Pyrrolo[1,2-*a*][1,3,5]triazine-2,4(1*H*,3*H*)-diones. Part II.[1] Synthesis from 3,4-Disubstituted 2-Aminopyrroles

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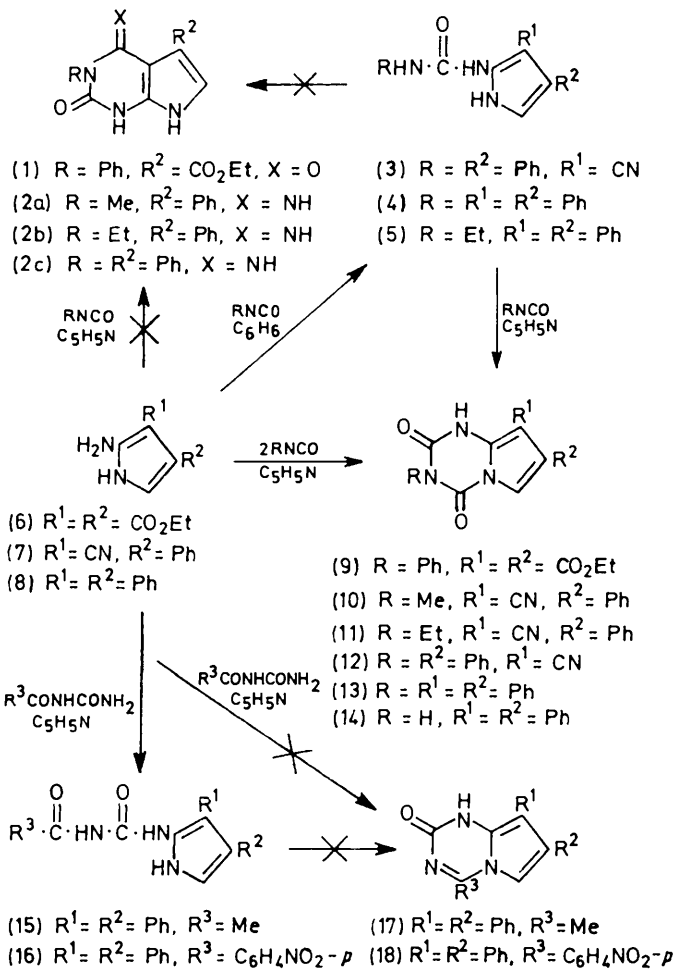
Treatment of 2-aminopyrroles, containing electron-withdrawing groups in positions 3 and 4, with aryl or alkyl isocyanates is shown to yield 3,7,8-trisubstituted pyrrolo[1,2-*a*][1,3,5]triazine-2,4(1*H*,3*H*)-diones. The intermediacy, in the reaction, of either (pyrrol-2-yl)ureas or 1-amido-2-aminopyrroles is discussed.

SEVERAL bicyclic and tricyclic heteroaromatic systems containing a bridgehead nitrogen atom have been synthesised by reaction of carbonyl isothiocyanates (RCO·NCS, where R = CO_2Et or Ph) with various 5-membered heterocycles containing an amino-function α to a ring nitrogen atom.[2] This reaction has not yet been extended to give a general method for the synthesis of ring systems derived from 2-aminopyrrole precursors. Such an omission could be due to the lack of reactivity of the 2-aminopyrroles or, more likely, to their scarcity or instability. An attempted synthesis, in these laboratories, of the pyrrolopyrimidine (1) by treatment of 2-amino-3,4-bisethoxycarbonylpyrrole (6) with phenyl isocyanate in refluxing pyridine afforded, instead, the pyrrolotriazine (9).[3]

We were thus led to investigate further the synthesis of pyrrolo[1,2-*a*][1,3,5]triazines from suitable 2-aminopyrroles. A recently reported one-step synthesis of 3,4-disubstituted 2-aminopyrroles[4] has now made these compounds more readily available, and two suitable aminopyrroles (7) and (8) were synthesised in this way.

