Pyrrolo[2,3-*d*]pyrimidines. Synthesis from 4-Pyrimidylhydrazones, a 2-Bis(methylthio)methyleneaminopyrrole-3-carbonitrile, and a Pyrrolo-[2,3-*d*][1,3]thiazine-2(1*H*)-thione

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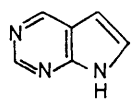
The synthesis of pyrrolo[2,3-*d*]pyrimidines and 5,6,7,8-tetrahydropyrimido[4,5-*b*]indoles by means of a thermally induced cyclisation of 4-pyrimidylhydrazones is shown to be of limited generality owing to the high reaction temperatures required, and to steric constraints on the [3,3] sigmatropic shift involved.

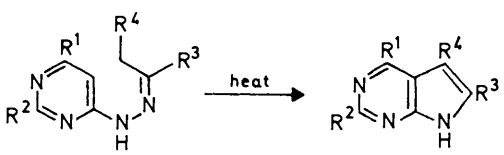
4,7-Dihydro-4-imino-5-phenylpyrrolo[2,3-*d*][1,3]thiazine-2(1*H*)-thione was conveniently prepared from 2-amino-4-phenylpyrrole-3-carbonitrile and proved to be a useful intermediate, both for the production of two series of 4-iminopyrrolo[2,3-*d*]pyrimidines, and for the synthesis of a 1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dithione and two 2-thioxo-4-ketones.

ONLY three successful routes to pyrrolo[2,3-*d*]pyrimidines (1) had been reported at the start of our work. Crooks and Robinson [1] had described a thermally induced conversion of 4-pyrimidylhydrazones [*e.g.* (2) and (3)] into pyrrolo[2,3-*d*]pyrimidines [(11) and (12)], a reaction similar to Fischer's indole synthesis, and Taylor and Hendess [2] had demonstrated that 2-amino-5-mercaptopyrrole-3-carbonitrile could be induced to react with formamidine acetate to yield the 4-aminopyrrolo[2,3-*d*]pyrimidine (26) directly, although with much decomposition of the pyrrole. A similar reaction [3] with 2-amino-5-bromopyrrole-3,4-dicarbonitrile had furnished the corresponding aminopyrrolopyrimidine (27) in better yield. Both of the latter groups [2,3] had also reported the synthesis of a series of 4-amino- and 4-alkylamino-pyrrolopyrimidines (28) by a three-step route from similar starting materials involving 2-methoxymethyleneamino- and 2-amidinopyrroles as intermediates.

In view of our previous work on the closely related pyrrolo[2,3-*b*]pyridines,[4] we first investigated the extension of the route from pyrimidines. The pyrimidylhydrazines were prepared by literature methods and converted into the 4-pyrimidylhydrazones (4)—(10) by direct condensation with the appropriate carbonyl compounds. Each hydrazone was heated under reflux in 2,2′-oxydiethanol or 2,2′-ethylenedioxydiethanol in a nitrogen atmosphere until no further evolution of ammonia occurred or, if no basic gas was detected, until the reaction mixture began to decompose. The method proved to be of limited generality in that only two



(1)



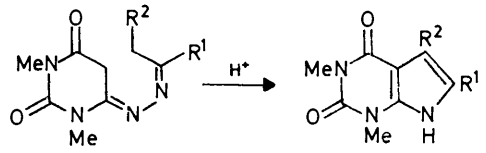
(2) $R^1=R^2=H$, $R^3R^4=[CH_2]_4$
(3) $R^1=R^2=H$, $R^3=R^4=Me$
(4) $R^1=R^2=R^3=Me$, $R^4=Ph$
(5) $R^1=R^2=Me$, $R^3=Ph$, $R^4=H$
(6) $R^1=R^2=Me$, $R^3R^4=[CH_2]_4$
(7) $R^1=R^2=R^3=R^4=Me$
(8) $R^1=H$, $R^2=Me$, $R^3R^4=[CH_2]_4$
(9) $R^1=R^2=Ph$, $R^3R^4=[CH_2]_4$
(10) $R^1=R^2=R^3=Ph$, $R^3=H$

(11) $R^1=R^2=H$, $R^3R^4=[CH_2]_4$
(12) $R^1=R^2=H$, $R^3=R^4=Me$
(13) $R^1=R^2=Me$, $R^3R^4=[CH_2]_4$
(14) $R^1=H$, $R^2=Me$, $R^3R^4=[CH_2]_4$

[1] P. A. Crooks and B. Robinson, *Chem. and Ind.*, 1967, 549.
[2] E. C. Taylor and R. W. Hendess, *J. Amer. Chem. Soc.*, 1965, **87**, 1995.
[3] R. L. Tolman, R. K. Robins, and L. B. Townsend, *J. Amer. Chem. Soc.*, 1968, **90**, 524; 1968, **91**, 2102.
[4] R. Herbert and D. G. Wibberley, *J. Chem. Soc.* (C), 1969, 1505.

hydrazones [(6) and (8)] were successfully cyclised. The resulting 5,6,7,8-tetrahydropyrimido[4,5-*b*]indoles, (13) and (14), were identified by their spectra, in particular the shift in the i.r. absorption in the NH region (3330 ⟶ 3150 cm^{-1}), and the absence of any signal indicative of a pyrimidine 5-proton in the n.m.r. spectra. Here, as in earlier work,[1,3] the high temperatures required in thermally induced cyclisations cause extensive decomposition and the formation of by-products.

A series of hydrazones [(15)—(19)] were synthesised in which protonation was expected to occur on an exocyclic O atom rather than on a ring N atom, in order to investigate their acid-catalysed cyclisation. Only the cyclohexanone and benzyl methyl ketone hydrazones [(15) and (16)] could be cyclised by heating



(15) $R^1R^2 = [CH_2]_4$ (20) $R^1R^2 = [CH_2]_4$

(16) R^1 = Me, R^2 = Ph (21) R^1 = Me, R^2 = Ph

(17) R^1 = H, R^2 = Me (22) $R^1 = R^2$ = Me

(18) R^1 = H, R^2 = Ph

(19) $R^1 = R^2$ = Me

in acetic acid solution. The propionaldehyde and phenylacetaldehyde hydrazones [(17) and (18)] yielded unchanged starting material, the hydrazone (15) gave a much higher yield of the pyrimido[4,5-*b*]-indole (20) by thermal cyclisation, and the butanone hydrazone (19) was similarly successfully cyclised to the pyrrolo[2,3-*b*]pyrimidine (22). During our work Senda and Hirota [5] recorded the synthesis of seven pyrrolo-[2,3-*b*]pyrimidines derived from 1,3-dimethyl-2,6-dioxo-4-pyrimidylhydrazones, including the examples we have reported here [(20)—(22)]. These authors gave no spectroscopic or analytical data but our practical results are in accord with their findings. The same authors, however, state that acid-catalysed cyclisations are unsuccessful and that the thermally induced cyclisations proceed by an intramolecular nucleophilic attack at the pyrimidine 5-position. There is no evidence that any Fischer indole-type cyclisations involve such a nucleophilic attack, but, rather than the intramolecular electrophilic mechanism normally postulated for acid-catalysed reaction, we suggest, in common with other workers,[6] that thermally induced reactions are best represented by a concerted mechanism. In such a process the formation of the new C–C bond would involve a [3,3] sigmatropic shift and would be markedly affected by large substituents at position 4. The final cyclisation to an indolised product would require several subsequent steps where an acid catalyst would be advantageous.

1,3-Dimethyl-5,6,7,8-tetrahydro-1*H*-pyrimido[4,5-*b*]-indole-2,4(3*H*,9*H*)-dione (20) was injected intraperitoneally into mice which had been inoculated with R_1 lymphoma and TLX/5 Ascites tumours. There was no increase in survival time in the treated animals compared with a control group.

