899. 3-*Amino*-4-*cyano*-3-*pyrrolines: their Hydrolysis to* 3-*Pyrrolidones and their Reaction with Hydrogen Sulphide.*

By J. F. Cavalla.

Cyclisation of basic αω-dinitriles gives good yields of the corresponding basic unsaturated amino-nitriles of surprising stability. Hydrolysis of these to the ketones is difficult. With hydrogen sulphide a system $HS{\cdot}CR{:}CR'{\cdot}CS{\cdot}NH_2$ is formed which can be cyclised with aldehydes or, with base, converted into dienes by elimination of hydrogen sulphide. Some anomalies in the physical characteristics of these compounds are discussed.

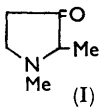
The Thorpe–Ziegler cyclisation of αω-dinitriles has been widely used as a means of preparing alicyclic ketones [1] but only very occasionally in the preparation of heterocyclic ketones. In the course of other work [2] large quantities of 1,2-dimethyl-3-pyrrolidone (I) were needed which previously had been prepared by Dieckmann cyclisation of the

[1] Rodd, "Chemistry of Carbon Compounds," Elsevier, Amsterdam, 1953, Vol. II, p. 271; Thorpe, *J.*, 1909, **95**, 1901.

[2] Cavalla, Davoll, Dean, Franklin, Temple, Wax, and Winder, *J. Med. Pharm. Chem.*, 1961, **4**, 1.

appropriate diester and acid hydrolysis. This cyclisation was not wholly satisfactory for large-scale working, and recourse was made to the cyclisation of the dinitrile (II), prepared by treating β-methylaminopropionitrile with lactonitrile. Since work on this subject has now stopped, the results obtained are presented here.

The dinitrile (II) was readily cyclised in t-butyl alcohol by catalytic amounts of sodium t-butoxide. Substituting acetone cyanohydrin for lactonitrile gave the analogous 2,2-dimethyl compound. At no time during these cyclisations were dimeric compounds encountered analogous to those obtained by Thompson [3] in the cyclisation of adiponitrile, although techniques encouraging the formation of such compounds were employed. The Rast molecular-weight determinations, however, did give consistently high values for both the 2-methyl and the 2,2-dimethyl compound. In conformity with similar compounds [4,5] it was readily shown from their ultraviolet spectra that the cyclised products had the enamine (III) and not the imino-structure (IV).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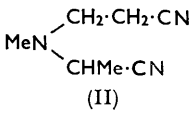
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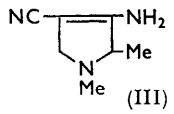
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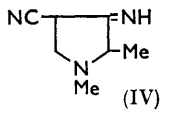

(IV)

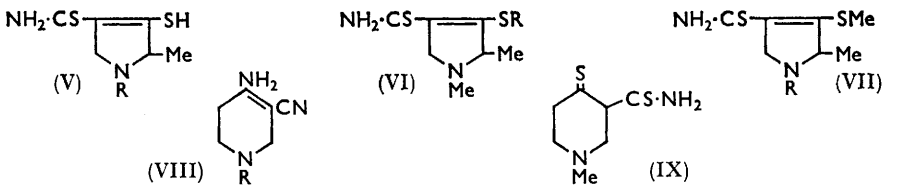
Hydrolysis of cyclic imino-nitriles or unsaturated amino-nitriles to the ketones presents occasional difficulty when the compounds are alicyclic [6] and frequent difficulty in the heterocyclic field.[7] We found that refluxing the pyrroline (III) with constant-boiling hydrochloric acid gave little or no ketonic material, but only black tars. With dilute alkali followed by concentrated acid small yields of the pyrrolidone were obtained, but for optimum results it was necessary to leave the amino-nitrile with cold concentrated acid at room temperature for a day before refluxing the mixture. By this means, consistent yields of around 60% of the pyrrolidones having various substituents on the nitrogen atom were obtained.

The grouping $-C(NH_2){:}C(CN)-$ has been shown to be very reactive in both alicyclic [8] and heterocyclic [9] compounds, but all the condensations effected with this grouping in other series, when repeated with the pyrroline (III), proved fruitless: either the pyrroline was recovered unchanged or tars were formed. Further, it was not possible to methylate or acetylate the amino-group or to reduce the double bond chemically or catalytically. Reduction with lithium aluminium hydride gave a triamine but yields were poor and the reaction was not examined further.

Hydrogen sulphide gave good yields of a novel compound, which appeared to have been formed by the normal addition of hydrogen sulphide to the nitrile group with the concomitant replacement of an amino-group to give, not a thioketone,[10] but an enolic thiol. The postulated structure for such a compound (V; R = Me) while satisfying the requirements of analysis did not account for some of the chemical and, in particular, physical properties. Thus the basic nature of the tertiary amino-group had been almost completely lost: potentiometric titration showed the strongly acidic character of the mercapto-group at pK 9·2, but no inflexion was apparent in the titration curve where one would expect to find a base. No reaction could be obtained with methyl iodide, yet if the compound was treated with alcoholic hydrochloric acid an unstable hydrochloride

[3] Thompson, *J. Amer. Chem. Soc.*, 1958, **80**, 5483.
[4] Hammer and Hines, *J. Amer. Chem. Soc.*, 1955, **77**, 3649.
[5] Baldwin, *J. Org. Chem.*, 1961, **26**, 3288.
[6] Irie, Tsuda, and Uyeo, *J.*, 1959, 1446; Baldwin, *J. Org. Chem.*, 1961, **26**, 3280.
[7] (*a*) Cook and Reed, *J.*, 1945, 403; (*b*) Bachmann and Barker, *J. Amer. Chem. Soc.*, 1947, **69**, 1535; (*c*) Welcher, Johnson, and Wystrach, *ibid.*, 1960, **82**, 4437; (*d*) Diamond, Ph.D. Thesis, Temple University, 1955.
[8] Lamant, *Ann. Chim.* (*France*), 1959, **4**, 87.
[9] Taylor and Loeffler, *J. Amer. Chem. Soc.*, 1960, **82**, 3147; Taylor and Hartke, *ibid.*, 1959, **81**, 2456.
[10] Nomura and Takeuchi, *Bull. Chem. Soc. Japan*, 1960, **33**, 1743.