Treatment of 2-amino-3-cyano-4-phenylpyrrole (7) with 2 mol. equiv. of methyl or ethyl isocyanate in dry refluxing pyridine afforded the corresponding pyrrolo-[1,2-*a*][1,3,5]triazine-2,4(1*H*,3*H*)-diones (10) and (11). The yields were low (*ca.* 20%) and the product was accompanied by much tarry material, presumably from the decomposition of the unstable 2-aminopyrrole precursor, and isolation of *NN'*-disubstituted ureas (formed by the action of water on the isocyanates). The ethyl derivative (11) was isolated in two crystalline forms, one green and one colourless, which differed only in their i.r. spectra. The pyrrolo[1,2-*a*][1,3,5]triazine-2,4(1*H*,3*H*)-diones (12) and (13) were similarly obtained although the yields were lower (*ca.* 10%).

It appeared possible that initial attack by the 2-aminopyrrole on the isocyanate afforded the intermediate pyrrolylureas (3)—(5) which would then further react with a second molecule of isocyanate to give the pyrrolotriazinediones (9)—(13). The pyrrolylureas (3) and (4) were obtained by treatment of the corresponding aminopyrroles with phenyl isocyanate in refluxing benzene. 1-(3-cyano-4-phenylpyrrol-2-yl)-3-phenylurea (3) was caused to react, in refluxing pyridine, with a further quantity of phenyl isocyanate to afford the dione (12) which was identical with the previously obtained sample. 1-(3,4-Diphenylpyrrol-2-yl)-3-phenylurea (4) could not, however, be induced to react with further isocyanate under similar conditions. Attempts to isolate the intermediate 1-alkyl-3-pyrrolylureas were not so successful,



(1) R = Ph, R^2 = CO_2Et, X = O
(2a) R = Me, R^2 = Ph, X = NH
(2b) R = Et, R^2 = Ph, X = NH
(2c) R = R^2 = Ph, X = NH

(3) R = R^2 = Ph, R^1 = CN
(4) R = R^1 = R^2 = Ph
(5) R = Et, R^1 = R^2 = Ph

(6) R^1 = R^2 = CO_2Et
(7) R^1 = CN, R^2 = Ph
(8) R^1 = R^2 = Ph

(9) R = Ph, R^1 = R^2 = CO_2Et
(10) R = Me, R^1 = CN, R^2 = Ph
(11) R = Et, R^1 = CN, R^2 = Ph
(12) R = R^2 = Ph, R^1 = CN
(13) R = R^1 = R^2 = Ph
(14) R = H, R^1 = R^2 = Ph

(15) R^1 = R^2 = Ph, R^3 = Me
(16) R^1 = R^2 = Ph, R^3 = $C_6H_4NO_2$-*p*
(17) R^1 = R^2 = Ph, R^3 = Me
(18) R^1 = R^2 = Ph, R^3 = $C_6H_4NO_2$-*p*

