Pyrazolopyridines. Part II.[1] Preparation of 3-Substituted 2-Aryl-2*H*-pyrazolo[4,3-*b*]pyridines. Acid-catalysed Cyclisation of 2-Arylaminomethyl-3-nitropyridines

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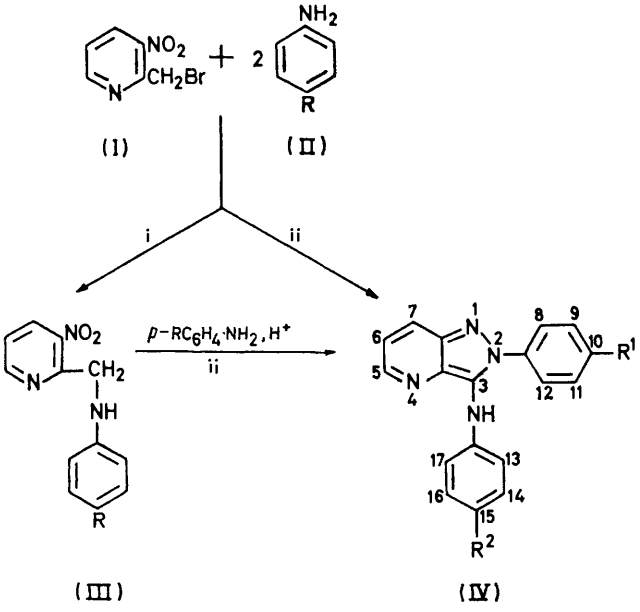
The reactions of 2-arylaminomethyl-3-nitropyridines with primary aromatic amines, hydrogen chloride, and ethanol gave 3-arylamino-, 3-chloro-, and 3-ethoxy-2-arylpyrazolo[4,3-*b*]pyridines, respectively. Cyclisation of 2-arylaminomethyl-3-nitropyridines in acetic acid yielded 2-arylpyrazolo[4,3-*b*]pyridin-3(2*H*)-ones. Mechanisms for the formation of these compounds are suggested.

We have shown [1] that treatment of 2-bromomethyl-3-nitropyridine (I) with primary aromatic amines (IIa, b, and e) in ethanol at room temperature yields the 2-arylaminomethyl-3-nitropyridines (IIIa, b, and e) whereas in boiling ethanol the products are the 2-aryl-3-arylamino-2*H*-pyrazolo[4,3-*b*]pyridines (IVa, b, and e). These pyrazolopyridines were also obtained by treatment of the 2-arylaminomethyl-3-nitropyridines (IIIa, b, and e) with the corresponding aromatic amine hydrobromides in boiling ethanol.

[1] Part I, J. Hurst and D. G. Wibberley, *J. Chem. Soc.* (C), 1968, 1487.

We have now obtained the 2-aryl-3-arylamino-2*H*-pyrazolo[4,3-*b*]pyridines (IVc and d) directly from 2-bromomethyl-3-nitropyridine (I), and also by isolation and subsequent cyclisation of the 2-arylaminomethyl-3-nitropyridines (IIIc and d) in the presence of the corresponding amine and toluene-*p*-sulphonic acid. No reaction occurred when the 2-arylaminomethyl-3-nitropyridines were treated with the aromatic amines in the absence of acid.

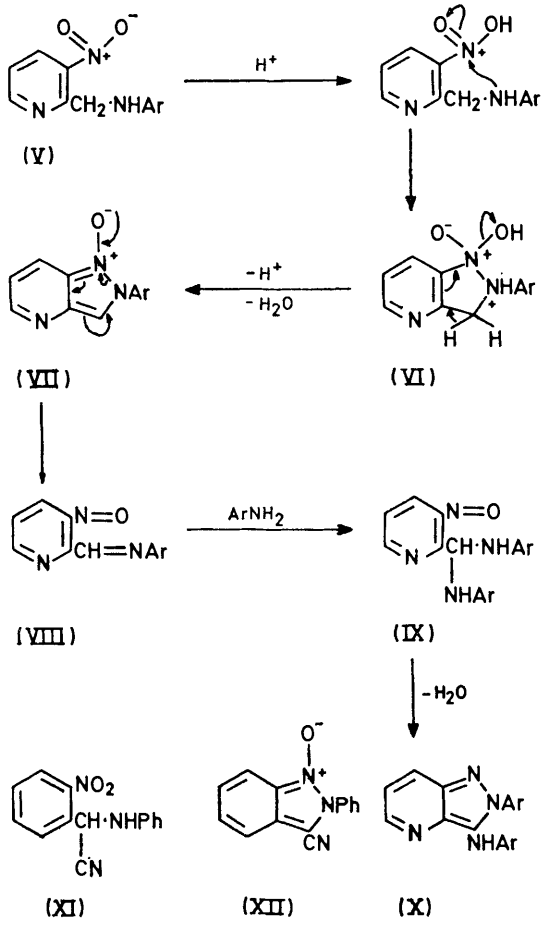
Substituent interactions in *ortho*-substituted nitrobenzenes have been reviewed; [2] examples include cyclodehydrations between a nitro-group and the amino-group of an adjacent side-chain. We therefore suggest



SCHEME 1

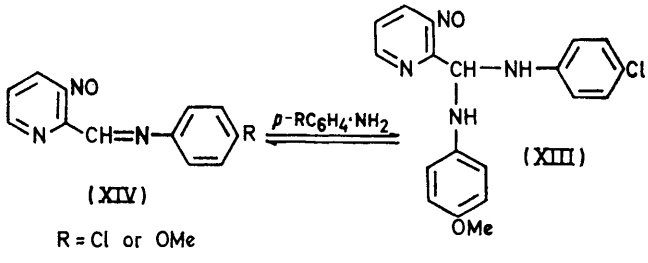
that the formation of the 2-aryl-3-arylamino-2*H*-pyrazolo[4,3-*b*]pyridines (X) from the 2-arylaminomethyl-3-nitropyridines (V) involves an initial acid-catalysed cyclodehydration (Scheme 2).