2-Amino-4-phenylpyrrole-3-carbonitrile (23) was readily prepared [7] and converted into the monoamide (24), 2-acetamido-4-phenylpyrrole-3-carboxamide, and the urea (25) by standard methods. However, the attempted conversion of all these compounds into pyrrolo[2,3-*d*]pyrimidines by methods previously used for other fused pyrrolopyrimidines was unsuccessful. Thus the amino-nitrile (23) and formamide or guanidine yielded tarry intractable products, the amide (24) and dry hydrogen chloride in ethanol gave the amine (23), and the same amide (24) was recovered unchanged after treatment with ethanolic ammonia at 100°. The pyrrolylurea (25) could not be induced to cyclise on treatment with bases, acetic acid, or phosphoric trichloride. Attempted cyclodehydration of 2-acetamido-4-phenylpyrrole-3-carboxamide by a number of methods was also unsuccessful: *e.g.* treatment with hydrochloric acid yielded the 2-amino-compound and refluxing in 2,2′-oxydiethanol gave the acylamino-nitrile (24). All these cyclisations require, at some stage, the attack of a nucleophile on a 3-carbonitrile or a 3-carboxamide, and the electrophilicity of such groups will be reduced by the π-excessive character of the pyrrole nucleus. An ester group is more electrophilic then a nitrile or an amide so we directed our attention to the synthesis of potentially useful *ortho*-amino-esters.

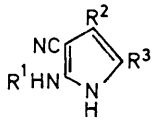
The known pyrrole diesters (29) and (30) were readily converted into the mononitro-derivatives (31) and (32) by treatment with a mixture of nitric and sulphuric acids at room temperature. Prolonged treatment of the methyl ester (39) gave the dinitro-derivative (33). The mononitro-esters (31) and (32) were reduced to the corresponding amines (35) and (36) with hydrogen over palladium–charcoal and the amine (36) was acetylated with acetyl chloride in dimethoxyethane in the presence of potassium carbonate. Attempted conversion of the acetamido-ester (37) into ethyl 2-methyl-4,7-dihydro-4-oxo-3*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylate by heating with aqueous or ethanolic ammonia in a steel bomb at 100° yielded the amino-diester (36), and stirring with ethanolic ammonia at room temperature for 30 days yielded the pyrrole-4-carboxamide (40).

Dimethyl 2-aminopyrrole-3,4-dicarboxylate (35) was dissolved in dry pyridine and heated under reflux with dry phenyl isocyanate. The product, isolated after removal of solvents and a little diphenylurea, proved to be not the expected pyrrolo[2,3-*d*]pyrimidine (41) but dimethyl 1,2,3,4-tetrahydro-2,4-dioxo-3-phenylpyrrolo-[1,2-*a*][1,3,5]triazine-7,8-dicarboxylate (42). This is the first synthesis of a pyrrolo[1,2-*a*][1,3,5]triazine, but

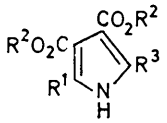
[5] S. Senda and K. Hirota, *Chem. Letters*, 1972, 367.
[6] B. Robinson, *Chem. Rev.*, 1969, **69**, 227; T. L. Gilchrist and R. C. Storr, 'Organic Reactions and Orbital Symmetry,' Cambridge University Press, 1972, p. 234.
[7] K. Gewald, *Z. Chem.*, 1961, **1**, 349.

further work [8] has shown that this is a general method for the preparation of such compounds and that reasonable intermediates are the ureides (38) and biurets (39). Treatment of dimethyl 2-amino-1-methylpyrrole-3,4-dicarboxylate with phenyl isocyanate in pyridine gave only an intractable tar.

Functional groups containing SH or S are usually powerful nucleophiles and the failures, described above, of any *N*-containing nucleophile to react with 3-cyano,

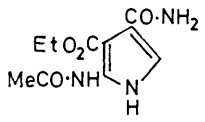


(23) $R^1 = R^3 = H$, $R^2 = Ph$
(24) $R^1 = MeCO$, $R^2 = Ph$, $R^3 = H$
(25) $R^1 = PhNHCO$, $R^2 = Ph$, $R^3 = H$



(29) $R^1 = R^3 = H$, $R^2 = Me$
(30) $R^1 = R^3 = H$, $R^2 = Et$
(31) $R^1 = NO_2$, $R^2 = Me$, $R^3 = H$
(32) $R^1 = NO_2$, $R^2 = Et$, $R^3 = H$
(33) $R^1 = R^3 = NO_2$, $R^2 = Me$
(34) $R^1 = NO_2$, $R^2 = R^3 = H$
(35) $R^1 = NH_2$, $R^2 = Me$, $R^3 = H$
(36) $R^1 = NH_2$, $R^2 = Et$, $R^3 = H$
(37) $R^1 = MeCO{\cdot}NH$, $R^2 = Et$, $R^3 = H$
(38) $R^1 = PhNH{\cdot}CO{\cdot}NH$, $R^2 = Me$, $R^3 = H$
(39) $R^1 = PhN(CO{\cdot}NHPh){\cdot}CONH$, $R^2 = Me$, $R^3 = H$

(26) $R^1 = H$, $R^2 = CN$, $R^3 = SH$
(27) $R^1 = H$, $R^2 = CN$, $R^3 = Br$
(28) $R^1 = H$ or alkyl, R^2, R^3 = various



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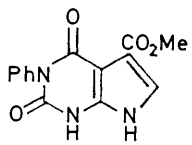

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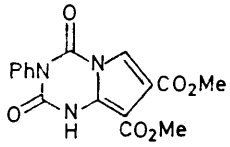


(42)

longer period of refluxing of the pyrrole (23) with carbon disulphide and pyridine gave the pyrrolopyrimidinethione (45) directly.

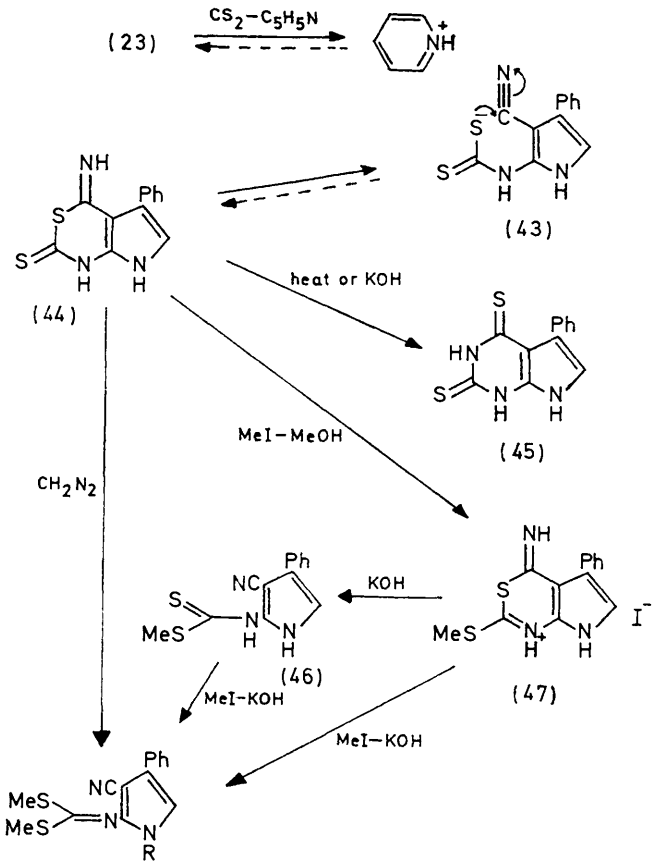
Four different methylation products could be obtained from the 4-iminopyrrolothiazine-2(1*H*)-thione (44) by variation of conditions. Thus use of methyl iodide in methanol under reflux for 1 h gave the pyrrolothiazine hydroiodide (47), the structure of which was shown by its n.m.r. and mass spectra and its ready hydrolysis to the -carbamoyl, or -alkoxycarbonyl functions led us to consider the intramolecular cyclisation of dithiocarbamates (43). The product from such a cyclisation would be a pyrrolo[2,3-*d*][1,3]thiazine-2(1*H*)-thione (44) and, although such compounds are unknown, fused imidazo[1,3]thiazine-2(1*H*)-thiones have been converted into purines by treatment with base.[9] Similar treatment of (44) could presumably yield the pyrrolo[2,3-*d*]-pyrimidinedithione (45). 2-Amino-4-phenylpyrrole-3-carbonitrile with an excess of carbon disulphide and pyridine for 2 under reflux yielded the required pyrrolothiazine-2(1*H*)-thione (44). Treatment of the product (44) with aqueous potassium hydroxide on a steam-bath for 0·5 h yielded the required pyrrolopyrimidinedithione (45) (50%) together with the pyrrole (23) (21%). A methyl dithiocarbamate (46). Treatment of the pyrrolothiazine (44) with methyl iodide in the presence of potassium hydroxide, or of the dithiocarbamate (46) with the same reagents, or of the same pyrrolothiazine (44) with diazomethane yielded the bis(methylthio)-methyleneaminopyrrole (48). Prolonged treatment [of (44)] with diazomethane yielded the trimethylated product (49) in yields which increased with increased time of reaction. The thiazine ring is thus extremely susceptible to ring-opening at the 3,4-bond and may well exist partly in the dithiocarbamic acid form (43) in polar solvents.

