838. *Applications of Proton Resonance Spectroscopy to Structural Problems. Part XXII.*[1] *3-Amino-4-cyanopyrrolines and their Transformation Products*

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Proton resonance spectra of the title compounds and some novel analogues confirm most of the structures previously suggested [2] and allow rationalisation of structure-physicochemical properties in this series.

A previous Paper [2] by one of us described the cyclisation of *N*-1-cyanoethyl-*N*-2-cyanoethylmethylamine (I) to 3-amino-4-cyano-1,2-dimethyl-3-pyrroline (II), reaction of compound (II) with hydrogen sulphides, and further transformations. Tentative structures were proposed [2] for the products but it appeared difficult to reconcile them with all the physical properties, *e.g.*, the apparent lack of basicity of compound (III). We have now examined these and related compounds by nuclear magnetic resonance (n.m.r.) spectroscopy. The results (Tables 1 and 2) confirm most of the previous structures;

Table 1

N.m.r. spectra of 3-pyrrolines (τ values for dichlorotetrafluoroacetone deuterohydrate except where otherwise specified)

Com-pound	Groups at position indicated									Notes
	1		2	3		4		5		
(II)	Me	7·12	Me 8·44 (2, *J* = 7); H *ca.* 5·7	NH_2	3·58 ^{a}	CN		H_2	5·93	*b, c*
(VII)	Me	7·18	Me_2 8·44	NH_2	3·53 ^{a}	CN		H_2	5·95	*b, c*
(X)	Me	7·17	Me_2 8·44	NH_2	2·61 ^{a}	$CSNH_2$	1·7 ^{a}	H_2	5·9	
(III)	Me	7·01	Me 8·35 (2, *J* = 7); H *ca.* 5·6	SH		$CSNH_2$	1·5 ^{a}	H_2	*ca.* 5·6	*d*
(VIII)	Me	7·11	Me_2 8·5	SH		$CSNH_2$	1·45 ^{a}	H_2	*ca.* 5·6	
(V)	CH_2Ph	5·6, 2·46	Me 8·42 (2, *J* = 7); H *ca.* 5·6	SH		$CSNH_2$	1·5 ^{a}	H_2	*ca.* 5·6	
(XIII)	CH_2Ph	5·45, ^{e} 2·48 ^{e}	Me_2 8·3	SH		$CSNH_2$	1·45 ^{a}	H_2	5·8	
(XVI)	Me	7·02	Me 8·42 (2, *J* = 7); H 5·76 (4, *J* = 7)	SMe	6·83	$CSNH_2$	1·4 ^{a}	H_2	5·39	*c, d*

For groups in the 2-position spin–spin coupling is indicated, in brackets, by the multiplicity followed by the spin–spin coupling in c./sec.

a, Measurement in Me_2SO. *b*, Measurements in $CHCl_3$ gave essentially similar results. *c*, Measurements in D_2O–D_2SO_4 gave essentially similar results. *d*, Measurements in HCO_2H gave essentially similar results. *e*, Measurements in $CF_3{\cdot}CO_2H$.

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[1] Part XXI, A. R. Katritzky and R. E. Reavill, *J.*, 1965, 3825.

[2] J. F. Cavalla, *J.*, 1962, 4664.

however, structure (IV), previously suggested for the methylation product of compound (V), should, it is now shown, be replaced by structure (VI).

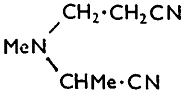
TABLE 2

N.m.r. spectra of 4-pyrrolines (τ values measured in dichlorotetrafluoroacetone deuterohydrate)

	Groups at positions indicated					
Compound	1		2	3	4	
(XIV)	CH_2Ph	5·15, 2·52	Me_2 8·48	:S	$CSNH_2$	H 1·35
(IX)	Me	6·56	Me_2 8·5	:S	$CSNH_2$	H 1·1
(XV)	Me	6·61	Me_2 8·56	:S	CN	H 1·72

The Δ^3-pyrrolines (Table 1) in dichlorotetrafluoroacetone deuterohydrate [3] show the expected features; in particular, the methylene peak at 5·6—5·95 τ and the absence of a vinylic proton exclude any Δ^4-pyrroline structures. The 1-methyl absorbs at 7·01—7·45 τ; a given dimethyl in the 2-position causes a sharp singlet at 8·3—8·5 τ whereas a single methyl in the 2-position shows as a doublet (J = 7 c./sec.) at 8·35—8·44 τ. A 3-amino-group may be seen in dimethyl sulphoxide solution as a broad band at 3·5—3·9 τ.