was obtained. The possibility that the basic character of the tertiary nitrogen was in some way being masked by the strongly acidic mercapto-group was contraindicated by the properties of the methylated product (VI; R = Me) which, like the thiol, showed few of the basic properties expected of a tertiary amine. The hydrochloride of this compound



appeared even more unstable than that of the thiol (V; R = Me). Other compounds having benzyl (VI; R = CH_2Ph) and diethylaminoethyl (VI; R = $Et_2N{\cdot}CH_2{\cdot}CH_2$) groups on the sulphur atom also failed to reveal the basic character of a normal pyrroline; moreover, when an ethoxycarbonyl group was added the resulting compound (VI; R = CO_2Et) was quite as acidic as the thiol.

Although the *N*-benzyl compound (V; R = CH_2Ph) exhibits only acidic properties, like its *N*-methyl analogue, methylation gives a compound (VII; R = CH_2Ph) having p*K* 5·65 and clearly exhibiting basic characteristics. No wholly rational explanation for this behaviour can be advanced but evidence of structural dissimilarities between the thiol (V; R = CH_2Ph) and the sulphide (VII; R = CH_2Ph) can be seen in their ultraviolet absorption spectra; the analogous methyl compounds (V and VII; R = Me) have practically identical ultraviolet spectra.

The tetrahydropyridine [7a] (VIII) was also treated with hydrogen sulphide, giving the thioamide (IX). This was shown by examination of its ultraviolet absorption spectra to exist only partly in the tetrahydropyridine form, although in alkaline solution the sulphur atom was wholly converted into the thiol form. Methylation converted the molecule completely into the tetrahydropyridine. Like the analogous pyrrolines these compounds exhibit only very minor basic characteristics; their hydrochlorides (both unstable) were even more difficult to prepare than those of the pyrrolines.

The thioamide group in both the mercapto- and the methylthio-pyrrolines was not free to react normally; no thiazole was formed on treatment with ω-bromoacetophenone, nor was the amido-group replaced on refluxing the compounds with butylamine. With benzaldehyde and dry hydrogen chloride the mercapto-thioamide (V; R = Me) gave the pyrrolothiazine (X; R = H) which had recovered completely the basic characteristics of the original pyrroline (III). On use of *p*-dimethylaminobenzaldehyde the analogous compound (X; R = Me_2N) was obtained which appeared less stable than the unsubstituted compound; attempts to recrystallise the free base resulted in decomposition.

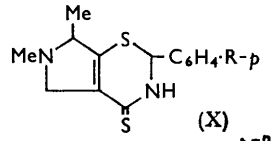
Oxidation of the pyrroline thioamides did not remove any of the uncertainties regarding their structures: with mild oxidising agents (iodine, air, or dilute hydrogen peroxide) no disulphide was formed; vigorous oxidation (concentrated nitric acid or hydrogen peroxide) gave good yields of crystalline products of unknown structure.

Basic degradation of the thiol (V; R = Me) resulted in different compounds, depending on the strength of the base. The compound obtained in best yield was the pyrrole (XI; R = Me), which resulted from the reaction of the thiol with hot aqueous potassium carbonate. With hot aqueous sodium hydroxide the reaction was carried a stage further and the amide (XII) was obtained in poor yield. With cold aqueous sodium hydroxide the thiol gave a compound tentatively assigned the structure (XIII) which must result from the degradation of two molecules of the thiol.

Reductive desulphurisation of the pyrrolinethiol (V; R = Me) was not satisfactory although one experiment did appear to give the desulphurated compound (XIV), isolated as its picrate.

The pyrrole (XI; R = Me) had the properties of a thioamide clearly manifest: with ω-bromoacetophenone, the thiazole (XV; R = H) was obtained in excellent yield. Substitution of ω-bromo-4-nitroacetophenone gave the nitro-compound (XV; R = NO_2) which could be reduced to the aniline.

The ester-nitrile (XVI), on cyclisation, gave the aminopyrroline ester (XVII) which was easier to hydrolyse to the ketone (I) than the nitrile (III) but less easy to prepare.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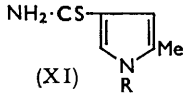
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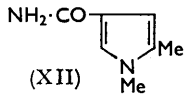
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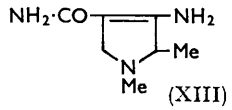
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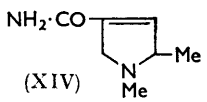
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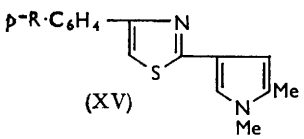
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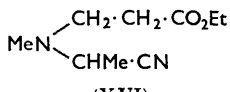
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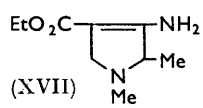
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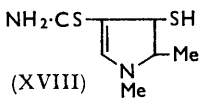
Like the nitrile, the ester (XVII) could not be cyclised with guanidine or formamide, nor could the double bond be catalytically reduced. Unlike the nitrile, the ester partially decomposed on storage at room temperature to give a black solid which had retained its crystalline form.