The 4-iminopyrrolothiazine-2(1*H*)-thione (44) proved to be a versatile intermediate for the synthesis of 3-substituted pyrrolo[2,3-*d*]pyrimidine-2(1*H*)-thiones

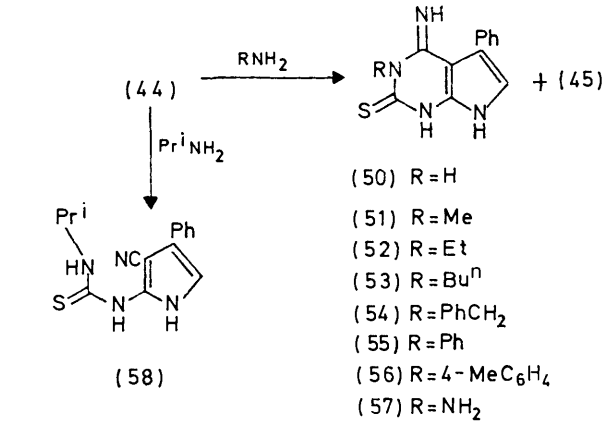
[8] J. R. Traynor, Ph.D. Thesis, University of Aston in Birmingham, 1973.

[9] E. C. Taylor, A. McKillop, and R. N. Warrener, *Tetrahedron*, 1967, **23**, 891.

[(50)—(57)]. Treatment of (44) with aqueous amines under reflux for a short period furnished various amounts



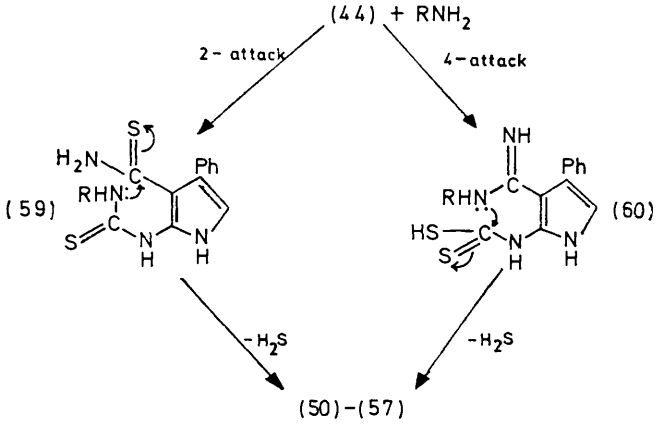
of the required 3-substituted pyrrolo[2,3-*d*]pyrimidine-2(1*H*)-thiones (50)—(57) together with the pyrrolopyrimidinedithione (45). The use of anhydrous amines



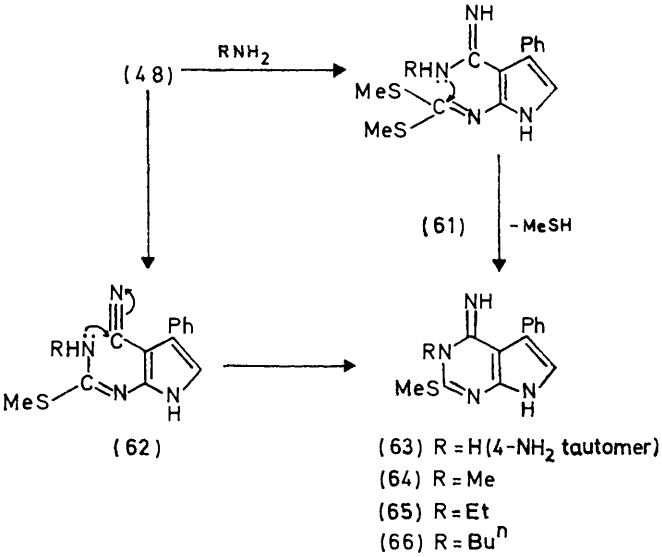
in sealed reaction vessels afforded only the desired 3-substituted compounds, usually in high yield (see Experimental section). Isopropylamine yielded the thioureido-nitrile (58) under both sets of reaction conditions.

[10] G. Wagner and L. Rothe, *Z. Chem.*, 1968, **8**, 377.

In theory the thiazine ring could be attacked by amines at either the 2- or the 4-position; hence both the *o*-thioureido-thioamide (59) and the *o*-amidino-dithiocarbamic acid (60) or tautomers or anions of these two compounds are reasonable intermediates in the formation of the 3-substituted pyrrolopyrimidines (50)—(57). In the case of isopropylamine, attack at the 2-position appears the most likely but, in the successful ring opening and ring closure reactions to yield the 3-substituted compounds (50)—(57) the weight of evidence appears to



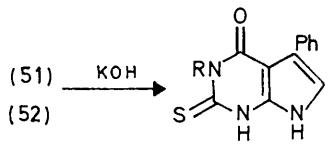
favour attack at the 4-position, with formation of intermediates of type (60). For example, previous workers [10] have demonstrated, by the isolation of intermediates, that amines attack benzothiazinedithiones at the 4-position. None of our earlier attempts to effect a nucleophilic attack by an N-containing group on the 3-carbonitrile, 3-carboxamide, or 3-ester had been successful so we had no evidence that (59) would cyclise in the manner indicated and, finally, intermediate (60) contains more reactive nucleophilic and electrophilic groupings than compound (59).



If amidines [*e.g.* (60)] are the intermediates in these reactions then the *o*-cyano-bis(methylthio)methyleneamino-pyrrole (48) should be a potential starting

material for a new route to pyrrolopyrimidines involving the amidines (61) as intermediates. In this case the alternative route *via* the thioureido-nitriles (62) is equally feasible. The 4-amines investigated gave excellent yields of the pyrrolopyrimidines (63)—(66). In the case of the product from ammonia spectroscopic evidence showed the presence of the 4-amino-tautomer (63). Two of the compounds [(64) and (66)] were also obtained by methylation of the corresponding thiols, (51) and (53).

The Dimroth rearrangement has been effected with certain pyrrolo[2,3-*d*]pyrimidines [2] and with other fused 3-substituted 4-iminopyrimidines.[11] Accordingly, the 3-methyl-4-iminopyrrolopyrimidine (51) was treated with hot aqueous alkali for several hours, until dissolution was complete. No evidence for a Dimroth rearrangement was obtained, however, and the only



(67) R = Me
(68) R = Et

isolated product was the pyrrolopyrimidin-4-one (67). The 3-ethyl derivative similarly yielded (68).

induced. A solution of the appropriate hydrazone was heated under reflux in 2,2′-oxydiethanol or 2,2′-ethylenedioxydiethanol in a nitrogen atmosphere, either until the evolution of alkaline vapours had ceased or until the reaction mixture began to char. The mixture was cooled, poured into water, and extracted with ether. The product was isolated by the stated procedure.

(B) *Acid-catalysed*. The hydrazone and acetic acid (10 cm³ per g) were heated together under reflux on a steam-bath for the stated time and the product was isolated as described.

The hydrazone (6) in 2,2′-oxydiethanol (24 h) [method (A)] yielded, on evaporation of the ethereal extract, 5,6,7,8-*tetrahydro*-2,4-*dimethyl*-9H-*pyrimido*[4,5-b]*indole* (13) (45%), needles, m.p. 243—245° (from ethanol–light petroleum, 3 : 1) (Found: C, 71·4; H, 7·4; N, 20·8%; M^+, 201. $C_{12}H_{15}N_3$ requires C, 71·6; H, 7·4; N, 20·8%; *M*, 201), $\nu_{max.}$ (KBr) 3150 (NH) cm^{-1}, τ ($CDCl_3$) 7·15 (4H, m, 5- and 8-H_2), 7·26 (3H, s, 2- or 4-Me), 7·29 (3H, s, 2- or 4-Me), and 8·14 (4H, m, 6- and 7-H_2). The hydrazone (8) in 2,2′-oxydiethanol (24 h) [method (A)] yielded, on evaporation of the ethereal extract, the 5,6,7,8-*tetrahydro*-2-*methyl*-9H-*pyrimido*[4,5-b]-*indole* (14) (98%), needles, m.p. 270—272° (from ethanol–light petroleum, 3 : 1) (Found: C, 66·7; H, 7·0; N, 20·3%; M^+, 187·110585. $C_{11}H_{13}N_3,0{\cdot}5H_2O$ requires C, 67·3; H, 7·1; N, 20·5%. $C_{11}H_{13}N_3$ requires *M*, 187·110942), $\nu_{max.}$ (Nujol) 3125 (NH) cm^{-1}, τ ($CDCl_3$) 1·80 (1H, s, 4-H), 7·72 (3H, s, 2-Me), 7·6—8·1 (4H, m, 5- and 8-H_2), and 8·4—8·9 (4H, m, 6- and 7-H_2). The hydrazone (15) in 2,2′-oxydiethanol (24 h) [method (A)] yielded, on pouring into water,

