α,α-Dioxoketene Dithioacetals as Starting Materials for the Synthesis of Polysubstituted Pyridines

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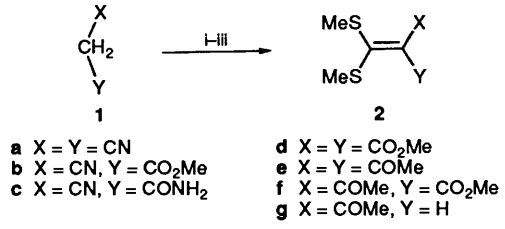
Reactions of 3-acetyl-4,4-bis(methylthio)but-3-en-2-one **2e** and methyl 2-acetyl-3,3-bis(methylthio)-prop-2-enoate **2f** with cyanothioacetamide, cyanoacetamide, or 2-amino-1,3,3-tricyanoprop-1-ene and base, followed by treatment with acid, give polysubstituted pyridines such as **8**, **10**, **11**, **13**, **15** and **16**. Further elaboration of these products leads to bicyclic systems such as thieno[2,3-*b*]pyridines **17** and **18** and pyrazolo[3,4-*c*]pyridine **21** and then to tricyclic systems including pyrazolo[3,4-*d*]thieno[2,3-*b*]pyridine **19** and dipyrazolo[3,4-*b*:3′,4′-*d*]pyridine **22**.

α-Oxoketene dithioacetals have proved useful starting materials for a variety of heterocyclic and homocyclic aromatic compounds.[1,2] Ketene dithioacetals **2** derived from β-dicarbonyl and related compounds **1** (Scheme 1) should be equally

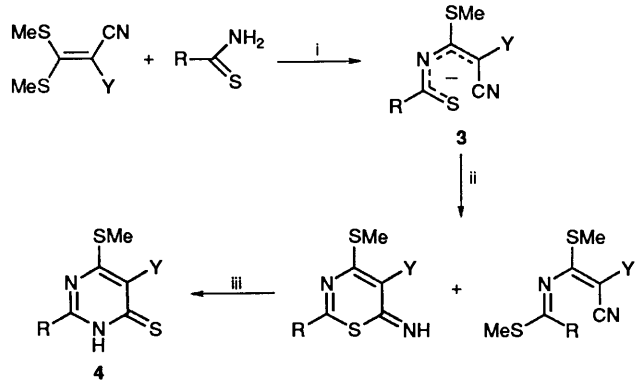


1 **2**

a X = Y = CN
b X = CN, Y = CO_2Me
c X = CN, Y = $CONH_2$
d X = Y = CO_2Me
e X = Y = COMe
f X = COMe, Y = CO_2Me
g X = COMe, Y = H

Scheme 1 *Reagents:* i, base; ii, CS_2; iii, MeI

valuable, but have been much less studied. Recently, reactions of dithioacetals **2a**, **b** with thioamides have been described.[3,4] Reaction of these compounds with thioacetamide or thiobenzamide in the presence of sodium hydride, followed by treatment with acid, gave methylthiopyrimidines **4**; the suggested mechanism is shown in Scheme 2. Methylation of the

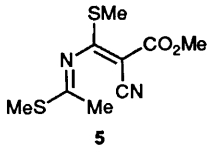


Scheme 2 *Reagents and conditions:* i, NaH; ii, H_3O^+; iii, Dimroth rearrangement

intermediate **3** gave stereoisomeric products, several of whose structures, *e.g.* **5**, were proved by X-ray crystallography.[5]

The dithioacetal **2c** behaved differently, giving pyrimidines **6**, and the diester **2d** gave an open-chain product **7** which failed to cyclise in acid.[4]

We now report some reactions of the ketene dithioacetals **2e**, **f** giving polysubstituted pyridine derivatives which have unusual



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substituents and substitution patterns, and which are useful for further elaboration to polycyclic systems.

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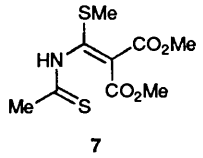

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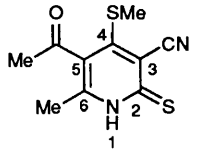
Our initial studies concerned reactions of dithioacetal **2e**, derived from pentane-2,4-dione,[6] with cyanothioacetamide; in the presence of either sodium hydride in DMF or sodium isopropoxide in isopropyl alcohol, a crystalline product was formed and readily isolated in 63% yield. A number of structures could be envisaged for the product such as **8**, formally arising from Michael attack by nitrogen and **9**, formally arising from initial carbanionic Michael attack.