A plausible explanation for the lack of basicity of some of the sulphur-containing compounds described above can be given by formulating them as vinylogous thioamides (*e.g.*, XVIII). Apart from the difficulty in explaining such a bond migration, the formulation suffers in requiring the presence of an isolated thiol group which has not been detected; also, it would not allow for the return of basicity with the 1-benzylpyrroline (VIII; R = CH_2Ph) and the pyrrolothiazines (X). Methylation might also be expected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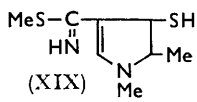
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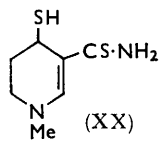
(XX)

to occur at the thioamide-sulphur to give a vinylogous isothiourea (XIX), but this could not be shown chemically. Finally, a similar structure (XX) can be synthesised for the tetrahydropyridine, but this compound exists only partly in the tetrahydropyridine form yet still displays no basic characteristics.

Experimental

Ultraviolet absorption spectra are for ethanol solutions, unless stated to the contrary.

N-1-*Cyanoethyl*-N-2-*cyanoethylmethylamine* (II).—β-Methylaminopropionitrile (84 g.) in benzene (100 ml.) was treated at 50° with lactonitrile (71 g.); reaction proceeded without further need of heat. The mixture was left at room temperature overnight, then free water was removed and the benzene solution concentrated and distilled, to give the *dinitrile* (124 g., 90%), b. p. 117—121°/1 mm., n_D^{20} 1·4522 (Found: C, 61·5; H, 7·7; N, 30·3. $C_7H_{11}N_3$ requires C, 61·3; H, 8·1; N, 30·6%).

3-*Amino*-4-*cyano*-1,2-*dimethyl*-3-*pyrroline* (III).—The dinitrile (II) (124 g.) was added dropwise in 1 hr. to a refluxing solution of sodium (1 g.) in t-butyl alcohol (250 ml.), and the mixture refluxed for a further 2 hr., cooled, diluted with ether (100 ml.), and left at room temperature, to give the pyrroline (106 g., 85%) as prismatic needles, m. p. 148—151°, $\lambda_{max.}$ 263 mμ (ε 12,780) [Found: C, 61·3; H, 8·2; N, 30·4%; *M* 172 (Rast), 139 (potentiometric titration). $C_7H_{11}N_3$ requires C, 61·3; H, 8·1; N, 30·6%; *M*, 137], p*K* 6·13. In most experiments overall yields in excess of 80% were obtained when the undistilled dinitrile, freed from traces of water by azeotropic distillation with benzene, was cyclised straightway.

3-*Amino*-4-*cyano*-1,2,2-*trimethyl*-3-*pyrroline*.—β-Methylaminopropionitrile (42 g.) was kept

at 50° with acetone cyanohydrin (42·5 g.) in benzene (150 ml.) for 6 hr., the free water separated, and the solution dried by adding more benzene (250 ml.) and removing residual water azeotropically. The dry benzene solution was concentrated and the residue, in t-butyl alcohol (150 ml.), added to a solution of sodium (0·6 g.) in t-butyl alcohol (100 ml.) and refluxed for 3 hr. The cold solution was treated with ether (150 ml.) and left, to give the *pyrroline* (24 g., 32%) as prisms, m. p. 146—149°, $\lambda_{max.}$ 262 mμ (ε 12,600) [Found: C, 63·9; H, 8·8; N, 27·5%; *M*, 184 (Rast), 155 (potentiometric titration). $C_8H_{13}N_3$ requires C, 63·5; H, 8·7; N, 27·8%; *M*, 151), p*K* 6·37.

Acid Hydrolysis of 3-*Amino*-4-*cyano*-1,2-*dimethyl*-3-*pyrroline*.—The pyrroline (713 g.) was added with stirring in 0·5 hr. to concentrated hydrochloric acid (2·3 l.); the temperature rose from 12° to 30°. The mixture was cooled to 21°, then stirred at room temperature overnight, to give a pale buff solution containing free ammonium chloride. The mixture was warmed slowly during 5 hr. to the b. p. and kept there for 1 hr., during which much carbon dioxide was evolved. The solution was cooled, ethanol (0·5 l.) added, and the ammonium chloride filtered off. The filtrate was concentrated under reduced pressure, 10N-sodium hydroxide (900 ml.) added, and the mixture filtered and extracted with ether (6 × 150 ml.). The extracts were dried (Na_2SO_4), concentrated, and distilled, to give 1,2-dimethyl-3-pyrrolidone [2] (321 g., 54%) b. p. 51°/21 mm., n_D^{20} 1·4440 (Found: C, 60·4; H, 9·4; N, 13·7. Calc. for C_5H_9NO: C, 60·6; H, 9·2; N, 14·3%).

3-*Amino*-1-*butyl*-4-*cyano*-2-*methyl*-3-*pyrroline*.—By the technique described above, β-butylaminopropionitrile gave the *pyrroline* (55%) as prisms, m. p. 105°, $\lambda_{max.}$ 263 mμ (ε 12,500) (Found: C, 66·6; H, 9·4; N, 23·5. $C_{10}H_{17}N_3$ requires C, 67·0; H, 9·6; N, 23·4%).

3-*Amino*-4-*cyano*-2-*methyl*-1-*pentyl*-3-*pyrroline*.—This compound was isolated initially as an oil, b. p. 160—164°/2·0 mm., which slowly solidified giving plates (60%), m. p. 42—44°, $\lambda_{max.}$ 263 mμ (ε 11,300) (Found: C, 68·5; H, 10·2; N, 21·5. $C_{11}H_{19}N_3$ requires C, 68·4; H, 9·9; N, 21·7%).

3-*Amino*-1-*benzyl*-4-*cyano*-2-*methyl*-3-*pyrroline*.—This *compound* was obtained similarly as needles (73%), m. p. 108° (Found: C, 73·5; H, 7·4; N, 19·4. $C_{13}H_{15}N_3$ requires C, 73·2; H, 7·1; N, 19·7%).