Although the pyrroline (II) yielded with hydrogen sulphide only one product, the structure of which is now confirmed as (III) (Table 1), the homologous pyrroline (VII) under similar conditions has now given three products: the expected thiol (VIII), a thione (IX), presumably formed by air oxidation, and the amine (X) derived by partial reaction. Again, 3-amino-1-benzyl-4-cyano-2-methyl-3-pyrroline (XI) gave only compound (V) with hydrogen sulphide, but the 2,2-dimethyl analogue (XII) has yielded both the thiol (XIII) and the thione (XIV). We cannot at present rationalise this difference in behaviour.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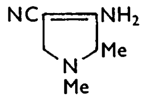
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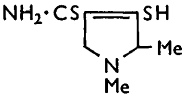
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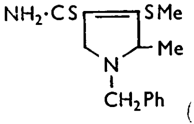
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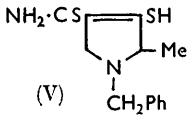
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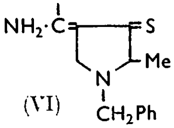
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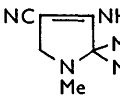
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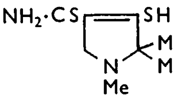
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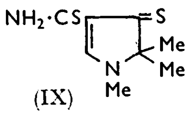
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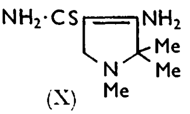
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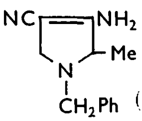
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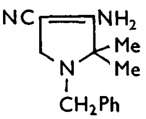
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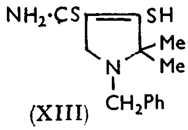
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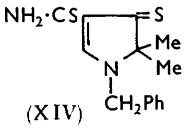
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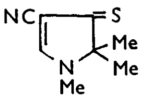
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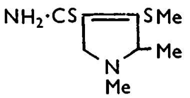
(XVI)

The oxidation of thione-thioamide (IX) with iodine gave the thione-nitrile (XV) in good yield, whereas, although the thioles (III) and (VIII) consumed oxidant, they formed no crystalline product. The structures of the 4-pyrroline-3-thiones are finally based on their n.m.r. spectra (Table 2),[4] and in particular on the 5-position vinyl proton peak at 1·1—

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[3] Personal communication from L. E. LuValle.

[4] N.m.r. spectra of 3-pyrrolines have been previously reported by R. L. Hinman and S. Theodoropulos, *J. Org. Chem.*, 1963, **28**, 3052.

1·22 τ. The low field at which this peak occurs reflects the electron-withdrawing nitrogen atom in the α-position and the two β-position electron-withdrawing substituents.

Compound (VI) showed *S*-methyl at 7·64 τ, *i.e.*, at *ca.* 1 p.p.m. to higher field than for the 1-methyl-3-methylthio-3-pyrroline (XVI). This indicates a difference of structure from (IV) (previously postulated) and the ultraviolet spectra and basicity data can best be rationalised in terms of structure (VI).

As reported previously the 3-mercapto-3-pyrroline (III) shows no basic properties on potentiometric titration under normal conditions; its basic p*K* has now been determined by the ultraviolet method as 2·55, and that of the 3-methylthio-analogue[5] as 2·65. The much lower basicity compared with that (6·13)[2] of compound (II) must be due to the adverse inductive effect of the sulphur atom(s); the magnitude of the effect is surprising.[6] The 1-benzyl-3-mercapto-3-pyrroline (V) is also a weak base, but its methylation product (VI) has[2] a basic p*K* of 5·65. Ultraviolet spectra are compared in Table 3, and afford further evidence for structure (VI).