Physical and analytical data for the pyrimidylhydrazones *

Compound	Yield (%)	M.p. (°C)	Found C(%)	Found H(%)	Found N(%)	Found M^+	Formula	Required C(%)	Required H(%)	Required N(%)	Required *M*
(4)	37	67—68	70·0	7·0	21·0	254	$C_{15}H_{18}N_4$	70·8	7·1	21·6	254
(5) *	54	130—133									
(6)	87	129—130	66·1	8·3	25·8	218	$C_{12}H_{18}N_4$	66·1	8·3	25·7	218
(7) *	43	190—193									
(8)	24	115—116	58·8	7·8	25·2	204	$C_{11}H_{16}N_4,H_2O$	59·4	8·1	25·2	204
(9)	70	158—159	77·0	6·5	16·1	342	$C_{22}H_{22}N_4$	77·2	6·4	16·4	342
(10)	75	181—182	79·0	6·5	15·3	364	$C_{24}H_{20}N_4$	79·1	6·6	15·4	364
(15)	78	134—135	57·4	7·2	22·3	250	$C_{12}H_{18}N_4O_2$	57·6	7·2	22·4	250
(16)	83	133·5—134	60·2	6·3	18·4	286	$C_{15}H_{18}N_4O_2,0{\cdot}5H_2O$	60·5	6·4	18·9	286
(17)	61	196—197	51·2	6·7	26·5	210	$C_9H_{14}N_4O_2$	51·4	6·7	26·6	210
(18)	69	157 (decomp.)	61·7	6·0	20·8	272	$C_{14}H_{16}N_4O_2$	61·7	5·9	20·6	272
(19)	84	130—132	53·5	7·1	25·0	224	$C_{10}H_{16}N_4O_2$	53·5	7·1	25·0	224

* Satisfactory i.r. and n.m.r. spectra were obtained for all compounds; (5) and (7) were used without further purification.

Treatment of the pyrrolopyrimidinedithione (45) with methyl iodide and aqueous alkali yielded 2,4-bismethylthio-5-phenylpyrrolo[2,3-*d*]pyrimidine.

EXPERIMENTAL

I.r. spectra were determined, for Nujol mulls or potassium bromide discs, with a Unicam SP 200, n.m.r. spectra with a Varian A-60A, and mass spectra with an A.E.I. MS9 spectrometer. ' Light petroleum ' refers to the fraction of b.p. 60—80°. An asterisk after a chemical shift value indicates that the signal disappeared on deuteriation.

Pyrimidylhydrazones (*Table*).—Equimolar quantities of the 4-pyrimidylhydrazine and the carbonyl compound were heated on a steam-bath in the absence of solvent, or [in the case of 6-hydrazino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione or volatile carbonyl materials] with an equal volume of ethanol, for 5—20 min.

Cyclisation of the Pyrimidylhydrazones.—(A) *Thermally*

5,6,7,8-tetrahydro-1,3-dimethyl-9*H*-pyrimido[4,5-*b*]indole-2,4(1*H*,3*H*)-dione (20) (80%) [also obtained (54%) by method (B) (3 h)], needles, m.p. 325° (decomp.) (from ethanol) (Found: C, 60·6; H, 6·5; N, 17·3%; M^+, 233. Calc. for $C_{12}H_{15}N_3O_2,0{\cdot}33H_2O$: C, 60·3; H, 6·5; N, 17·6%. Calc. for $C_{12}H_{15}N_3O_2$: *M*, 233), $\nu_{max.}$ (KBr) 3200 (NH), 2800 (aliphatic CH), and 1680 and 1670 (C=O) cm^{-1}, τ [$(CD_3)_2SO$] 6·40—6·70 (4H, m, 5- and 8-H_2), 6·53 (6H, s, 1- and 3-Me), and 7·30—7·60 (4H, m, 6- and 7-H_2). The hydrazone (16), by method (B), yielded, after evaporation to dryness and trituration with ether, 1,3,6-trimethyl-5-phenyl-7*H*-pyrrolo-[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (21) (42%), needles, m.p. 300° (decomp.) (from dimethylformamide–water, 3 : 1) (Found: C, 64·9; H, 5·6; N, 15·6%; M^+, 269. Calc. for $C_{15}H_{15}N_3O_2,0{\cdot}5H_2O$: C, 64·7; H, 5·7; N, 15·1%. Calc. for

[11] E. C. Taylor and A. McKillop, ' The Chemistry of Cyclic Enamino-nitriles and *o*-Aminonitriles,' Interscience, New York, 1970.

$C_{15}H_{16}N_3O_2$: *M*, 269), $\nu_{max.}$ (KBr) 3150 (NH), 1680 and 1670 (C=O) cm^{-1}. The hydrazone (19) in 2,2′-oxydiethanol (7 h) [method (A)] yielded, on trituration of the residue from evaporation of the ethereal extract with ethyl acetate, 1,3,5,6-tetramethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (22) (60%), needles, m.p. 300° (decomp.) (from ethanol) (Found: C, 57·5; H, 6·2; N, 20·1%; M^+, 207·100471. Calc. for $C_{10}H_{13}N_3O_2$: C, 57·9; H, 6·3; N, 20·3%; *M*, 207·100770), $\nu_{max.}$ (Nujol) 3200 (NH), and 1690 (C=O) cm^{-1}. The hydrazones (4) [method (A)] and (19) [method (B)] both gave gums from which low yields of solids were obtained which were not fully characterised. Unchanged starting materials were obtained from the hydrazones (9) [method (A), 2,2′-oxydiethanol] and (17) and (18) [method (B)] and intractable tars from the hydrazones (5) and (7) [method (A), 2,2′-oxydiethanol] and (9) [method (A), 2,2′-ethylenedioxydiethanol].

2-*Acetamido*-4-*phenylpyrrole*-3-*carbonitrile* (4).—2-Amino-4-phenylpyrrole-3-carbonitrile (0·69) [prepared [4] in 52% yield; m.p. 175° (decomp.)] was heated with acetic anhydride (6 cm^3) on a steam-bath for 10 min. The mixture was cooled to yield the *acetamidopyrrole* (0·55 g, 75%), plates, m.p. 290° (decomp.) (from methanol) (Found: C, 68·5; H, 5·1; N, 17·9%; M^+, 225·090350. $C_{13}H_{11}N_{30}$ requires C, 69·3; H, 4·9; N, 18·6%; *M*, 225·090207), $\nu_{max.}$ (Nujol) 3300 and 3225 (NH), 2250 (C≡N), and 1665 (amide C=O) cm^{-1}, τ [$(CD_3)_2SO$] 2·94 (1H, s, 5-H) and 2·2—2·7 (5H, m, Ph).

N-(3-*Cyano*-4-*phenylpyrrol*-2-*yl*)-N′-*phenylurea* (25).—2-Amino-4-phenylpyrrole-3-carbonitrile (0·9 g) and freshly distilled phenyl isocyanate (0·7 g) were heated under reflux in dry benzene (50 cm^3) for 15 h to give the *pyrrolylurea* (0·8 g, 54%), needles, m.p. 199—200° (from benzene) (Found: C, 70·7; H, 4·7; N, 18·1%; M^+, 302·116184. $C_{18}H_{14}N_4O$ requires C, 71·5; H, 4·6; N, 18·5%; *M*, 302·116754), $\nu_{max.}$ (Nujol) 3380, 3375, and 3300 (NH), 2250 (C≡N), and 1695 (C=O cm^{-1}.