3-*Amino*-4-*cyano*-2-*methyl*-1-*phenethyl*-3-*pyrroline*.—This *pyrroline* was obtained similarly, as hard needles (77%), m. p. 113—114° (Found: C, 73·8; H, 7·8; N, 18·3. $C_{14}H_{17}N_3$ requires C, 74·0; H, 7·5; N, 18·5%).

1-*Butyl*-2-*methyl*-3-*pyrrolidone*.—Acid hydrolysis of the appropriate amino-nitrile (details as above) gave the *ketone* (61%), b. p. 78—82°/7 mm., n_D^{20} 1·4500 (Found: C, 69·8; H, 11·3; N, 9·1. $C_9H_{17}NO$ requires C, 69·6; H, 11·0; N, 9·0%).

Similar hydrolyses gave:

2-*Methyl*-1-*pentyl*-3-*pyrrolidone* (50%), b. p. 88—90°/9 mm., n_D^{20} 1·4500 (Found: C, 70·7; H, 11·5; N, 8·1. $C_{10}H_{19}NO$ requires C, 71·0; H, 11·3; N, 8·3%); 1-benzyl-2-methyl-3-pyrrolidone [2] (much foaming during the preparation, 70%), m. p. 108°/1 mm., n_D^{20} 1·5261; and 2-*methyl*-1-*phenethyl*-3-*pyrrolidone* (57%), b. p. 129°/0·9 mm., n_D^{20} 1·5265 (Found: C, 76·5; H, 8·5; N, 6·8. $C_{13}H_{17}NO$ requires C, 76·8; H, 8·4; N, 6·9%).

4-*Amino*-3-*cyano*-1,2,5,6-*tetrahydro*-1-*methylpyridine* (VIII).—Cyclisation of *NN*-di-(2-cyanoethyl)methylamine (572 g.) with a solution from sodium (11 g.) in t-butyl alcohol (1·7 l.) as described above, followed by the addition of light petroleum (b. p. 40—60°; 1 l.), gave the tetrahydropyridine (396 g., 70%) as needles, m. p. 125—127° (Cook and Reed [7a] give m. p. 122—123°), $\lambda_{max.}$ 263 mμ (ε 12,150), p*K* 6·8.

3-*Mercapto*-1,2-*dimethyl*-4-*thiocarbamoyl*-3-*pyrroline* (V; R = Me).—3-Amino-4-cyano-1.2-dimethyl-3-pyrroline (137 g.) in propan-2-ol (1 l.) was treated with triethanolamine (100 ml.) then, with stirring at 60°, with a fine stream of hydrogen sulphide for 7 hr. The solution was allowed to cool overnight and the yellow solid, m. p. 154—156° (decomp.), which had begun to separate about 2 hr. after passage of gas commenced, was filtered off (81·6 g.). The filtrate was re-treated in a similar manner with hydrogen sulphide, to give two further crops (47·1 g. and 11·0 g., total 74%). Crystallisation of a portion from hot water gave the *thioamide* as massive needles, m. p. 160—161° (decomp.), $\lambda_{max.}$ 214, 296, and 373 mμ (ε 11,420, 1840, and 23,200; this absorption pattern was little changed in 0·1N-NaOH or -HCl) (Found: C, 44·9; H, 6·5; N, 14·8; S, 34·2. $C_7H_{12}N_2S_2$ requires C, 44·7; H, 6·4; N, 14·9; S, 34·0%), p*K* 9·2.

The pyrroline (1·88 g.), suspended in propan-2-ol (30 ml.), was treated with a stream of hydrogen chloride at 5°, the solid dissolving. Slow continued passage of the gas gave a yellow

solid. The mixture was concentrated under reduced pressure and the residue triturated with propan-2-ol, to furnish the *hydrochloride* (2·05 g., 90%), m. p. 109—111° (Found: Cl, 16·1; N, 12·7. $C_7H_{12}N_2S_2$,HCl requires Cl, 15·8; N, 12·4%), p*K* 2·55 and 9·2. Treatment of this solid with water resulted in dissolution followed by deposition of the original pyrroline base, m. p. and mixed m. p. 160—161° (decomp.).

1,2-*Dimethyl*-3-*methylthio*-4-*thiocarbamoyl*-3-*pyrroline* (VI; R = Me).—The thiol (V; R = Me) (37·6 g.) in N-sodium hydroxide (200 ml.) was treated with potassium carbonate (28·6 g.) and then, with stirring at 20°, with dimethyl sulphate (29·8 g.). The mixture was stirred for 3 hr., then filtered to give the *methylthio-derivative* (28·4 g., 70%) as needles, m. p. 229—230° (decomp.), $\lambda_{max.}$ 214, 300, and 379 mμ (ε 16,440, 1990, and 23,550) (Found: C, 47·4; H, 7·1; N, 13·5; S, 31·4. $C_8H_{14}N_2S_2$ requires C, 47·5; H, 7·0; N, 13·9; S, 31·7%), p*K* neutral (the titration curve was identical with a control).

The sulphide (1·0 g.) was suspended in propan-2-ol (30 ml.) and treated with hydrogen chloride without external cooling. The solid did not dissolve but appeared to change its form; the temperature rose to 50°. After 20 min. the mixture was concentrated under reduced pressure and triturated with propan-2-ol, to furnish the *hydrochloride* (1·05 g.) as a yellow powder, m. p. 171—175°. This could not be crystallised or treated with water without decomposition (Found: Cl, 15·3. $C_8H_{14}N_2S_2$,HCl requires Cl, 14·9%); it had p*K* 2·6.