TABLE 3

Ultraviolet spectra ($\lambda_{max.}$ in mμ, log ε in parentheses)

Compounds	pK_a *			0·1N-HCl			0·1N-NaOH	
3-Amino-compounds								
(I)	6·13				259 (4·10)			263 (4·09)
(VII)	6·37				259 (4·09)			263 (4·06)
(XI)	5·51			208 (3·95)	260 (4·06)		217 (4·18) †	264 (3·98)
(XII)	5·10			207 (3·78)	259 (4·10)		216 (4·20) †	262 (4·07)
				Ethanol ‡				
3-Mercapto-compounds								
(III)	2·55, 9·20		214 (4·06)	296 (3·26)	373 (4·37)	248 (3·52)	291 (3·48)	368 (4·33)
(VIII)	9·68		210 (4·10)	299 (3·39)	375 (4·37)	256 § (3·49)	296 (3·49)	369 (4·33)
(V)	8·55		208 (4·33)	304 (3·55)	375 (4·31)	249 (3·66)	291 (3·60)	365 (4·31)
(XIII)	9·10		208 (4·32)	298 (3·47)	376 (4·32)	256 § (3·49)	300 (3·52)	370 (4·27)
				0·1N-HCl				
Methylated-compounds								
(XVI)	2·65		256 (3·92)	311 (3·90)	372 (3·45)	240 (3·61)	303 (3·60)	365 (4·24)
(VI)	5·65	207 (4·28)		317 (3·84)	376 (3·83)		298 (3·96)	
4-Pyrroline-3-thiones								
(IX)	Neutral		268 (3·87)	326 (4·06)		260 (3·71)	327 (4·10)	380 (4·33)
(XIV)	Neutral		265 (3·97)	336 (4·06)	382 (4·29)	265 (3·92)	333 (4·15)	382 (4·32)
(XV)	Neutral	202 † (3·83)	266 (3·87)		382 (4·34)	268 (3·85)		382 (4·35)

* Determined in 50% ethanol. † Not wholly reliable. ‡ The 3-mercapto-compounds are not stable in 0·1N-HCl. § Shoulder.

EXPERIMENTAL

Reaction of 3-*Amino*-4-*cyano*-1,2,2-*trimethyl*-3-*pyrroline with Hydrogen Sulphide.*—A slow stream of hydrogen sulphide was passed through a stirred solution of 3-amino-4-cyano-1,2,2-trimethyl-3-pyrroline (45 g.) in propan-2-ol (350 ml.) containing pyridine (10 ml.) and triethylamine (10 ml.) at 50—60° for 20 hr. On being cooled and set aside, the solution deposited a yellow crystalline solid (26·5 g.), m. p. 138—142° (decomp.). The mother-liquor from this gave, on treatment with ether (100 ml.), a semi-crystalline solid (2 g.), m. p. 194—204° (decomp.) which, on recrystallisation from ethanol, gave 3-*mercapto*-1,2,2-*trimethyl*-4-*thiocarbamoyl*-3-*pyrroline* (VIII) as yellow plates (1·2 g.), m. p. 207—209° (decomp.) (Found: C, 47·3; H, 7·4; N, 13·6; S, 31·5. $C_8H_{14}N_2S_2$ requires C, 47·5; H, 7·0; N, 13·9; S, 31·7%).

The original solid (26·5 g.) was then recrystallised exhaustively from propan-2-ol to give

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[5] E. E. Sager, M. R. Schooley, A. S. Carr, and S. F. Acree, *J. Res. Nat. Bur. Stand.*, 1945, **35**, 521.

[6] Cf. J. Clark and D. D. Perrins, *Quart. Rev.*, 1964, **18**, 295.

1,2,2-*trimethyl*-4-*thiocarbamoyl*-4-*pyrroline*-3-*thione* (IX) as long yellow needles (6·5 g.), m. p. 219—221° (Found: C, 48·3; H, 6·2; N, 13·9; S, 32·2. $C_8H_{12}N_2S_2$ requires C, 48·0; H, 6·0; N, 14·0; S, 32·0%).

The bulked mother-liquors from this purification were concentrated and left to give almost colourless plates (4·3 g.), m. p. 180—203° (decomp.), which on crystallisation from propan-2-ol gave 3-*amino*-1,2,2-*trimethyl*-4-*thiocarbamoyl*-3-*pyrroline* (X) as colourless rhombs (3·4 g.), m. p. 204—207° (decomp.) (Found: C, 51·6; H, 8·2; N, 23·0; S, 16·8. $C_8H_{15}N_3S$ requires C, 51·9; H, 8·2; N, 22·7; S, 17·2%).