Dimethyl 2-*Nitropyrrole*-3,4-*dicarboxylate* (31).—Dimethyl pyrrole-3,4-dicarboxylate (6·0 g) was dissolved in concentrated sulphuric acid. Fuming nitric acid (2·3 g) was added and the solution stirred at room temperature for 0·5 h, then poured onto ice. The precipitated solid was collected, washed with water, and dried to yield the *nitropyrrole* (31) (5·9 g, 67%), prisms, m.p. 170—171° (from benzene) (Found: C, 41·4; H, 3·6; N, 12·0%; M^+, 228. $C_8H_8N_2O_6$ requires C, 42·1; H, 3·5; N, 12·2%; *M*, 228), $\nu_{max.}$ (KBr) 3225 (NH), 1735 and 1705 (C=O), and 1520 and 1360 (NO_2) cm^{-1}, τ ($CDCl_3$) 2·75 (1H, s, 5-H), 6·00 (3H, s, 3-CO_2Me), and 6·15 (3H, s, 4-CO_2Me). The nitropyrrole (31) (1·90 g) and methyl iodide (4·2 g) were added to a solution of sodium methoxide (0·53 g) in methanol (15 cm^3) at 0°. The mixture was left at room temperature for 20 h to yield *dimethyl* 1-*methyl*-2-*nitropyrrole*-3,4-*dicarboxylate*, m.p. 174—175° (from ethanol) (Found: C, 43·8; H, 4·1; N, 11·2%; M^+, 242·054317. $C_9H_{10}N_2O_6$ requires C, 44·6; H, 4·1; N, 11·5%; *M*, 242·053879), $\nu_{max.}$ (Nujol) 1730 and 1710 (C=O) and 1510 and 1330 (NO_2) cm^{-1}.

Dimethyl 2,5-*Dinitropyrrole*-3,4-*dicarboxylate* (33).—A similar nitration but with a reaction time of 40 h yielded the dinitropyrrole (33) (59%), m.p. 145—147° (from ethanol), M^+ 273, $\nu_{max.}$ (KBr) 3150 (NH), 1730 (C=O), 1530 and 1350 (NO_2) cm^{-1}, τ ($CDCl_3$) 6·03 (6H, s, 3- and 4-CO_2Me).

Diethyl 2-*Nitropyrrole*-3,4-*dicarboxylate* (32).—A similar nitration of diethyl pyrrole-3,4-dicarboxylate (24 h) yielded, after extraction of the aqueous solution adjusted to pH 6·0 with ether, the *nitropyrrole* (32), needles, m.p. 127—128° (from ethyl acetate–light petroleum, 1 : 1) (Found: C, 47·1; H, 4·7; N, 11·1%; M^+, 256. $C_{10}H_{12}N_2O_6$ requires C, 46·9; H, 4·7; N, 10·9%; *M*, 256), $\nu_{max.}$ (KBr) 3200 (NH), 1735 and 1700 (C=O), and 1530 and 1350 (NO_2) cm^{-1}, τ ($CDCl_3$) —1·30br (1H, s, NH), 2·46 (1H, s, 5-H), 5·60 (2H, q, *J* 7 Hz, 3-$CO_2{\cdot}CH_2{\cdot}CH_3$), 5·66 (2H, q, *J* 7 Hz, 4-$CO_2{\cdot}CH_2{\cdot}CH_3$), and 8·60 (3H, t, *J* 7 Hz, 4-$CO_2{\cdot}CH_2{\cdot}CH_3$).

Dimethyl 2-*Aminopyrrole*-3,4-*dicarboxylate* (35).—A solution of the nitropyrrole (31) (4·0 g) in ethanol (160 cm^3) was shaken in the presence of 10% palladium–charcoal (0·4 g) under hydrogen (4 atm) for 2·5 h and then filtered through Celite. The filtrate and washings were decolourised (charcoal) and evaporated to yield the *aminopyrrole* (3·7 g, 94%), m.p. 163—164° (from ethanol) (Found: M^+, 198·062942. $C_8H_{10}N_2O_4$ requires *M*, 198·064051), $\nu_{max.}$ (Nujol) 3450, 3275 and 3200 (NH), and 1720 and 1700 (C=O) cm^{-1}, τ (Me_2CO) 2·31 (1H, s, 5-H), 6·06 (3H, s, 4-CO_2Me), and 6·18 (3H, s, 3-CO_2Me). Similar reduction of dimethyl 1-methyl-2-nitropyrrole-3,4-dicarboxylate (1·20 g; 6 atm; 11 h) yielded dimethyl 2-amino-1-methylpyrrole-3,4-dicarboxylate (0·3 g, 55%) as a grey solid which decomposed rapidly on exposure to air at room temperature (Found: M^+, 212·080294. $C_9H_{12}N_2O_4$ requires *M*, 212·079700), $\nu_{max.}$ (Nujol) 3475 and 3350 (NH) and 1710 and 1670 (C=O) cm^{-1}.

Diethyl 2-*Aminopyrrole*-3,4-*dicarboxylate* (36).—Similar reduction of the nitro-ester (32) (1·0 g; 4 atm; 3 h) yielded the *aminopyrrole* (36) (0·95 g, 93%), prisms, m.p. 204—205° (from 1,2-dimethoxyethane) (Found: C, 53·1; H, 6·2; N, 12·3%; M^+, 226. $C_{10}H_{10}N_2O_4$ requires C, 53·1; H, 6·2; N, 12·4%; *M*, 226), $\nu_{max.}$ (Nujol) 3450, 3300, and 3200 (NH) and 1700 and 1665 (C=O) cm^{-1}, τ [$(CD_3)_2SO$] —0·80* (1H, s, NH), 2·90 (1H, s, 5-H), 5·52 (4H, q, *J* 7·5 Hz, 3- and 4-$CO_2{\cdot}CH_2{\cdot}CH_3$), and 8·40 (6H, t, *J* 7·5 Hz, 3- and 4-$CO_2{\cdot}CH_2{\cdot}CH_3$). Treatment of the amine (2·26 g) in 1,2-dimethoxyethane (120 cm^3) with potassium carbonate (5·0 g) and acetyl chloride (1·0 cm^3) for 20 h at 45° yielded, after filtration and evaporation, the corresponding 2-acetamidopyrrole (37) (1·9 g, 70%), $\nu_{max.}$ 3400 (NH), 1730, 1680, and 1670 (C=O) cm^{-1}, τ ($CDCl_3$) —1·15br* (1H, s, pyrrole NH), —0·15* (1H, s, NH·CO), 2·95 (1H, d, *J* 2 Hz, 5-H), 7·75 (3H, s, COMe), and 8·62 and 8·67 (6H, 2 × t, *J* 7 Hz, $CO_2{\cdot}CH_2{\cdot}CH_3$).

2-*Nitropyrrole*-3,4-*dicarboxylic Acid* (34).—The ester (31) (0·5 g) and 20% NaOH (5·0 cm^3) were heated under reflux for 30 min. The solution was cooled, acidified with hydrochloric acid, and extracted continuously with ether for 18 h. Evaporation of the extract yielded the *acid* (34) (0·25 g, 57%), m.p. 220° (decomp.) (from ethanol) (Found: M^+, 200·007509. $C_6H_4N_2O_6$ requires *M*, 200·006931), $\nu_{max.}$ (Nujol) 3450 and 3200 (NH), 1710 and 1685 (C=O), and 1530 and 1360 (NO_2) cm^{-1}, τ (Me_2CO), 2·31 (1H, d, 5-H) and 3·22br* (2H, s, 3- and 4-CO_2H).

2-*Acetamido*-4-*phenylpyrrole*-3-*carboxamide*.—The nitrile (24) (0·54 g), dissolved in sulphuric acid (3·8 g) and water (0·4 g), was stirred for 1·5 h at room temperature and then poured onto ice to yield the *diamide* (0·47 g, 80%), needles, m.p. 192—193° (from aqueous ethanol) (Found: C, 64·8; H, 5·7; N, 16·5%; M^+, 243·098385. $C_{13}H_{13}N_3O_2$ requires C, 64·2; H, 5·4; N, 17·3%; *M*, 243·100770), $\nu_{max.}$ (Nujol) 3350 and 3175 (NH) and 1660 and 1665 (C=O) cm^{-1}.