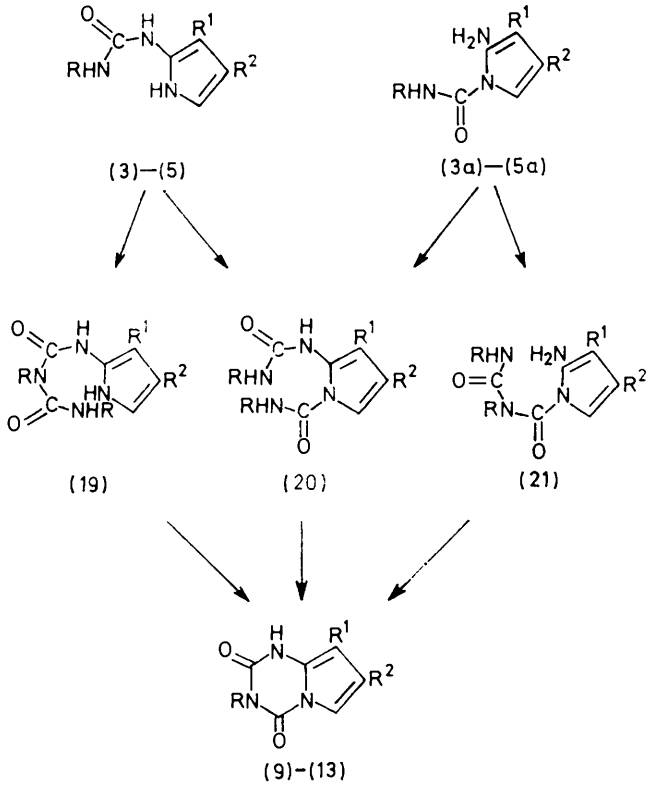
but a small quantity of 1-(3,4-diphenylpyrrol-2-yl)-3-ethylurea (5) was isolated by reaction of 2-amino-3,4-diphenylpyrrole and ethyl isocyanate in refluxing pyridine, although this reaction failed to yield the expected 3-ethyl-7,8-diphenylpyrrolo[1,2-*a*][1,3,5]triazinedione.

In another reaction treatment of 2-amino-3,4-diphenylpyrrole (8) with *N*-acetylurea or *N*-*p*-nitrobenzoylurea in refluxing pyridine afforded the corresponding 1-acyl-3-(pyrrol-2-yl)ureas (15) and (16) but no evidence of

[1] Part I, J. R. Traynor and D. G. Wibberley, preceding paper.
[2] L. Caprano and J. H. Schrepfer, *Chem. Ber.*, 1971, **104**, 3039.
[3] T. D. Duffy, Ph.D. Thesis, University of Aston in Birmingham, 1973.
[4] K. Gewald, *Z. Chem.*, 1961, **1**, 349.

the pyrrolotriazines (17) and (18). 1-(3,4-Diphenylpyrrol-2-yl)-3-(4-nitrobenzoyl)urea (16) also failed to cyclise on treatment with triethylamine or polyphosphoric acid. 2-Amino-3,4-diphenylpyrrole (8) and biuret in refluxing pyridine gave an impure compound, the spectrum of which was consistant with the pyrrolotriazine structure (14).

In view of the fact that the compounds (3), (5), (15), and (16) could not be induced to cyclise on treatment with pyridine and, in the case of (3) and (5), further isocyanate, it would seem that the 1-amido-2-aminopyrroles (3a)—(5a) could be the normal intermediates in pyridine-catalysed preparations of the pyrrolotriazines. Reaction of a further mole of isocyanate with the two possible intermediates [(3—5) or (3a—5a)] could then yield any of the three further intermediates (19)—(21) all of which could lose RNH_2 to give the pyrrolotriazines (9)—(13). Consideration of the expected acidities of the 2-aminopyrroles and the intermediates concerned, together with the yields obtained from, and course taken by, the various reactions would suggest ease of pyrrole anion formation to be a factor of major importance in the reaction.



Throughout the work no evidence of the formation of any pyrrolo[2,3-*d*]pyrimidines (1) and (2a—c) was seen. On comparison with the reactions of other *o*-aminonitriles [5] and *o*-aminoesters [6] such compounds might have been expected, although the delocalisation of the pyrrole nitrogen lone pair would serve to lessen the electrophilicity of the exocyclic groups at the pyrrole 3-position.

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

EXPERIMENTAL

Spectra were determined as described in the preceding paper.