3-*Benzylthio*-1,2-*dimethyl*-4-*thiocarbamoyl*-3-*pyrroline* (VI; R = CH_2Ph).—3-Mercapto-1,2-dimethyl-4-thiocarbamoyl-3-pyrroline (5·64 g.) in 1 : 1 aqueous dimethylformamide (50 ml.) containing potassium carbonate (3·84 g.) was treated dropwise with stirring with benzyl chloride (4·2 g.); an oil separated. The mixture was stirred for 2 hr., treated with water (150 ml.), and extracted with chloroform (3 × 50 ml.), and the bulked extracts were washed with N-sodium hydroxide (30 ml.) and water (3 × 30 ml.), dried (Na_2SO_4), and concentrated under reduced pressure to 20 ml. Dilution with ether gave the *benzylthio-compound* (1 g., 12%) as a yellow solid which crystallised from aqueous ethanol as the hemiethanolate, m. p. 163—164° (decomp.), $\lambda_{max.}$ 211 and 377 mμ (ε 21,200 and 22,300) (Found: C, 59·9; H, 7·0; N, 9·2; S, 21·2. $C_{14}H_{18}N_2S_2$,0·5C_2H_5·OH requires C, 59·8; H, 7·0; N, 9·3; S, 21·2%), p*K* neutral.

3-2′-*Diethylaminoethylthio*-1,2-*dimethyl*-4-*thiocarbamoyl*-3-*pyrroline* (VI; R = $Et_2N{\cdot}CH_2{\cdot}CH_2$).—3-Mercapto-1,2-dimethyl-4-thiocarbamoyl-3-pyrroline (18·8 g.) in N-sodium hydroxide (110 ml.) was treated at room temperature with diethylaminoethyl chloride hydrochloride (20·6 g.) in N-sodium hydroxide (120 ml.). The solution darkened but no heat was evolved. The mixture was stirred for 4 hr., during which an oil separated which quickly solidified. This solid, crystallised from aqueous ethanol–ether, gave the *pyrroline* (10 g., 35%) as yellow plates, m. p. 177—179° (decomp.), $\lambda_{max.}$ 202, 211, 299, and 376 mμ (ε 13,800, 13,600, 2300, and 22,300) (Found: C, 54·5; H, 8·9; N, 14·4; S, 22·2%; equiv., 285. $C_{13}H_{25}N_3S_2$ requires C, 54·3; H, 8·8; N, 14·6; S, 22·3%; *M*, 287), p*K* 5·95.

3-*Ethoxycarbonylthio*-1,1-*dimethyl*-4-*thiocarbamoyl*-3-*pyrroline* (VI; R = CO_2Et).—3-Mercapto-1,2-dimethyl-4-thiocarbamoyl-3-pyrroline (5·64 g.) in dimethylformamide (25 ml.) was treated with potassium carbonate (3·84 g.) in water and then, at room temperature with stirring, with ethyl chloroformate (4 g.). After a vigorous reaction the resulting orange solution was stirred for 3 hr., diluted with water (250 ml.), and extracted with chloroform (5 × 50 ml.). The bulked extracts were washed with water (2 × 50 ml.), dried (Na_2SO_4), and concentrated under reduced pressure to a red oil (3 g.). This crystallised from propan-2-ol–ether to give the *pyrroline* (0·7 g.) as orange plates, m. p. 170—171° (decomp.), $\lambda_{max.}$ 204, 227, 303, and 417 mμ (ε 10,400, 10,200, 4060, and 27,300) (Found: C, 46·2; H, 6·3; N, 10·7; S, 24·7%; equiv., 266. $C_{10}H_{16}N_2O_2S_2$ requires C, 46·2; H, 6·2; N, 10·8; S, 24·6%; *M*, 260) p*K* 8·75.

1-*Benzyl*-3-*mercapto*-2-*methyl*-4-*thiocarbamoyl*-3-*pyrroline* (V; CH_2Ph).—In the conditions given for the analogous methyl compound (V; R = Me) treatment of 3-amino-1-benzyl-4-cyano-2-methyl-3-pyrroline with hydrogen sulphide gave the *mercaptopyrroline* (66%) as yellow needles, m. p. 160—161° (decomp.), $\lambda_{max.}$ 208, 304, and 375 mμ (ε 21,300, 3550, and 20,500) (Found: C, 59·5; H, 6·4; N, 10·6; S, 23·9. $C_{13}H_{16}N_2S_2$ requires C, 59·1; H, 6·1; N, 10·6; S, 24·2%), p*K* 8·55.

1-*Benzyl*-2-*methyl*-3-*methylthio*-4-*thiocarbamoyl*-3-*pyrroline* (VII; R = CH_2Ph).—Methylation of the preceding thiol as described previously gave the *sulphide* (75%) as a yellow powder which crystallised from aqueous ethanol as needles, m. p. 124—125° (decomp.), $\lambda_{max.}$ 207, 316, and 394 mμ (ε 22,000, 6850, and 8050) (Found: C, 60·0; H, 6·4; N, 9·8; S, 23·2%; equiv., 285. $C_{14}H_{18}N_2S_2$ requires C, 60·4; H, 6·5; N, 10·1; S, 23·0%; *M*, 278), p*K* 5·65.

1-*Methyl*-4-*thio*-3-*thiocarbamoylpiperidine* (IX).—Treatment of 4-amino-3-cyano-1,2,5,6-tetrahydro-1-methylpyridine with hydrogen sulphide as described above gave the *thione* (72%), m. p. 163—166° (decomp.), as a mixture of mainly the thione and some enolic thiol, $\lambda_{max.}$ 204, 223, 269, and 303 mμ (ε 7980, 5190, 4790, and 2440), in 0·1N-sodium hydroxide, $\lambda_{max.}$ 217, 298, and 362 mμ (ε 11,200, 4730, and 13,200) (Found: C, 44·6; H, 6·5; N, 14·8; S, 33·8%; equiv., 191. $C_7H_{12}N_2S_2$ requires C, 44·7; H, 6·4; N, 14·9; S, 34·0%; *M*, 188), p*K* 9·0.

