mixture was extracted three times with dichloromethane (total 300 ml). The combined extracts were washed with water (80 ml), dried, and the solvent evaporated. *Bis*-(methylthio)-4-morpholinoacetoneitrile (7) was distilled, forming a yellow oil (26.0 g, 60%), b.p. 128 °C at 2 mmHg (Found: C, 44.0; H, 6.45; N, 12.8. C₈H₁₄N₂OS₂ requires C, 44.0; H, 6.4; N, 12.8%); δ(CDCl₃) 3.8 (4 H, t, 2 CH₂O), 3.0 (4 H, t, 2 CH₂N), and 2.33 (6 H, s, 2 MeS); ν_{max.} (liquid film) 1 120vs cm⁻¹.

(d) A suspension of the methiodide (6.38 g, 20 mmol) in acetonitrile (60 ml) was stirred whilst mercury(II) cyanide (11.13 g, 44 mmol) was added all at once. After stirring for 8 h, the pale yellow precipitate was filtered off, the filtrate evaporated, and the residue dissolved in benzene. A little more mercury salt was filtered off, the benzene evaporated off, and *methylthio*-4-morpholinomalononitrile (8) distilled *in vacuo*, forming a pale yellow oil (1.90 g, 48%), b.p. 110 °C at 1.7 mmHg (Found: C, 49.0; H, 5.6; N, 21.6. C₈H₁₁N₃OS requires C, 48.7; H, 5.6; N, 21.3%); δ(CDCl₃) 3.8 (4 H, m, 2 CH₂O), 2.9 (4 H, m, 2 CH₂N), and 2.42 (3 H, s, MeS); ν_{max.} (liq. film) 2 240vw (CN), 1 460s, 1 270s, and 1 120vs (COC) cm⁻¹. The same compound was obtained when the nitrile (7) was stirred with mercury(II) cyanide in acetonitrile at room temperature for 5.5 h.

When the bisnitrile (8) was distilled at 3 mmHg, darkening occurred and the yellow distillate contained a colourless sublimate which was filtered off and formed prisms (from ethanol) of morpholinomalononitrile (10), m.p. 141 °C (lit.,⁷ m.p. 140 °C) (Found: C, 55.7; H, 6.1; N, 27.7. Calc. for C₇H₉N₃O: C, 55.6; H, 6.0; N, 27.8%).

Reaction of Bis(methylthio)-4-morpholinoacetoneitrile (7) with Morpholine.—The nitrile (8.72 g, 0.04 mol) and morpholine (5.22 g, 0.06 mol) were heated together at 130–135 °C for 1.5 h. Colourless needle crystals of thiocyanate soon began to form and methanethiol (smell, lead acetate paper) was evolved. The dark red product was allowed to stand in ice for 4 h, and the crystals filtered off, washed with ether, and dried (5.7 g). These consisted of a mixture of thiocyanate (5; X = SCN) and dimorpholinoacetoneitrile (9) which were separated by crystallisation from boiling absolute ethanol, in which the former is only moderately soluble, giving *tris*-(3-oxapentamethylene)guanidinium thiocyanate as large colourless rods (3.0 g), m.p. 270–272 °C (Found: C, 51.1; H, 7.4; N, 17.1; S, 9.9. C₁₄H₂₄N₄O₃S requires C, 51.2; H, 7.3; N, 17.1; S, 9.75%), δ[(CD₃)₂SO] 3.9 (12 H, m, 6 CH₂O) and 3.5 (12 H, m, 6 CH₂N); ν_{max.} (Nujol) 2 060m (SCN), 1 560vs, and 1 110 s (COC) cm⁻¹. A saturated aqueous solution of the thiocyanate, upon

addition of solid potassium iodide, gave the corresponding iodide identical with that described above.

The ethanolic filtrate from the thiocyanate was evaporated, the residue dissolved in benzene, filtered from a small amount of the latter, and the benzene evaporated giving crystals (1.21 g) which formed colourless needles (from methanol) of bis-(4-morpholino)acetonitrile, m.p. 122–123 °C (lit.,⁸ m.p. 123.5–124.5 °C) (Found: C, 56.5; H, 8.1; N, 19.6. Calc. for C₁₀H₁₇N₃O₂: C, 56.9; H, 8.1; N, 19.9%); δ (CDCl₃) 3.8 (9 H, t with partially resolved s under, 4 CH₂O and CH), and 2.7 (8 H, t, 4 CH₂N); ν_{\max} . (Nujol) 2 220vw (CN), 1 280s, 1 150s, 1 120vs (COC), 1 030s, and 870vs cm⁻¹.