Reaction of 3-*Amino*-1-*benzyl*-4-*cyano*-2,2-*dimethyl*-3-*pyrroline with Hydrogen Sulphide*.—A slow stream of hydrogen sulphide was passed through a stirred solution of 3-amino-1-benzyl-4-cyano-2,2-dimethyl-3-pyrroline (20 g.) in propan-2-ol (500 ml.) with pyridine (60 ml.) and triethanolamine (40 ml.) at 50—60° for 24 hr. On being cooled and set aside, a yellow solid separated (2·0 g.), m. p. 204—216° (decomp.) which, after boiling with aqueous propan-2-ol or propan-2-ol alone, gave pure 1-*benzyl*-3-*mercapto*-2,2-*dimethyl*-4-*thiocarbamoyl*-3-*pyrroline* (XIII) as yellow microcrystals (1·7 g.), m. p. 220—221° (decomp.) (Found: C, 60·5; H, 6·6; N, 10·1; S, 22·9. $C_{14}H_{18}N_2S_2$ requires C, 60·4; H, 6·5; N, 10·1; S, 23·0%).

The mother-liquor was treated with more pyridine (25 ml.) then retreated as before with hydrogen sulphide (further 24 hr.). On standing, the solution deposited leaf-like plates (4·4 g.), m. p. 185—197°, which after two crystallisations from propan-2-ol gave 1-*benzyl*-2,2-*dimethyl*-4-*thiocarbamoyl*-4-*pyrroline*-3-*thione* (XIV) as yellow needles, m. p. 194—199° (Found: C, 60·9; H, 6·0; N, 10·2; S, 23·0. $C_{14}H_{16}N_2S_2$ requires C, 60·9; H, 5·8; N, 10·1; S, 23·2%).

The mother-liquor from this material was concentrated and treated with ether to give a pale yellow solid (5·1 g.), m. p. 150—160°, which was shown by its i.r. spectrum to be predominantly starting material.

3-*Amino*-1-*benzyl*-4-*cyano*-2,2-*dimethyl*-3-*pyrroline* (XII).—β-Benzylaminopropionitrile (666 g.) was kept with acetone cyanohydrin (372 g., 1·05 mol.) at 50° for 3 days, benzene (1 l.) was added and the water separated. The solution was then boiled under reflux, using a Dean and Stark head, until free from water (8 hr.). More acetone cyanohydrin (40 ml.) was then added and the reflux continued for a further 8 hr. A total of 63 ml. of water was collected (theory 74·5 ml.). The solution was concentrated and the residue cyclised with a solution of sodium (19·5 g.) in boiling t-butyl alcohol (1 l.), as described earlier,[2] to give the crude pyrroline (594 g., 60%), m. p. 161—168°, which, on two crystallisations from propan-2-ol, gave white plates, m. p. 182—184° (Found: C, 73·9; H, 7·8; N, 18·7. $C_{14}H_{17}N_3$ requires C, 74·0; H, 7·5; N, 18·5%).

4-*Cyano*-1,2,2-*trimethyl*-4-*pyrroline*-3-*thione* (XV).—1,2,2-Trimethyl-4-thiocarbamoyl-3-pyrroline-3-thione (100 mg.) in warm ethanol (20 ml.) containing sodium acetate trihydrate (0·136 g.) was titrated with 0·1N-I_2/KI to visual excess (reqd. 11·5 ml.); the solution was concentrated, water added, and the product isolated with chloroform and crystallised from propan-2-ol to give yellow needles of the *nitrile* (70 mg.), m. p. 201—203° (Found: C, 57·8; H, 6·2; N, 17·1; S, 19·1. $C_8H_{10}N_2S$ requires C, 57·8; H, 6·1; N, 16·9; S, 19·3%).

The n.m.r. spectra were measured at 40 Mc./sec. on a Perkin-Elmer spectrometer with sample spinning. Concentrations were *ca.* 10% w/v.

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