1,2,5,6-*Tetrahydro*-1-*methyl*-4-*methylthio*-3-*thiocarbamoylpyridine*.—When 1-methyl-4-thio-3-thiocarbamoylpiperidine (18·8 g.) in methanol (100 ml.) was treated at room temperature with stirring with 0·5N-sodium hydroxide (100 ml.) and potassium carbonate (13·8 g.), followed by dimethyl sulphate (15 g.), the temperature rose to 60°. The mixture was stirred for 3 hr., then concentrated under reduced pressure to remove the methanol; the precipitated *sulphide* (8 g., 40%) crystallised from hot water as needles, m. p. 157—158° (decomp.), $\lambda_{max.}$ 205, 298, and 370 mμ (ε 12,500, 2010, and 20,800) (Found: C, 47·3; H, 6·8; N, 13·7; S, 31·6. $C_8H_{14}N_2S_2$ requires C, 47·5; H, 7·0; N, 13·9; S, 31·7%), p*K* neutral.

2,3,4,5,6,7-*Hexahydro*-6,7-*dimethyl*-2-*phenyl*-4-*thiopyrrolo*[3,4-e][1,3]*thiazine* (X; R = H)—3-Mercapto-1,2-dimethyl-4-thiocarbamoyl-3-pyrroline (12 g.) in propan-2-ol (200 ml.) was treated with benzaldehyde (20 ml.) and then, at 0—5° with stirring, with a slow stream of hydrogen chloride until all solid had dissolved. The solution was stirred for 1 hr. and concentrated under reduced pressure to an oil; the oil was suspended in propan-2-ol (200 ml.) which was then removed. Crystallisation of the residue from aqueous propan-2-ol gave the *thione hydrochloride hydrate* (17 g., 78%) as yellow needles, m. p. 153—156° (decomp.), $\lambda_{max.}$ 204 and 351 mμ (ε 18,600 and 12,600) (Found: C, 51·0; H, 5·8; N, 8·3; S, 19·2. $C_{14}H_{16}N_2S_2,HCl,H_2O$ requires C, 50·8; H, 5·8; N, 8·5; S, 19·4%), p*K* 5·85. Treatment of a cold aqueous solution of this material (5 g.) with aqueous sodium hydrogen carbonate gave the base. This was extracted with chloroform (3 × 70 ml.), and the extracts were dried (Na_2SO_4) and concentrated under reduced pressure to 40 ml. at <25°. Addition of light petroleum (b. p. 40—60°; 100 ml.) to this solution gave the *pyrrolothiazine* (2·8 g., 67%) as needles, m. p. 206—209° (decomp.), shrinking at 165°, $\lambda_{max.}$ 203 and 350 mμ (ε 20,360 and 13,750) (Found: C, 60·9; H, 5·8; N, 10·1; S, 23·2. $C_{14}H_{16}N_2S_2$ requires C, 60·6; H, 5·7; N, 10·2; S, 23·6%), p*K* 5·8. This compound decomposes slightly when treated with hot chloroform.

p-*Dimethylaminophenyl*-2,3,4,5,6,7-*hexahydro*-6,7-*dimethyl*-4-*thiopyrrolo*[3,4-e][1,3]*thiazine* (X; R = Me_2N).—In a manner similar to the previous experiment, the thiol (9·4 g.) in propan-2-ol (120 ml.) was treated with *p*-dimethylaminobenzaldehyde (14·9 g.) and then with hydrogen chloride. The product (16·2 g., 79%) crystallised from aqueous propan-2-ol as lime-coloured needles of the *thione dihydrochloride hydrate*, m. p. 203—205° (decomp.), $\lambda_{max.}$ 204, 267, and 347 mμ (ε 27,800, 20,000, and 15,000) (Found: C, 46·7; H, 6·1; N, 9·7; Cl, 17·4. $C_{16}H_{21}N_3S_2,2HCl,H_2O$ requires C, 46·8; H, 6·1; N, 10·2; Cl, 17·3%), p*K* 3·10 and 5·93. Treatment of an aqueous solution of this material (1·0 g.) with sodium hydrogen carbonate gave the *base*, isolated with cold chloroform and crystallising from chloroform–light petroleum (b. p. 40—60°) as yellow prisms (0·5 g., 65%), m. p. 142—144° (decomp.), $\lambda_{max.}$ 204, 265, and 347 mμ (ε 29,000, 20,700, and 15,400) (Found: C, 59·9; H, 6·8; N, 12·6; S, 20·2. $C_{16}H_{21}N_3S_2$ requires C, 60·2; H, 6·6; N, 13·2; S, 20·0%). The substance dissolved during the potentiometric titration but, inexplicably, no inflection was given on the curve.

Oxidation of 1,2-*Dimethyl*-3-*methylthio*-4-*thiocarbamoyl*-3-*pyrroline*.—(*a*) *With concentrated nitric acid.* The sulphide (5 g.) was added portionwise in 30 min. to stirred concentrated nitric acid (60 ml.), then the stirred mixture was boiled for 3 hr. and concentrated under reduced pressure. A solution of the residue in hot ethanol (50 ml.) gave, on storage, a white solid (2·53 g.), m. p. 248° (decomp.). This *substance* crystallised from aqueous propan-2-ol as needles, m. p. 262° (decomp.) (Found: C, 37·8; H, 5·9; N, 5·6; S, 13·2%; equiv., 247. $C_8H_{15}NO_6S$ requires C, 37·9; H, 6·0; N, 5·5; S, 12·6%; *M*, 253), p*K* 3·2, $\nu_{max.}$ 3375s, 2960, 2750, 2593, 1768, 1726s, 1648, 1478, 1453, 1423, 1388, 1279s, 1259s, 1222, 1189s, 1101, 1061s, 1017, 990, 865, 757, and 744 cm.$^{-1}$ in a potassium bromide disc. There was no absorption in the ultraviolet region.