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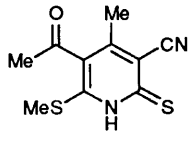

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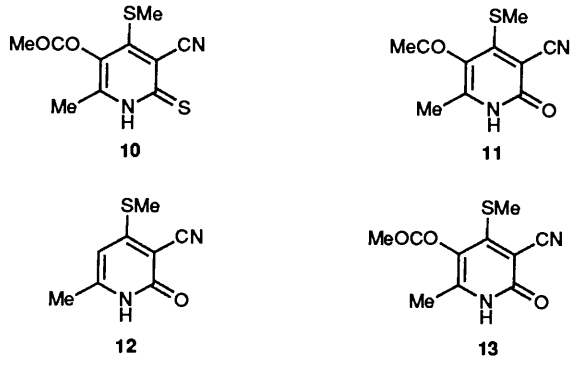
Such structures are not readily distinguished by spectroscopic methods, but X-ray crystallography confirmed that the main product was 5-acetyl-3-cyano-6-methyl-4-methylthiopyridine-2(1*H*)-thione **8**.[7] It should be noted, however, that NMR spectra of samples of crude product showed additional signals, and we suspect that some of the isomer **9** was also formed.

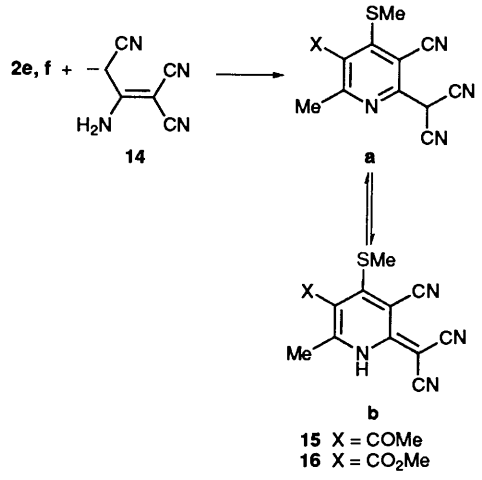
An analogous reaction of the dithioacetal **2f** with cyanothioacetamide gave the corresponding ester **10**.

Reaction with cyanoacetamide was analogous, the diketone **2e** giving the acetyl derivative **11** and the keto ester **2f** giving the ester **13**, whose structure was also confirmed by X-ray crystallography.[7] (When a reaction of the diketone with cyanoacetamide in the presence of sodium isopropoxide in isopropyl alcohol was prolonged, a second compound was also



obtained, which appeared to be identical with that obtained by a reaction of **2g** with cyanoacetamide under similar conditions **12**.[8] This may arise by base-induced deacetylation of **11** by a process akin to the Haller–Bauer cleavage,[9] though we are aware of no close precedent. Note that base-induced deacetylation of a ketene *N,S*-acetal has also been reported.[10])

Reactions of the dithioacetals **2e, f** with the anion of malononitrile dimer **14** gave the novel trinitriles **15, 16** (Scheme 3). These compounds are potentially tautomeric, and we have

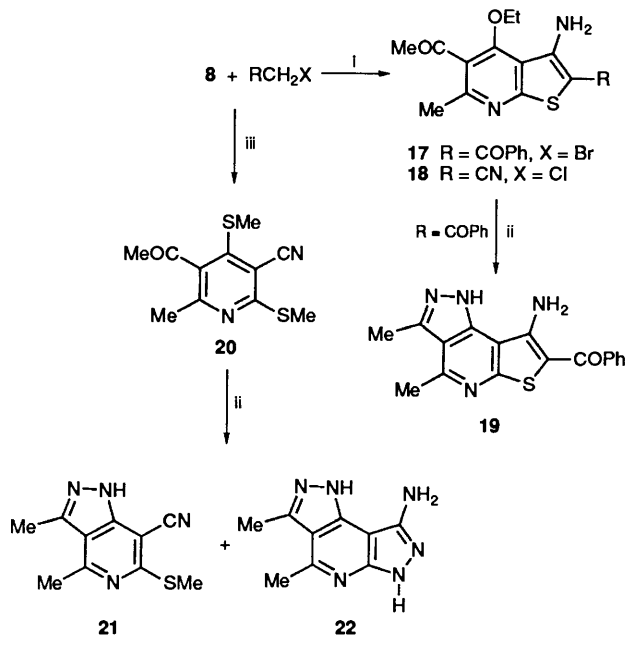


Scheme 3

been so far unable to establish which tautomer predominates. The IR spectra show NH stretching vibrations at *ca.* 3240 cm^{-1}, and the NMR spectra in [$^2H_6$]DMSO show only those signals assigned to methyl groups and an exchangeable proton. The evidence favours **15b**, **16b**, but more work will be required to establish this preference unequivocally.