3,4-Disubstituted 2-Aminopyrroles.— ω-Aminoacetophenone hydrochloride (2·57 g) in ethanol (70%; 30 cm³), was added dropwise over 15 min to a mixture of benzyl cyanide (2·34 g) and sodium hydroxide (1·1 g) which was stirred and vigorously refluxed in ethanol (70%; 50 cm³). The mixture was refluxed for a further 0·5 h after the addition was completed then quickly cooled and poured onto crushed ice to yield 2-*amino*-3,4-*diphenylpyrrole* (8) (1·45 g, 42%), plates, m.p. 279—280° (from methanol) (Found: C, 81·8; H, 12·1; N, 6·0%; M^+, 234·114782. $C_{16}H_{14}N_2$ requires C, 82·1; H, 12·0; N, 6·0%; *M*, 234·115693), $\nu_{max.}$ 3420 and 3220 (NH) and 1605 (C=C) cm^{-1}. In a similar manner ω-aminoacetophenone hydrochloride and malononitrile gave 2-amino-3-cyano-4-phenylpyrrole (7) (58%), grey plates, m.p. 175° (from benzene, subl.) (lit.,[4] 172—174°), $\nu_{max.}$ 3380, 3250 (NH), and 2200 (C≡N) cm^{-1}.

Pyrrolo[1,2-a][1,3,5]*triazine*-2,4(1H,3H)-*diones.*— *General method.* The stated amount of the 2-aminopyrrole and 2 mol. equiv. of the appropriate isocyanate were heated under reflux, in sufficient dry pyridine to cause solution, for the stated time. The pyridine was removed under reduced pressure and the resultant oil triturated with chloroform to afford, either as the chloroform-soluble (superscript *a*) or chloroform-insoluble (superscript *b*) fraction, the pyrrolotriazine. The corresponding *NN'*-dialkylureas were obtained as by-products. The following compounds were thus synthesised: 8-*cyano*-3-*methyl*-7-*phenylpyrrolo*[1,2-a][1,3,5]*triazine*-2,4(1H,3H)-*dione*[a] (10) (22%) (0·01 mol; 5 h), needles, m.p. 338—340° (decomp.) (from dimethylformamide) (Found: C, 62·5; H, 4·2; N, 21·0%; M^+, 266·079989. $C_{14}H_{10}N_4O_2$ requires C, 63·2; H, 3·8; N, 21·1%; *M*, 266·080370), $\nu_{max.}$ 3400 (NH), 2250 (C≡N), 1740, and 1680 (C=O), and 1640 (C=C) cm^{-1}; 8-*cyano*-3-*ethyl*-7-*phenylpyrrolo*-[1,2-a][1,3,5]*triazine*-2,4(1H,3H)-*dione*[a] (11) (14·5%) (0·01 mol; 15 h), recrystallised from methanol as green needles, m.p. 292—294° and (on concentration of the methanolic mother liquors) colourless needles, m.p. 291—293° (Found: C, 64·0; H, 4·5; N, 20·0%; M^+, 280·095719. $C_{15}H_{12}N_4O_2$ requires C, 64·0; H, 4·3; N, 20·0%; *M*, 280·096019), $\nu_{max.}$ (green needles) 3140 (NH), 2250 (C≡N), 1755 and 1710 (C=O), and 1640 (C=C) cm^{-1}, $\nu_{max.}$ (colourless needles) 3130 (NH), 2250 (C≡N), 1740 and 1695 (C=O), and 1630 (C=C) cm^{-1}, τ ($CDCl_3$) 2·32 (1H, s, 6-H), 2·53 (5H, s, 8-Ph), 6·02 (2H, q, *J* 7 Hz, 3-C*H*$_2$Me), and 8·70 (3H, t, *J* 7 Hz, 3-CH$_2$*Me*); 8-*cyano*-3,7-*diphenylpyrrolo*[1,2-a][1,3,5]*triazine*-2,4(1H,3H)-*dione*[b] (12) (8%) (0·003 mol; 3 h), pale yellow plates, m.p. 305° (decomp.) (subl.; from ethanol–acetone) (Found: C, 66·1; H, 3·7; N, 16·2%; M^+, 328·094710. $C_{19}H_{12}N_4O_2,H_2O$ requires C, 66·0; H, 4·0; N, 16·2%. $C_{19}H_{12}N_4O_2$ requires *M*, 328·096019), $\nu_{max.}$ 3400 (NH), 2250 (C≡N), 1745 and 1690 (C=O), and 1640 (C=C) cm^{-1}; 3,7,8-*triphenylpyrrolo*[1,2-a]-[1,3,5]*triazine*-2,4(1H,3H)-*dione*[b] (13) (10·5%) (0·002 mol; 3 h), prisms, m.p. 210—212° (from ethanol–acetone) [Found: M^+, 379; (M^+ — PhNCO), 260·095294. $C_{24}H_{17}N_3O_2$ requires *M*, 379; (*M* — PhNCO), 260·094958], $\nu_{max.}$ 3350 (NH), 1700 and 1600 (C=O), and 1595 (C=C) cm^{-1}.