(*b*) *With hydrogen peroxide.* When the sulphide (0·5 g.), suspended in water (10 ml.), was treated with hydrogen peroxide (100-vol.; 1·5 ml.) the temperature rose to 80°. The solution was concentrated under reduced pressure, giving a white solid which was dissolved in hot water (10 ml.) and treated with hot propan-2-ol (20 ml.). A *substance* (0·4 g.) resulted as small cubes, m. p >360°, $\lambda_{max.}$ 221, and 255 mμ (ε 3880 and 6810) (Found: C, 39·2; H, 5·1; N, 11·3;

S, 25·4. $C_8H_{12}N_2O_3S_2$ requires C, 38·7; H, 4·9; N, 11·3; S, 25·8%), p*K* neutral, $\nu_{max.}$ 3435, 3040, 1478, 1458, 1428, 1398, 1325, 1314, 1231s, 1211s, 1158, 1097, 1041, 990, 926, 878, 823, 800, and 708 cm.$^{-1}$ in a potassium bromide disc.

Oxidation of 3-*Mercapto*-1,2-*dimethyl*-4-*thiocarbamoyl*-3-*pyrroline with Hydrogen Peroxide.*—The thiol (0·5 g.) in water (10 ml.) was treated with hydrogen peroxide (100-vol.; 1·5 ml.) as for the sulphide above, to give a *substance* (0·26 g.) crystallising from aqueous propan-2-ol as cubes, m. p. 217—219° (decomp.), $\lambda_{max.}$ 221 and 255 mμ (ε 3890 and 6690) (Found: C, 36·2; H, 4·3; N, 11·6; S, 27·6%; equiv., 233. $C_7H_{10}N_2O_3S_2$ requires C, 35·9; H, 4·3; N, 12·0; S, 27·3%; *M*, 231), p*K* 6·4, $\nu_{max.}$ 3460, 3040, 2750, 1644, 1461, 1393, 1360, 1333, 1251s, 1215s, 1198s, 1180s, 1111, 1081, 1040s, 993, 913, 850, and 787 cm.$^{-1}$ in a potassium bromide disc.

1,2-*Dimethyl*-4-*thiocarbamoylpyrrole* (XI; R = Me).—3-Mercapto-1,2-dimethyl-4-thiocarbamoyl-3-pyrroline (35 g.; passing a 40-mesh sieve), in water (500 ml.), was stirred with potassium carbonate (130 g.) at 100° for 6 hr. in the dark. On cooling, the *pyrrole* (24 g., 83%) separated as a buff solid which crystallised from methanol–ether as pale yellow prisms, m. p. 206—209°, $\lambda_{max.}$ 208, 261, and 320 mμ (ε 16,400, 11,100, and 11,300) (Found: C, 54·8; H, 6·6; N, 17·8; S, 21·2. $C_7H_{10}N_2S$ requires C, 54·5; H, 6·5; N, 18·2; S, 20·8%). The substance was neutral.

1-*Benzyl*-2-*methyl*-4-*thiocarbamoylpyrrole* (XI; R = CH_2Ph).—This *compound* was prepared in 40% yield by following the conditions given for the methyl analogue. It crystallised from methanol–ether as light brown needles, m. p. 174—175°, $\lambda_{max.}$ 205, 259, and 317 mμ (ε 24,900, 11,400, and 11,100) (Found: N, 11·8; S, 13·5. $C_{13}H_{14}N_2S$ requires N, 11·8; S, 13·9%). It was neutral.

4-*Carbamoyl*-1,2-*dimethylpyrrole* (XII).—3-Mercapto-1,2-dimethyl-4-thiocarbamoyl-3-pyrroline (1 g.) was held at 95° for 30 min. in 5N-sodium hydroxide (20 ml.), then cooled, and the resulting oil (0·3 g., 41%) was isolated with chloroform. Crystallisation from methanol–ether gave the *amide* as plates, m. p. 159—161°, $\lambda_{max.}$ 206, 235, and 253 (shoulder) mμ (ε 20,600, 8300, and 5400) (Found: C, 60·7; H, 7·2; N, 20·0; S, 0. $C_7H_{10}N_2O$ requires C, 60·9; H, 7·3; N, 20·3%). The substance was neutral.

3-*Amino*-1,2-*dimethyl*-4-*thiocarbamoyl*-3-*pyrroline* (XIII).—1,2-Dimethyl-4-thiocarbamoyl-3-pyrroline (10 g.), suspended in water (70 ml.), was treated at 20° with 10N-sodium hydroxide (70 ml.) and left overnight and the solid (1·7 g.), m. p. 188—192° (decomp.), was then collected. Crystallisation from ethanol gave the *pyrroline hydrate* as octagonal plates, m. p. 200—202°, $\lambda_{max.}$ 207, 280, and 343 mμ (ε 9440, 11,100, and 17,200) (Found: C, 44·5; H, 8·0; N, 22·3; S, 17·2%; equiv., 189. $C_7H_{13}N_3S,H_2O$ requires C, 44·4; H, 8·0; N, 22·2; S, 16·9%; *M*, 189), p*K* 6·6.