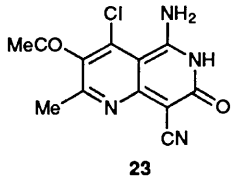
Some illustrative reactions, designed to demonstrate the potential usefulness of the products described above for further heterocyclic syntheses, are represented in Scheme 4. Thus, reaction of the pyridinethione **8** with phenacyl bromide and potassium carbonate in ethanol gave the thienopyridine **17**, with concurrent replacement of the 4-methylthio group by ethoxy. Further reaction with hydrazine then gave an example, compound **19**, of the uncommon[11] pyrazolo[3,4-*d*]thieno[2,3-*b*]pyridine ring system. Similarly reaction of the pyridinethione **8** with chloroacetonitrile gave the cyanothienopyridine **18**.

Methylation of the pyridinethione **8** in ethanolic sodium hydroxide gave the thioether **20**. Further reaction with hydrazine then gave the pyrazolo[3,4-*c*]pyridine **21** and the dipyrazolo[3,4-*b*:3′,4′-*d*]pyridine **22**, another example of an uncommon ring system.[12] (The tricyclic compound **22** was high-melting and insoluble in most solvents, and we were unable to obtain acceptable or consistent elemental analyses, and although the molecular ion was observed in the CI mass



Scheme 4 *Reagents:* i, K_2CO_3, EtOH; ii, N_2H_4; iii, MeI, NaOH, EtOH

spectrum it was too weak for accurate mass measurement, and attempts to observe it *via* FAB were unsuccessful.) A reaction of the trinitrile **15** with hydrogen chloride in acetic acid resulted in displacement of the 4-methylthio group by chloride as well as cyclisation, to give the naphthyridinone **23** or tautomer.



Experimental

M.p.s are uncorrected. IR spectra were recorded on a Perkin-Elmer 1710 FTIR spectrometer for Nujol mulls unless otherwise stated. NMR spectra were recorded on a Brüker AC300 spectrometer at 300 MHz for solutions in mixtures of $CDCl_3$ and [$^2H_6$]dimethyl sulfoxide with tetramethylsilane (TMS) as internal standard unless otherwise recorded. Mass spectra were obtained on Finnigan 4500 (low resolution) and Kratos Concept (high resolution) spectrometers using electron impact (EI) or chemical ionisation with ammonia (CI).

3-Acetyl-4,4-bis(methylthio)but-3-en-2-one **2e**,[6] methyl 2-acetyl-3,3-bis(methylthio)prop-2-enoate **2f**,[6] cyanothioacetamide[13] and 2-amino-1,3,3-tricyanoprop-1-ene ('malononitrile dimer')[14] were prepared by literature methods.

5-Acetyl-3-cyano-6-methyl-4-methylthiopyridine-2(1H)-*thione* **8**.—*Method A*. Sodium hydride (0.53 g, 23 mmol) was suspended in dry *N,N*-dimethylformamide (DMF) (30 cm^3). Cyanothioacetamide (1.47 g, 15 mmol) and 3-acetyl-4,4-bis(methylthio)but-3-en-2-one **2e** (3.0 g, 15 mmol) were added and the mixture was stirred at room temperature under argon for 48 h. The solvent was evaporated under reduced pressure and the residue was dissolved in ethanol. The mixture was acidified to pH 4 with conc. hydrochloric acid and stirred at room temperature for 48 h. The mixture was filtered and the solid was recrystallised from methanol to give the *pyridinethione*

8 (2.2 g, 63%), m.p. 200–202 °C (decomp.); ν_{max}/cm^{-1} 3166, 2226, 1697, 1650, 1643 and 1625; δ 2.36 (3 H, s), 2.44 (3 H, s), 2.48 (3 H, s), 2.9 (br, exch.) and 3.85 (br, exch.) (total 1 H, NH, SH); *m/z* 238 (M^+) (Found: C, 50.6; H, 4.3; N, 11.6. $C_{10}H_{10}N_2OS_2$ requires C, 50.4; H, 4.2; N, 11.75%).