[6] A. H. Cook and G. H. Thomas, *J. Chem. Soc.*, 1950, 1888; L. Caprano, W. Ebner, and J. H. Schrepfer, *Chem. Ber.*, 1970, **103**, 82.

1-*Alkyl*(*or Aryl*)-3-(3,4-*disubstituted pyrrol*-2-*yl*)*ureas*.—2-Amino-3-cyano-4-phenylpyrrole (7) (0·28 g) and phenyl isocyanate (0·18 g) were heated under reflux in dry benzene (10 cm³) for 0·5 h. The mixture was cooled and filtered to give 1-(3-*cyano*-4-*phenylpyrrol*-2-*yl*)-3-*phenylurea* (3) (0·23 g, 50%), mauve needles, m.p. 269—271° (decomp.) (from dimethylformamide) (Found: C, 71·5; H, 4·8; N, 18·5%; M^+, 302. $C_{18}H_{14}N_4O$ requires C, 71·5; H, 4·6; N, 18·5%; *M*, 302), $\nu_{max.}$ 3400 (NH), 2250 (C≡N), 1700 (C=O), and 1640 (C=C) cm^{-1}.

The 2-aminopyrrole (8) (0·23 g) and phenyl isocyanate (0·13 g) were treated in a similar manner to give 1-(3,4-*diphenylpyrrol*-2-*yl*)-3-*phenylurea* (4) (0·32 g, 92%), needles, m.p. 204—205° (from ethanol) (Found: C, 76·3; H, 5·8; N, 11·2%; M^+, 353·153147. $C_{23}H_{19}N_3O,0{\cdot}5H_2O$ requires C, 76·2; H, 5·5; N, 11·6%. $C_{23}H_{19}N_3O$ requires *M*, 353·152804), $\nu_{max.}$ 3300 (NH) and 1660 (C=O) cm^{-1}.

2-Amino-3-cyano-4-phenylpyrrole (7) (0·92 g) and ethyl isocyanate (0·35 g) did not react when similarly treated but when heated under reflux in pyridine (2 h and 10 h) afforded intractable tars.

The aminopyrrole (8) (1·17 g) and ethyl isocyanate (0·089 g) similarly treated in dry pyridine (16 h) gave 1-(3,4-*diphenylpyrrol*-2-*yl*)-3-*ethylurea* (5) (6·5%), needles, m.p. 328—330° (from ethanol) (Found: M^+, 305·153371. $C_{19}H_{19}N_3O$ requires *M*, 305·152804), $\nu_{max.}$ 1660 (C=O) cm^{-1}; no identifiable compounds could be gained from the pyridine mother liquors.