4-*Carbamoyl*-1,2-*dimethyl*-3-*pyrroline Picrate* (cf. XIV).—3-Mercapto-1,2-dimethyl-4-thiocarbamoyl-3-pyrroline (5 g.) in cold 5N-sodium hydroxide (50 ml.) was treated cautiously with 1 : 1 nickel–aluminium alloy (10 g.); the temperature of the mixture rose to 90°. Water (20 ml.) was added, and the mixture kept at 95° for 2 hr., cooled to 35°, filtered, and extracted with chloroform (5 × 50 ml.). The bulked extracts were dried (Na_2SO_4), then concentrated under reduced pressure and treated with an excess of picric acid (1 g.) in ethanol (20 ml.). Overnight, the *pyrroline picrate* (0·3 g.) separated as needles, m. p. 154—156°, $\lambda_{max.}$ 259 mμ ($E^{1\%}_{1cm.}$ 427, this corresponds to *M* = 365—370 if absorption is due to picric acid [11]) (Found: C, 42·2; H, 4·2; N, 18·7; S, 0. $C_7H_{12}N_2O,C_6H_3N_3O_7$ requires C, 42·3; H, 4·1; N, 19·0%; *M*, 369).

2-(1,5-*Dimethylpyrrol*-3-*yl*)-4-*phenylthiazole* (XV; R = H).—1,2-Dimethyl-4-thiocarbamoylpyrrole (6·16 g.) in propan-2-ol (200 ml.) was refluxed for 1 hr. with ω-bromoacetophenone (7·96 g.), to give a yellow solution which, on cooling, gave the *thiazole hydrobromide* (12·5 g., 93%) as needles, m. p. 212—215°, $\lambda_{max.}$ 250 and 352 mμ (ε 11,900 and 18,500 in 0·1N-HCl) (Found: C, 53·4; H, 4·7; N, 8·2. $C_{15}H_{14}N_2S,HBr$ requires C, 53·7; H, 4·5; N, 8·4%), p*K* 2·7. The free *thiazole* crystallised from chloroform–light petroleum (b. p. 40—60°) as orange prisms, m. p. 134—135°, $\lambda_{max.}$ 208, 246, 280, and 314 mμ (ε 25,300, 22,500, 13,300, and 11,900) (Found: C, 70·8; H, 5·6; S, 12·5. $C_{15}H_{14}N_2S$ requires C, 70·9; H, 5·6; S, 12·6%).

2-(1,5-*Dimethylpyrrol*-3-*yl*)-4-p-*nitrophenylthiazole* (XV; R = NO_2).—1,2-Dimethyl-4-thiocarbamoylpyrrole (0·77 g.) in propan-2-ol (50 ml.) was refluxed for 1 hr. with ω-bromo-*p*-nitroacetophenone (1·22 g.); a solid separated from the hot solution. The mixture was cooled and the *thiazole hydrobromide* (1·7 g., 90%) collected and crystallised from chloroform–ether as

[11] Cunningham, Dawson, and Spring, *J.*, 1951, 2305.

yellow needles, m. p. 245° (decomp.), $\lambda_{max.}$ 243 and 352 mμ (ε 8280 and 16,500) in 0·1N-HCl (Found: C, 47·8; H, 3·8; N, 11·0. $C_{15}H_{13}N_3O_2$,HBr requires C, 47·4; H, 3·7; N, 11·1%), pK 2·55.

4-p-*Aminophenyl*-2-(1,5-*dimethylpyrrol*-3-*yl*)*thiazole* (XV; R = NH_2).—2-(1,5-Dimethylpyrrol-3-yl)-4-*p*-nitrophenylthiazole hydrobromide (1·3 g.) in ethanol (100 ml.) was shaken with hydrogen, 5N-hydrobromic acid (0·55 ml.), and 10% palladised charcoal (0·25 g.); the stoicheiometric volume was absorbed in 10 min. The catalyst was filtered off and the filtrate concentrated under reduced pressure and treated with ether, to give the *thiazole dihydrobromide* (9·2 g., 63%) which crystallised from aqueous propan-2-ol containing a small quantity of hydrobromic acid as bronze needles, m. p. 300° (decomp.), $\lambda_{max.}$ 243 and 351 mμ (ε 11,900 and 18,400; in 0·1N-HCl) (Found: C, 42·0; H, 4·1; S, 7·6. $C_{15}H_{15}N_3S$,2HBr requires C, 41·8; H, 4·0; S, 7·4%), pK 2·55 and 3·80.

3-*Amino*-4-*ethoxycarbonyl*-1,2-*dimethyl*-3-*pyrroline* (XVII).—Ethyl β-methylaminopropionate (330 g.) was mixed with lactonitrile (187 g.), followed, when the initial reaction had ceased, by benzene (400 ml.). The free water (35 ml.) was removed and the solution refluxed, any further water (10 ml.) being collected azeotropically. The solution was concentrated, then added to a refluxing solution of sodium (11·6 g.) in t-butyl alcohol (800 ml.) and refluxed for 3 hr. The solution was concentrated under reduced pressure, dissolved in water (500 ml.), treated with acetic acid (30 ml.), and extracted with chloroform (2 × 200 ml.) and ethyl acetate (2 × 200 ml.). Concentration of the extracts and distillation gave the *pyrroline* (280 g., 60%), b. p. 116°/1·6 mm., m. p. 74—78°, $\lambda_{max.}$ 280 mμ (ε 15,400) (Found: C, 58·8; H, 9·0; N, 15·4. $C_9H_{16}N_2O_2$ requires C, 58·7; H, 8·8; N, 15·2%), pK 7·1.

When treated with hydrochloric acid as described for the analogous nitrile, the ethoxycarbonylpyrroline gave 1,2-dimethyl-3-pyrrolidone, b. p. 48°/18 mm., n_D^{20} 1·4423, in 70% yield.

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