Method B. A similar reaction carried out with sodium in isopropyl alcohol in place of sodium hydride in DMF and with a reaction time of 1 h under reflux gave the pyridinethione **8** in the same yield.

3-*Cyano*-5-*methoxycarbonyl*-6-*methyl*-4-*methylthiopyridine*-2(1H)-*thione* **10**.—A reaction was carried out as described under method A above, with methyl 2-acetyl-3,3-bis(methylthio)prop-2-enoate **2f** in place of **2e** to give the 5-*methoxycarbonylpyridinethione* **10** (1.9 g, 55%), m.p. 190 °C (from ethanol); ν_{max}/cm^{-1} 3165, 2926, 2215 and 1729; δ 2.49 (3 H, s), 2.71 (3 H, s), 3.2 (br, exch., 1 H) and 3.92 (3 H, s, OCH_3); *m/z* 254 (M^+) (Found: C, 47.0; H, 3.7; N, 10.8. $C_{10}H_{10}N_2O_2S_2$ requires C, 47.2; H, 4.0; N, 11.0%).

Reactions of 3-*Acetyl*-4,4-*bis*(*methylthio*)*but*-3-*en*-2-*one* **2e** *with Cyanoacetamide.—Reaction A.* A mixture of sodium hydride (0.7 g, 30 mmol), cyanoacetamide (1.23 g, 15 mmol), 3-acetyl-4,4-bis(methylthio)but-3-en-2-one **2e** (3.0 g, 15 mmol), dry DMF (50 cm^3) and dry benzene (50 cm^3) was stirred under argon at room temperature for 48 h. The solvents were evaporated under reduced pressure, and the semi-solid residue was dissolved in ethanol and acidified to pH 4. The resulting precipitate was filtered and recrystallised from ethanol to give 5-*acetyl*-3-*cyano*-6-*methyl*-4-*methylthiopyridin*-2(1H)-*one* **11** (1.7 g, 52%), m.p. 225–227 °C; ν_{max}/cm^{-1} 2924, 2854, 2225, 1702 and 1655; δ[$(CD_3)_2CO$–$CDCl_3$] 1.69 (3 H, s, 6-CH_3), 1.91 (3 H, s, SCH_3), 2.07 (3 H, s, $COCH_3$) and 2.99 (br, exch.); *m/z* 222 (M^+) (Found: C, 54.1; H, 4.4; N, 12.5. $C_{10}H_{10}N_2O_2S$ requires C, 54.0; H, 4.4; N, 12.6%).

Reaction B. A reaction carried out as described for the preparation of the pyridinethione **8** by method B gave the 5-acetylpyridin-2-one **11** (28%) and 2-cyano-6-methyl-4-methylthiopyridin-2(1*H*)-one **12** (53%), m.p. > 300 °C (from acetic acid); ν_{max}/cm^{-1} 3113, 2212, 1659 and 1622; δ 2.25 (3 H, s, 6-CH_3), 2.55 (3 H, s, SCH_3), 6.23 (1 H, s, 5-H) and 12.3 (br, exch., 1 H, NH); *m/z* 180 (M^+) (lit.,[8]).

3-*Cyano*-5-*methoxycarbonyl*-6-*methyl*-4-*methylthiopyridin*-2(1H)-*one* **13**.—Pyridinone **13** was prepared as described for the corresponding pyridinethione **8**, method A, but with cyanoacetamide in place of cyanothioacetamide to give the *pyridinone* **13** (2.1 g, 65%), m.p. 178–180 °C (from ethanol); δ 2.24 (3 H, s, 6-CH_3), 2.58 (3 H, s, SCH_3), 3.78 (3 H, s, OCH_3) and 3.1 (br) and 12.6 (br), (both exch., total 1 H, NH, OH); *m/z* 238 (M^+) (Found: C, 50.7; H, 4.1; N, 11.7. $C_{10}H_{10}N_2O_3S$ requires C, 50.4; H, 4.2; N, 11.8%).