2-*Amino*-4-*phenylpyrrole*-3-*carboxamide*.—Dry hydrogen chloride was bubbled through a solution of 2-acetamido-4-phenylpyrrole-3-carbonitrile (1·25 g) in ethanol (30 cm^3)

for 10 h at room temperature (initial rise in temperature to 55°). The mixture was then heated under reflux for 10 min, cooled, and filtered to yield the 3-*carboxamide* (1·05 g, 94%), plates, m.p. 250° (decomp.) (from acetic acid) (Found: C, 56·0; H, 5·3; N, 17·5%; M^+, 201·091073. $C_{11}H_{11}N_3O_2,H_2O$ requires C, 55·7; H, 6·3; N, 17·7%. $C_{11}H_{11}N_3O$ requires M, 201·090207), $\nu_{max.}$ (Nujol) 3250, 3100, and 3050 (NH) and 1690 (C=O) cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 2·38 (5H, m, Ph) and 5·03 [2H, s, 2-H_2 (due to protonation at C-2 by solvent)].

The same amide was obtained in lower (24%) yield by hydrolysis of 2-acetamido-4-phenylpyrrole-3-carbonitrile with 10M-hydrochloric acid for 1 h under reflux. Attempted hydrolysis of 2-amino-4-phenylpyrrole-3-carbonitrile (23) with cold or warm sulphuric acid or sodium hydroxide in the presence of water yielded tars from which the required amide could not be isolated.

Attempted Cyclisation of Pyrrole-3-carbonitriles.—Only intractable solids were obtained by treatment of 2-amino-4-phenylpyrrole-3-carbonitrile with either boiling formamide or guanidine hydrochloride and sodium ethoxide in ethanol. Treatment of 2-acetamido-4-phenylpyrrole-3-carbonitrile with ethanolic ammonia at 100° for 20 h in a steel bomb yielded unchanged starting material (90%) and the same amido-nitrile was hydrolysed to the 2-amino-4-phenylpyrrole-3-carboxamide (see above) on attempted cyclisation with ethanolic hydrogen chloride. The urea (25) was unchanged on treatment with pyridine under reflux (4 h) or with sodium methoxide in methanol under reflux (16 h) and dark intractable products were formed on attempted cyclisation with phosphoric trichloride or dimethylformamide (reflux 18 h).

Attempted Cyclisation of Pyrrole 3-Esters.—Diethyl 2-acetamido-3,4-dicarboxylate (37) (0·2 g), ethanol (20 cm^3), and ammonia (*d* 0·88; 30 cm^3) were heated in a steel bomb at 100° for 18 h to yield, after removal of solvent, the amino-diester (36) (0·1 g, 41%). Hydrolysis to yield the same amino-diester also occurred when the reaction was repeated with ethanolic ammonia. A similar solution with ethanolic ammonia was stirred at room temperature for 30 days. Removal of the solvent left a tarry solid which on trituration with ether yielded *ethyl 2-acetamido-4-carbamoylpyrrole-3-carboxylate* (40) (0·2 g, 45%), m.p. 285° (decomp.) (from aqueous ethanol) (Found: C, 49·2; H, 5·4; N, 17·6%; M^+, 239·091680. $C_{10}H_{13}N_3O_4$ requires C, 49·3; H, 5·5; N, 17·2%; M, 239·090598), $\nu_{max.}$ (Nujol) 3400 and 3200 (NH), and 1680, 1660, and 1650 (C=O) cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 2·30 (1H, d, 5-H), 5·52 (2H, q, J 7 Hz, 3-$CO_2{\cdot}CH_2{\cdot}CH_3$), 7·50 (3H, s, 2-NH·CO·$CH_3$), and 8·53 (3H, t, J 7 Hz, 3-$CO_2{\cdot}CH_2{\cdot}CH_3$).

The amino-diester (35) (0·4 g), freshly distilled phenyl isocyanate (1·0 g), and anhydrous pyridine (10 cm^3) were heated together under reflux for 3 h in a carefully dried apparatus. The solvent was removed and the resultant gum triturated with chloroform to give diphenylurea (0·15 g). The chloroform filtrate was evaporated to yield a tarry solid which on trituration with acetone gave *dimethyl 1,2,3,4-tetrahydro-2,4-dioxo-3-phenylpyrrolo*[1,2-a][1,3,5]*triazine-6,7-dicarboxylate* (0·35 g, 51%), needles, m.p. 263—264° (from methanol) (Found: C, 55·8; H, 4·0; N, 12·3%; M^+, 343·080109. $C_{14}H_{11}N_3O_4$ requires C, 55·9; H, 3·8; N, 12·3%; M, 343·080427), $\nu_{max.}$ (Nujol) 3225 (NH) and 1750, 1720, 1715, and 1680 (C=O) cm^{-1}, τ [$(CD_3)_2SO$] 2·50 (5H, s, Ph), 4·43 (1H, s, 5-H), and 6·20 (6H, s, 6- and 7-CO_2Me). A similar reaction with dimethyl 2-amino-1-methylpyrrole-3,4-dicarboxylate in pyridine gave a black tar from which diphenylurea was the only solid product isolated.

4,7-Dihydro-4-imino-5-phenylpyrrolo[2,3-d][1,3]*thiazine-2(1H)-thione* (44).—2-Amino-4-phenylpyrrole-3-carbonitrile (3) (5·0 g), carbon disulphide (50 cm^3), and pyridine (40 cm^3) were refluxed for 2 h. Addition of diethyl ether (100 cm^3) gave the *pyrrolothiazine* (44) (5·4 g, 76%), yellow plates, m.p. >360° (from a large volume of methanol) (Found: C, 55·6; H, 3·4; N, 16·2; S, 24·7%; M^+, 259·024450. $C_{12}H_9N_3S_2$ requires C, 55·3; H, 3·3; N, 15·9; S, 24·4%; M, 259·023789), $\nu_{max.}$ 3400 (=NH), 3250 (thiazine NH), and 3100 (pyrrole NH) cm^{-1}.

5-Phenyl-1H-pyrrolo[2,3-d]*pyrimidine-2,4(3H,7H)-dithione* (45).—*Method* (A). The imine (44) (0·2 g) was heated with aqueous 5% potassium hydroxide (5 cm^3), on a steam-bath, for 30 min. The solution was cooled and the precipitated 2-amino-4-phenylpyrrole-3-carbonitrile (0·03 g, 21%) was collected and washed with water. The filtrate and washings were acidified with acetic acid to precipitate the *pyrrolopyrimidinedithione* (45) (0·10 g, 50%), m.p. >360°, which was purified by precipitation with acetic acid from a solution in aqueous 5% potassium hydroxide (Found: C, 55·1; H, 3·4; N, 15·9; S, 23·6%; M^+, 259·023179. $C_{12}H_9N_3S_2$ requires C, 55·6; H, 3·5; N, 16·2; S, 24·7%; M, 259·023789), $\nu_{max.}$ 3250 (pyrimidine NH) and 3100 (pyrrole NH) cm^{-1}.

Method (B). 2-Amino-4-phenylpyrrole-3-carbonitrile (0·5 g), carbon disulphide (5 cm^3), and pyridine (4 cm^3) were heated under reflux for 20 h to give the dithione (0·3 g, 42%), identical (i.r. and mass spectra and m.p.) with the product obtained by method (A).

4,7-Dihydro-4-imino-2-methylthio-5-phenylpyrrolo[2,3-d]-[1,3]*thiazine Hydroiodide* (47).—The pyrrolothiazine-2(1*H*)-thione (44) (0·5 g) and methyl iodide (1·5 g) were boiled under reflux in methanol (25 cm^3) for 1 h. The solution was filtered hot, concentrated to a small volume *in vacuo*, and allowed to cool. Addition of ether (25 cm^3) gave a pale yellow precipitate of the *pyrrolo*[2,3-d][1,3]*thiazinium iodide* (47) (0·72 g, 93%), yellow needles, m.p. 197—198° (from methanol and ethyl acetate) (Found: C, 39·0; H, 3·0; N, 10·2; S, 15·3%; *m/e*, 273·038161. $C_{13}H_{12}IN_3S_2$ requires C, 38·9; H, 3·0; N, 10·4; S, 15·9%; M^+ — HI, 273·039429), $\nu_{max.}$ (Nujol) 3400 (=NH), 3200 (pyrrole NH), and 2800 (=$\overset{+}{N}$H–) cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 2·38 (5H, s, Ph), 2·62 (1H, d, J 2·5 Hz, 6-H), and 7·13 (3H, s, 1-Me).