Synthesis of 8-*cyano*-3,7-*diphenylpyrrolo*[1,2-a][1,3,5]*triazine*-2,4(1H,3H)-*dione* (12) *from the phenylpyrrolylurea* (3). The pyrrolylurea (3) (0·6 g), phenyl isocyanate (0·25 g), and dry pyridine (10 cm³) were heated together under reflux for 15 h. Removal of the pyridine under reduced pressure gave a dark brown oily solid which on trituration with chloroform gave (3) (0·35 g). The chloroform washings evaporated to dryness gave a dark green solid. T.l.c. (alumina with acetic acid, or silica with ethanol) showed the presence of two components; the pyrrolylurea (3) as a minor component, and a component with the same R_F value as the authentic pyrrolotriazine as the major component. Repeated recrystallisation of the green solid from the minimum of ethanol gave the pyrrolotriazine (12) (0·03 g, 4·5%) as off-white plates identical (m.p., i.r. and mass spectra, and R_F value) with an authentic sample.

1-(3,4-Diphenylpyrrol-2-yl)-3-phenylurea (4) (0·53 g) and phenyl isocyanate were similarly treated. A quantitative recovery of (4) was obtained.

Reaction of 2-*Aminopyrroles with* 1-*Acylureas*.—2-Amino-3,4-diphenylpyrrole (8) (0·48 g), pyridine (5 cm³), and 1-acetylurea (0·21 g) were refluxed for 2 h. Removal of the pyridine under reduced pressure afforded a brown solid which was washed with chloroform to give 1-*acetyl*-3-(3,4-*diphenylpyrrol*-2-*yl*)*urea* (15) (0·43 g, 66%), needles, m.p. 248—249° (decomp.) (from methanol) (Found: C, 71·1; H, 5·3; N, 13·2%; M^+, 319. $C_{19}H_{17}N_3O_2$ requires C, 71·5; H, 5·3; N, 13·2%; *M*, 319), $\nu_{max.}$ 3300 (NH) and 1710 and 1670 (C=O) cm^{-1}.

The aminopyrrole (8) (0·88 g), *N*-*p*-nitrobenzoylurea (1·0 g), and pyridine (10 cm³) when heated under reflux (16 h) gave 1-(3,4-*diphenylpyrrol*-2-*yl*)-3-(4-*nitrobenzoyl*)*urea* (16) (1·48 g, 96%), orange needles, m.p. 230—231° (from dimethylformamide) (Found: C, 65·9; H, 4·5; N, 12·9. $C_{24}H_{18}N_4O_4,0{\cdot}5H_2O$ requires C, 66·2; H, 4·4; N, 12·9%), $\nu_{max.}$ 3400, 3300 (NH), 1695 and 1660 (C=O), 1530, and 1350 (NO_2) cm^{-1}.

2-Amino-3-cyano-4-phenylpyrrole (7) (1·22 g), 1-acetylurea (0·68 g), and pyridine (10 cm³) were refluxed (3 h) to afford a dark purple solid, from which a quantitative recovery of 1-acetylurea was made. No unchanged aminopyrrole could be isolated.

All attempts to cause ring closure of 1-(3,4-diphenylpyrrol-2-yl)-3-(4-nitrobenzoyl)urea (16) to 4-(4-nitrobenzoyl)-7,8-diphenylpyrrolo[1,2-*a*][1,3,5]triazin-2(1*H*)-one (18) using triethylamine, *NN*-diethylaniline, or polyphosphoric acid were unsuccessful.

Synthesis of 7,8-*Diphenylpyrrolo*[1,2-a][1,3,5]*triazine*-2,4(1H,3H)-*dione* (14).—2-Amino-3,4-diphenylpyrrole (8) (0·47 g), biuret (0·21 g), and pyridine (5 cm³) were heated under reflux for 15 h. Removal of the pyridine under reduced pressure gave a fawn solid which was washed with water, ethanol, and acetone to give the *pyrrolotriazine*, prisms (0·57 g, 94%), m.p. 303—305° (decomp.) (Found: M^+, 303·101349. $C_{18}H_{13}N_3O_2$ requires *M*, 303·100770), $\nu_{max.}$ 3400, 3300, 3230 (NH), and 1700 and 1680 (C=O) cm^{-1}.

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