5-*Acetyl*-3-*cyano*-2-(*dicyanomethyl*)-6-*methyl*-4-*methylthiopyridine* **15**.—The sodium salt of 2-amino-1,3,3-tricyanoprop-1-ene[14] (1.54 g, 10 mmol) was dissolved in isopropyl alcohol (20 cm^3) and 3-acetyl-4,4-bis(methylthio)but-3-en-2-one **2e** (2.04 g, 10 mmol) was added. The mixture was heated under reflux for 5 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethanol. The solution was acidified with conc. hydrochloric acid to pH 5. The resulting precipitate was filtered and recrystallised from acetic acid to give the *title compound* (1.5 g, 56%), m.p. 207–209 °C; ν_{max}/cm^{-1} 3234, 2225, 2208, 2187, 1705 and 1615; δ_H 2.31 (3 H, s), 2.47 (3 H, s), 2.62 (3 H, s) and 4.5 (br, exch., 1 H); δ_C 18.4, 18.6, 31.6, 99.0, 112.9, 116.8, 128.5, 150.0, 154.4, 156.8 and 199.3; *m/z* 270 (M^+) (Found: C, 57.9; H, 3.6; N, 20.7. $C_{13}H_{10}N_4OS$ requires C, 57.8; H, 3.7; N, 20.7%).

3-*Cyano*-2-(*dicyanomethyl*)-5-*methoxycarbonyl*-6-*methyl*-4-*methylthiopyridine* **16**. Compound **16** was prepared similarly, but with methyl 2-acetyl-3,3-bis(methylthio)prop-2-enoate **2f** in place of **2e** to give the *trinitrile* **16** (1.14 g, 40%), m.p. 235–237 °C (from acetic acid); ν_{max}/cm^{-1} 3244, 3112, 2209, 2193, 1729 and 1620; δ 2.41 (3 H, s), 2.61 (3 H, s), 3.83 (3 H, s, OCH_3) and 4.8 (br, exch., 1 H); *m/z* 286 (M^+) (Found: C, 54.6; H, 3.5; N, 19.5. $C_{13}H_{10}N_4O_2S$ requires C, 54.5; H, 3.5; N, 19.6%).

5-*Acetyl*-3-*amino*-2-*benzoyl*-4-*ethoxy*-6-*methylthieno*[2,3-b]*pyridine* **17**.—A mixture of the pyridinethione **8** (0.50 g, 2.1 mmol), phenacyl bromide (0.42 g, 2.1 mmol), anhydrous potassium carbonate (0.30 g, 3 mmol) and ethanol (50 cm^3) was heated under reflux for 2 h. Water (100 cm^3) was added, and the product was isolated by diethyl ether extraction to give the *title compound* (0.6 g, 80%), m.p. 100–102 °C (from aqueous ethanol), ν_{max}/cm^{-1} 3475, 3325, 1697 and 1605; δ 1.45 (3 H, t, CH_2CH_3), 2.52 (3 H, s, CH_3), 2.59 (3 H, s, CH_3), 4.17 (2 H, q, CH_2CH_3) and 1.76, 7.65 and 8.45 (exch., total 2 H, NH_2); *m/z* 354 (M^+) (Found: C, 64.2; H, 4.9; N, 8.0. $C_{19}H_{18}N_2O_3S$ requires C, 64.4; H, 5.1; N, 7.9%).

5-*Acetyl*-3-*amino*-2-*cyano*-4-*ethoxy*-6-*methylthieno*[2,3-b]*pyridine* **18**. Compound **18** was prepared similarly, but from chloroacetonitrile in place of phenacyl bromide, in 86% yield, m.p. 133–135 °C; ν_{max}/cm^{-1} 3420, 3328, 3217, 2197, 1692 and 1625; δ 1.42 (3 H, t, CH_2CH_3), 2.50 (3 H, s, CH_3), 2.57 (3 H, s, CH_3), 4.13 (2 H, q, CH_2CH_3) and 1.75, 5.45 and 6.14 (exch., total 2 H, NH_2) (Found: M^+, 275.0725. $C_{13}H_{13}N_3O_2S$ requires M^+, 275.0728).