2-Bis(methylthio)methyleneamino-4-phenylpyrrole-3-carbonitrile (48).—A solution of the pyrrolothiazine-2(1*H*)-thione (44) (1·0 g) and methyl iodide (2·0 g) in aqueous 5% potassium hydroxide (25 cm^3) was stirred for 1 h at room temperature. Filtration gave the *bis(methylthio)methyleneaminopyrrole* (48) (1·01 g, 91%), prisms, m.p. 139—139·5° (from ethyl acetate) (Found: C, 58·8; H, 4·4; N, 14·6; S, 22·1%; M^+, 287·053633. $C_{14}H_{13}N_3S_2$ requires C, 58·5; H, 4·5; N, 14·6; S, 22·3%; M, 287·055088), $\nu_{max.}$ (KBr) 3250 (NH) and 2240 (C=N) cm^{-1}, τ ($CDCl_3$) 2·2—2·7 (6H, m, NH and Ph), 3·25 (1H, d, 5-H), and 7·45 (6H, s, MeS). The same product (48) was obtained by methylation of the hydroiodide (47) and of methyl 3-cyano-4-phenylpyrrole-2-dithiocarbamate (46).

2-Bis(methylthio)methyleneamino-4-phenylpyrrole-3-carbonitrile (0·10 g) was heated under reflux with aqueous 5% potassium hydroxide (8 cm^3) until dissolution was complete (3 h). The mixture was cooled to 0° and filtered to give 2-amino-4-phenylpyrrole-3-carbonitrile (0·05 g, 70%).

A solution of the hydroiodide (47) (0·90 g) in aqueous 5%

potassium hydroxide (15 cm³) was stirred at room temperature for 1 h, then acidified with hydrochloric acid to give methyl 3-cyano-4-phenylpyrrole-2-dithiocarbamate (46) (0·90 g, 100%). Attempts to recrystallise the product resulted in its decomposition (Found: M^+, 273·037897. Calc. for $C_{13}H_{11}N_3S_2$: M, 273·039439).

2-Bis(methylthio)methyleneamino-1-methyl-4-phenylpyrrole-3-carbonitrile (49).—The pyrrolothiazine-2(1*H*)-thione (44) (1·0 g) was stirred with diazomethane (3·0 g) in diethyl ether for 24 h. The solvent was allowed to evaporate off and the resulting gum was chromatographed on a neutral alumina column with light petroleum (b.p. 40—60°)–diethyl ether as eluant. Removal of the solvent from the first fraction collected gave the N-*methylpyrrole* (49) (0·3 g, 26%), prisms, m.p. 154—155° (from ethyl acetate) (Found: C, 59·6; H, 5·2; N, 13·8; S, 21·5%; M^+, 301·070388. $C_{15}H_{15}N_3S_2$ requires C, 59·8; H, 5·0; N, 13·9; S, 21·3%; M, 301·070737), $\nu_{max.}$ 2250 (C≡N) cm⁻¹, τ ($CDCl_3$) 2·2—2·7 (5H, m, Ph), 3·20 (1H, s, 5-H), 6·31 (3H, s, SMe), 6·56 (3H, s, SMe), and 7·42 (3H, s, NMe).

A second fraction eluted gave the bis(methylthio)-methyleneaminopyrrole (48) (0·4 g, 36%).

The yield of (49) was increased to 35%, and that of (48) decreased to 9%, when the reaction time was increased to 36 h.

4,7-Dihydro-4-imino-5-phenyl-1H-pyrrolo[2,3-d]pyrimidine-2(3H)-thiones (50)—(57).—*Method* (A). The pyrrolothiazine-2(1*H*)-thione (44) (0·50 g) was heated under reflux for 25 min with a solution of n-butylamine (0·50 g) in water (10 cm³) to give the 3-*n-butylpyrrolopyrimidine* (53) (0·50 g, 87%), yellow plates, m.p. 230—231° (from a large volume of 95% ethanol) (Found: C, 64·5; H, 6·1; N, 18·7; S, 10·9%; M^+, 298·125620. $C_{16}H_{18}N_4S$ requires C, 64·4; H, 6·0; N, 18·8; S, 10·7%; M, 298·125212), $\nu_{max.}$ (Nujol) 3420 (=NH), 3200 (thioamide NH), and 3100 (pyrrole NH) cm⁻¹. Acidification of the aqueous filtrates and washings gave the pyrrolopyrimidinedithione (45) (0·01 g, 2%).

Method (B). The pyrrolothiazine-2(1*H*)-thione (44) (0·2 g) and n-butylamine (1·0 g) were heated at 100°, in a sealed tube, for 20 min to give the 3-n-butylpyrrolopyrimidine (53) (0·21 g, 91%), identical (m.p. and i.r. spectrum) with that prepared by method (A).

Similar treatment of the pyrrolothiazine-2(1*H*)-thione (44) (1·0 g) with 50% v/v water–ethylamine (15 cm³) [method (A)] yielded the 3-*ethylpyrrolopyrimidine* (52) (0·55 g, 86%), yellow plates, m.p. 245—246° (Found: C, 62·0; H, 5·1; N, 20·6%; M^+, 270·093385. $C_{14}H_{14}N_4S$ requires C, 62·2; H, 5·2; N, 20·7%; M, 270·093913), $\nu_{max.}$ (Nujol) 3410 (=NH), 3200 (thioamide NH), and 3100 (pyrrole NH) cm⁻¹, τ ($CF_3{\cdot}CO_2H$) 2·75 (5H, s, Ph), 3·15 (2H, s, 1- and 6-H), 5·30 (2H, q, J 7 Hz, N·CH_2·CH_3), and 8·46 (3H, t, J 7 Hz, N·CH_2·CH_3).

The aqueous filtrates and washings were acidified (glacial acetic acid) to give the pyrrolopyrimidine (45) (0·40 g, 40%).

The pyrrolothiazine-2(1*H*)-thione (44) was heated in a steel bomb with liquid ammonia (20 cm³) at 100° for 2 h. The residual yellow gum was triturated with ethyl acetate to give the 4-*aminopyrrolopyrimidine* (50) (0·80 g, 43%), pale yellow prisms, m.p. >360° (Found: M^+, 242·063599. $C_{12}H_{10}N_4S$ requires M, 242·062615), $\nu_{max.}$ (Nujol) 3375 (NH), 3300 (NH), and 3100 (NH) cm⁻¹. Concentration of the acetone washings gave the pyrrolopyrimidine (45) (0·20 g, 10%).

The pyrrolothiazine-2(1*H*)-thione (44) (1·0 g) and a solution of hydrazine hydrate (1·0 g) in water (5 cm³) were heated on a steam-bath for 5 min to give the 3-*aminopyrrolopyrimidine* (57) (0·9 g, 91%), plates, m.p. 290° (decomp.) (from aqueous dimethylformamide) (Found: C, 54·9; H, 4·8; N, 26·2%; M^+, 257·073619. $C_{12}H_{11}N_5S$,-0·5H_2O requires C, 54·2; H, 4·5; N, 26·3%. $C_{12}H_{11}N_5S$ requires M, 257·073513), $\nu_{max.}$ (Nujol) 3400 (NH), 3275 (NH), 3225 (NH), and 3150 (NH) cm⁻¹. The aqueous filtrates and washings were acidified (glacial acetic acid) to give the pyrrolopyrimidine (45) (0·02 g, 2%).

The pyrrolothiazine-2(1*H*)-thione (44) (0·5 g) and benzylamine (1·5 g) [method (B)] (4·5 h) gave the 3-*benzylpyrrolopyrimidine* (54) (0·60 g, 94%), m.p. 235—236° (Found: C, 68·4; H, 5·0; N, 16·8; S, 9·8%; M^+, 332·110441. $C_{19}H_{16}N_4S$ requires C, 68·7; H, 4·8; N, 16·9; S, 9·6%; M, 332·109563), $\nu_{max.}$ (Nujol) 3430 (=NH) and 3150 (thioamide and pyrrole NH) cm⁻¹.

A mixture of the pyrrolothiazine-2(1*H*)-thione (24) (1·0 g) and aniline (1·0 g) was heated under reflux for 3 h in a nitrogen atmosphere. Ether (30 cm³) was added and the precipitate collected. Further washing with ether gave the 3,5-*diphenylpyrrolopyrimidine* (55) (0·4 g, 33%), yellow prisms, m.p. >300° (from dilute aqueous ethanol) (Found: C, 65·6; H, 4·5; N, 16·8; S, 9·7%; M^+, 318·093321. $C_{18}H_{14}N_4S$,0·5H_2O requires C, 66·0; H, 4·5; N, 17·1; S, 9·8%. $C_{18}H_{14}N_8S$ requires M, 318·093913), $\nu_{max.}$ (Nujol) 3400 (=NH) cm⁻¹.