Reaction of Methylthio-4-morpholinomalononitrile (8) with Morpholine.—The nitrile (5.50 g), dissolved in morpholine (12 ml), was heated to boiling, when a vigorous reaction occurred with evolution of methanethiol. After boiling for a further 5 min, the dark red product was cooled in the refrigerator for 3 d and the solid filtered off, washed with carbon tetrachloride, and dried (3.3 g). It consisted of the guanidinium thiocyanate (5; X = SCN) and the enamino-nitrile (11) which were separated by boiling with benzene (60 ml) and the insoluble thiocyanate filtered off from the hot mixture. It gave colourless crystals from absolute ethanol, identical with those described above.

The benzene filtrate was evaporated to small volume and cooled, giving the enamino-nitrile as large, almost colourless, crystals whose n.m.r. spectrum after drying at room temperature showed the presence of benzene, which was lost with efflorescence on drying at 56 °C *in vacuo*. After crystallisation from carbon tetrachloride and drying at 56 °C as before, 3-amino-2,3-bis-(4-morpholino)acrylonitrile [(11) or its *E*-isomer] formed colourless crystals, m.p. 82–83 °C (Found: C, 55.3; H, 7.5; N, 23.5. C₁₁H₁₈N₄O₂ requires C, 55.5; H, 7.6; N, 23.5%); δ (CDCl₃) 4.8 (2 H, br s, replaceable, NH₂), 3.8 (8 H, t, 4 CH₂O), 3.4 (4 H, t, 2 CH₂N adjacent to CN), and 2.7 (4 H, t, 2 CH₂N adjacent to NH₂); λ_{\max} . (EtOH) 273 nm (ϵ 15 300); ν_{\max} . (Nujol) 3 500m, 3 420m, 3 320m, 3 170m, 2 160s (CN), 1 630vs, 1 570vs, and 1 110vs (COC) cm⁻¹.

Reaction of (Methylthio)acetonitrile with Sodium Ethoxide.—The nitrile (8.70 g, 0.1 mol) in ethanolic sodium ethoxide (55 ml; from 2.53 g, 0.11 g atom sodium) was refluxed for 2 h, cooled, and water (150 ml) added. The product was extracted with dichloromethane (3 × 50 ml), the extract washed with water, dried, and the solvent evaporated off. After setting aside the residue for 2 d in the refrigerator, the crystals were filtered off, triturated with ice-cold ethanol (2.5 ml), filtered again, and crystallised from methanol, giving colourless plates (2.0 g), m.p. 82 °C, of 4-amino-5-methylthio-2,6-bis(methylthiomethyl)pyrimidine (12) (Found: C, 41.5; H, 5.9; N, 16.0; S, 36.0. C₉H₁₅N₃S₃ requires C, 41.4; H, 5.75; N, 16.1; S, 36.8%); δ (CDCl₃) 6.5 (2 H, broad s, NH₂), 3.90 (2 H, s, CH₂ at C-2), 3.62 (2 H, s, CH₂ at C-6), 2.25 (3 H, s, MeS at C-5), 2.20 and 2.17 (each 3 H, s, MeSCH₂).

Column chromatography of the brown oily filtrate on silica gel, eluting with light petroleum–ethyl acetate (7 : 3 v/v) gave a strongly adsorbed fraction consisting of 3-amino-2,4-bis(methylthio)crotononitrile [(13) or the geometrical isomer] (Found: C, 41.9; H, 5.8; N, 15.8. C₆H₁₀N₂S₂ requires C, 41.4; H, 5.75; N, 16.1%); δ (CDCl₃) 5.7 (2 H, br s, NH₂), 3.61 (2 H, s, CH₂), 2.28 and 2.12 (each 3 H, s, MeS); λ_{\max} . (EtOH) 280 nm (ϵ 11 800).

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REFERENCES

- Part 2, S. A. Okecha and F. Stansfield, *J.C.S. Perkin I*, 1977, 1811.
- S. A. Okecha, unpublished work.
- T. Yamaguchi, K. Inomata, and T. Mukaiyama, *Bull. Chem. Soc. Japan*, 1968, **41**, 673.
- Reviewed by G. W. Kenner and A. Todd, in 'Heterocyclic Compounds,' vol. 6, ed. R. C. Elderfield, Wiley, New York, 1957, p. 247.
- F. H. McMillen and J. A. King, *J. Chem. Soc.*, 1948, 4145.
- H. Lecher, *Annalen*, 1925, **445**, 53.
- H. Gold and O. Bayer, *Chem. Ber.*, 1961, **94**, 2594.
- J. G. Erickson, *J. Org. Chem.*, 1955, **20**, 1569.