8-*Amino*-7-*benzoyl*-3,4-*dimethyl*-1H-*pyrazolo*[3,4-d]*thieno*-[2,3-b]*pyridine* **19** *and Tautomer.*—A mixture of the thienopyridine **17** (0.20 g, 0.6 mmol), hydrazine hydrate (2.01) and ethanol (50 cm^3) was heated under reflux for 1 h. The solution was concentrated and cooled, and the product was recovered by filtration to give the *title compound* (0.17 g, 98%), m.p. > 300 °C; ν_{max}/cm^{-1} 3433, 3330, 3312, 3133 and 1620; δ([$^2H_6$]DMSO) 1.88, 1.90, 2.00 and 2.03 (4 × s, total 6 H, CH_3, coalesced to 2 s on D_2O exch.), 6.6 (5 H, m, Ph) and 2.46 and 7.35 (both exch., total 2 H, NH_2); *m/z* 322 (M^+) (Found: C, 63.1; H, 4.2; N, 17.4. $C_{17}H_{14}N_4OS$ requires C, 63.3; H, 4.4; N, 17.4%).

5-*Acetyl*-3-*cyano*-6-*methyl*-2,4-*bis*(*methylthio*)*pyridine* **20**.—The pyridinethione **8** (1 g) was dissolved in a mixture of ethanol (10 cm^3) and 10% aqueous sodium hydroxide (5 cm^3). The solution was stirred at room temperature as an excess of iodomethane was added dropwise. Stirring was continued for 2 h, water was then added, and the solid product was recovered by filtration to give the *title compound* (95%), m.p. 102–104 °C (from ethanol); ν_{max}/cm^{-1} 2219 and 1699; δ 2.42, 2.53, 2.54 and 2.57 (all 3 H, s); *m/z* 252 (M^+) (Found: C, 52.2; H, 4.55; N, 10.85. $C_{11}H_{12}N_2OS_2$ requires C, 52.4; H, 4.8; N, 11.1%).

Reaction of 5-*Acetyl*-3-*cyano*-6-*methyl*-2,4-*bis*(*methylthio*)-*pyridine* **20** *with Hydrazine.*—A mixture of the bis(methylthio)pyridine **20** (0.1 g, 0.05 mmol), hydrazine hydrate (0.95 cm^3) and ethanol (10 cm^3) was heated under reflux for 1 h. The solvent was evaporated and the residue was recrystallised from acetic acid to give 8-*amino*-3,4-*dimethyl*-1H,6H-*dipyrazolo*[3,4-b:3′,4′-*d*]*pyridine* **22** and/or tautomers (30 mg, 75%), m.p. > 300 °C; ν_{max}/cm^{-1} 3418, 3384, 3181, 1657 and 1626; δ([$^2H_6$]DMSO) 2.62 (3 H, s, CH_3), 2.75 (3 H, s, CH_3), 5.4 (br, exch., 2 H, NH_2), 12.0 (br, exch., 1 H, NH) and 12.9 (br, exch., 1 H, NH); *m/z* 202 (M^+) (Found: C, 52.2; H, 4.9; N, 40.0. $C_9H_{10}N_6$ requires C, 53.4; H, 5.0; N, 41.5%). Concentration of the mother liquors gave 7-*cyano*-3,4-*dimethyl*-6-*methylthio*-1H-

pyrazolo[3,4-c]*pyridine* **21** and/or tautomer (10 mg, 25%), m.p. 133–135 °C (from ethanol); ν_{max}/cm^{-1} 3323, 2214 and 1612; δ 2.84 (3 H, s, CH_3), 2.8 (br, exch., 1 H, NH) and 2.84 (3 H, s, CH_3) (Found: M^+, 218.0629. $C_{10}H_{10}N_4S$ requires M^+, 218.0626).

3-*Acetyl*-5-*amino*-4-*chloro*-8-*cyano*-2-*methyl*-1,6-*naphthyridine*-7(6H)-*one* **23**.—The trinitrile **15** (0.4 g, 1.5 mmol) was heated under reflux in a solution of hydrogen chloride in acetic acid for 5 h. The mixture was cooled and the *title compound* **23** (0.3 g, 70%) was collected by filtration, m.p. > 300 °C (from acetic acid); ν_{max}/cm^{-1} 3478, 3370, 3259, 3125, 1683, 1674, 1670, 1652 and 1626; δ 2.42 (3 H, s, CH_3), 2.50 (3 H, s, CH_3) and 8.6, 10.0 and 10.6 (all br, exch., total 3 H, NH, OH) (Found: M^+, 276.0418. $C_{12}H_9ClN_4O_2$ requires M^+, 276.0414).

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