A mixture of the pyrrolothiazine-2(1*H*)-thione (44) (0·50 g) and 4-methylaniline (1·50 g) was heated in a sealed tube at 100° for 5 h to give the 3-p-*tolylpyrrolopyrimidine* (56) (0·29 g, 45%), m.p. 207—208° (Found: M, 332·107507. $C_{19}H_{16}N_4S$ requires M, 332·109563), $\nu_{max.}$ (Nujol) 3400 (NH), 3300 (NH), and 3150 (NH) cm⁻¹.

N-(3-Cyano-4-phenylpyrrol-2-yl)-N′-isopropylthiourea (58).—*Method* (A). A mixture of the pyrrolothiazine-2(1*H*)-thione (44) (0·25 g), isopropylamine (0·50 g), and water (3 cm³) was heated on a steam-bath for 30 min to give the *thiourea* (0·23 g, 84%), needles, m.p. 240° (decomp.) (from water–acetone, 1 : 3) (Found: C, 63·3; H, 5·8; N, 19·9%; M^+ 284·108572. $C_{15}H_{16}N_4S$ requires C, 63·4; H, 5·6; N, 19·7%; M, 284·109563), $\nu_{max.}$ (Nujol) 3325 (NH), 3175 (NH), 3125 (NH), and 2225 (C≡N) cm⁻¹. Acidification of the aqueous filtrates and washings gave the pyrrolopyrimidine (45) (0·05 g, 2%).

Method (B). The pyrrolothiazine-2(1*H*)-thione (44) (0·50 g) and isopropylamine (1·50 g) were heated in a sealed tube at 110° for 4·25 h to give the thiourea (58) (0·47 g, 85%).

4-Amino-2-methylthio-5-phenyl-7H-pyrrolo[2,3-d]pyrimidine (63).—2-Bis(methylthio)methyleneamino-4-phenylpyrrole-3-carbonitrile (48) (0·73 g) and liquid ammonia (*ca.* 5 cm³) were heated in a sealed tube at 100° for 1 h to yield the 4-*aminopyrrolopyrimidine* (63) (0·61 g, 93%), prisms, m.p. 291—292° (from ethanol) (Found: C, 59·8; H, 4·7; N, 21·5%; M, 256·079369. $C_{13}H_{12}N_4S$ requires C, 59·9; H, 4·8; N, 21·5%; M, 256·078264), $\nu_{max.}$ (Nujol) 3500 (NH), 3350 (NH), 3200 (NH), and 3100 (NH) cm⁻¹.

4,7-Dihydro-4-imino-3-methyl-2-methylthio-5-phenyl-3H-pyrrolo[2,3-d]pyrimidine (64).—*Method* (A). 2-Bis(methylthio)methyleneamino-4-phenylpyrrole-3-carbonitrile (28) (0·3 g) and aqueous 25% methylamine (10 cm³) were heated under reflux for 16 h to give the 3-*methylpyrrolopyrimidine* (64) (0·25 g, 88%), needles, m.p. 260° (decomp.) (from 95% ethanol) (Found: C, 62·4; H, 5·3; N, 20·6; S, 11·5%; M, 270·094978. $C_{14}H_{14}N_4S$ requires C, 62·2; H, 5·2; N, 20·7; S, 11·8%; M, 270·094978), $\nu_{max.}$ (Nujol) 3350 (=NH) and 3100 (pyrrole NH) cm⁻¹.

Method (B). The 4-iminopyrrolopyrimidine-2-thione (51) (0·3 g), aqueous 5% sodium hydroxide (10 cm³), and methyl iodide (1·0 g) were heated under reflux on a steam-bath for 1·5 to give the pyrrolopyrimidine (64) (0·30 g, 95%).

Similarly, 2-bis(methylthio)methyleneamino-4-phenylpyrrole-3-carbonitrile (48) (0·50 g) and anhydrous ethylamine (10 cm³) were heated at 100° for 3 h in a sealed tube to give the 3-*ethylpyrrolopyrimidine* (65) (0·50 g, 99%), needles, m.p. 230° (decomp.) (from absolute ethanol) (Found: C, 63·0; H, 5·7; N, 19·5; S, 11·5%; *M*, 284·10789. $C_{15}H_{16}N_4S$ requires C, 63·4; H, 5·6; N, 19·7; S, 11·3%; *M*, 284·109563), $\nu_{max.}$ (Nujol) 3350 (=NH) and 3100 (pyrrole NH) cm⁻¹. 2-Bis(methylthio)methyleneamino-4-phenylpyrrole-3-carbonitrile (48) (1·00 g) and n-butylamine (5 cm³) were heated for 12 h at 110° [method (A)] to give the 3-*butylpyrrolopyrimidine* (66) (1·00 g, 92%), prisms, m.p. 187—188° (from ethanol) (Found: C, 64·9; H, 6·4; N, 17·9; S, 10·5%; *M*, 312·140398. $C_{17}H_{20}N_4S$ requires: C, 65·4; H, 6·4; N, 17·9; S, 10·2%; *M*, 312·140861), $\nu_{max.}$ (Nujol) 3350 (=NH) and 3100 (pyrrole NH) cm⁻¹, τ ($CDCl_3$) 2·60 (5H, m, Ph), 3·38 (1H, s, 6-H), 5·80 (2H, m, $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}N$), 7·47 (3H, s, SMe), and 8·0—9·2 (7H, m, $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}N$).

3-n-Butyl-4,7-dihydro-4-imino-5-phenyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2(3*H*)-thione (53) (0·1 g), aqueous 5% sodium hydroxide (3 cm³), and methyl iodide (0·5 g) were heated under reflux for 1 h [method (B)] to give the pyrrolopyrimidine (66) (0·1 g, 95%).

2,4-*Bismethylthio*-5-*phenylpyrrolo*[2,3-d]*pyrimidine*.— 5-Phenyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dithione (45) (0·5 g) was dissolved in aqueous 5% potassium hydroxide (30 cm³), methyl iodide (2·0 g) was added, and the mixture was heated under reflux for 10 min to give the *bismethylthiopyrrolopyrimidine* (0·5 g, 90%), prisms, m.p. 247—248° (from ethyl acetate) (Found: C, 58·1; H, 4·8; N, 14·4; S, 22·6%; *M*, 287·052526. $C_{14}H_{13}N_3S_2$ requires C, 58·5; H, 4·5; N, 14·6; S, 22·3%; *M*, 287·055088), $\nu_{max.}$ (KBr) 3150 (NH) cm⁻¹, τ ($CDCl_3$) 2·5—2·6 (5H, m, Ph), 2·91 (1H, s, 6-H), 7·31 (3H, s, 2-SMe), and 7·41 (3H, s, 4-SMe).

2,3-*Dihydro*-3-*methyl*-2-*thioxo*-5-*phenyl*-1H-*pyrrolo*[2,3-d]-*pyrimidin*-4(7H)-*one* (67).—The 4-iminopyrrolopyrimidine-2-thione (51) (0·2 g) in aqueous 5% potassium hydroxide (10 cm³) was heated on a steam-bath for 24 h to give the *pyrrolopyrimidine* (67) (0·18 g, 87%), prisms, m.p. 310° (decomp.) (from ethanol) (Found: C, 60·4; H, 4·3; N, 16·3; S, 12·6%; M^+, 257. $C_{13}H_{11}N_3OS$ requires C, 60·7; H, 4·3; N, 16·3; S, 12·5%; *M*, 257), $\nu_{max.}$ 3300 (pyrimidine NH), 3150 (pyrrole NH), and 1650 (C=O) cm⁻¹.

3-*Ethyl*-2,3-*dihydro*-2-*thioxo*-5-*phenyl*-1H-*pyrrolo*[2,3-d]-*pyrimidin*-4(7H)-*one* (68).—The 4-iminopyrrolopyrimidine-2-thione (52) (0·15 g) was heated under reflux with aqueous 5% potassium hydroxide (20 cm³) for 20 h to give the *pyrrolopyrimidinone* (68) (0·13 g, 86%), needles, m.p. 300° (decomp.) (from aqueous ethanol) (Found: C, 61·3; H, 4·9; N, 15·2; S, 11·5%; *M*, 271·077529. $C_{14}H_{13}N_3OS$ requires C, 62·0; H, 4·8; N, 15·5; S, 11·8%; *M*, 271·077929), $\nu_{max.}$ 3350 (pyrimidine NH), 3150 (pyrrole NH), and 1635 (C=O) cm⁻¹.

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