Nucleophilic attack by the arylamino-group is facilitated by protonation of the nitro-group. Furthermore, protonation of the pyridine nitrogen atom in the intermediate (VI) would increase the acidicity of the methylene group and aid dehydration to the 1-oxide (VII). It seems likely that electron withdrawal facilitates this type of cyclodehydration since *o*-nitrobenzylamine shows no tendency to cyclise [2] whereas the related cyano-compound (XI) can be converted into an indazole 1-oxide (XII) [3] and shares this behaviour with a number of its derivatives.[4] Ring opening of the pyrazolopyridine 1-oxide (VII) gives the anil (VIII), which then undergoes nucleophilic addition of the arylamine to give the bis(arylamino)methylpyridine (IX). The high reactivity of anils of this type towards nucleophiles has been recorded.[5] Cyclodehydration of the adduct (IX) yields the pyrazolopyridines (X).



SCHEME 2

In an attempt to show that the 2-bis(arylamino)-methyl-3-nitrosopyridines (IX) are intermediates, the reaction between 2-*p*-chloroanilinomethyl-3-nitropyridine (IIIb) and *p*-anisidine was investigated. Cyclisation of the adduct (XIII) formed in this case would be expected



to give a mixture of two products (IV; $R^1 = Cl$, $R^2 = OMe$ and $R^1 = OMe$, $R^2 = Cl$). A yellow solid was

[2] J. D. Loudon and G. Tennant, *Quart. Rev.*, 1964, **18**, 389.
[3] A. Reissert and F. Lemmer, *Ber.*, 1926, **59**, 351.
[4] L. C. Behr, *J. Amer. Chem. Soc.*, 1954, **76**, 3672; L. C. Behr, E. G. Alley, and O. Levand, *J. Org. Chem.*, 1962, **27**, 65.
[5] S. Miyano, N. Abe, A. Abe, and K. Hamachi, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 1131.

obtained from the reaction mixture by preparative t.l.c. The mass spectrum showed a peak at *m/e* 350 which could be due to either of the compounds (IV; R^1 = Cl. R^2 = OMe and R^1 = OMe, R^2 = Cl) or to a mixture of both. The n.m.r. spectrum indicated a mixture of products, showing strong absorptions at τ 6·17 and 6·29 attributable to the methoxy-groups in different environments.

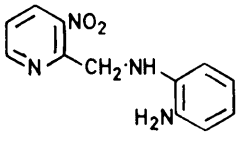
Additional peaks in the mass spectrum at *m/e* 354 and 346 indicated that the yellow solid also contained the dichloro- and dimethoxy-pyrazolo[4,3-*b*]pyridines (IVb and d). The formation of the latter (IVd) can be explained by the loss of *p*-chloroaniline from the adduct (XIII) to give the anil (XIV; R = OMe), which then reacts with *p*-anisidine. Addition of the liberated *p*-chloroaniline to the anil (XIV; R = Cl) followed by cyclodehydration would yield the dichloropyrazolopyridine (IVb). It is known that an amine can be displaced from an anil by other amines in this manner.[6]

Alternatively, the dichloro-compound (IVb) could be produced by partial hydrolysis of the anil (XIV; R = Cl) to give 3-nitrosopyridine-2-carbaldehyde and *p*-chloroaniline with subsequent addition of the latter to unchanged (XIV; R = Cl). Reactive anils undergo hydrolysis even when only traces of water are present and the formation of compounds (XVI) from anils of type (XV) has been explained on this basis.[6,7] Reaction of the liberated 3-nitrosopyridine-2-carbaldehyde with

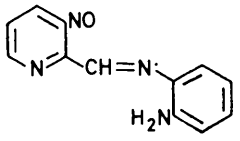
$$\underset{\text{(XV)}}{2\text{ArCH=NAr}} \xrightarrow{H_2O} \underset{\text{(XVI)}}{(\text{ArNH})_2\text{CHAr}} + \text{ArCHO}$$

2 equiv. of *p*-anisidine would give the dimethoxy-compound (IVd).

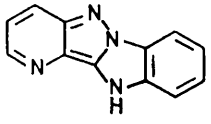
2-*o*-Aminoanilinomethyl-3-nitropyridine (XVII) was prepared by treatment of 2-bromomethyl-3-nitropyridine (I) with *o*-phenylenediamine. Cyclisation of this compound (XVII) in boiling ethanol in the presence of



(XVII)



(XVIII)



(XIX)

toluene-*p*-sulphonic acid yielded the pyrido[3′,2′:3,4]-pyrazolo[1,5-*a*]benzimidazole (XIX) and involves an intramolecular nucleophilic addition of the *o*-amino-group in the intermediate anil (XVIII).

The reaction between 2-bromomethyl-3-nitropyridine (I) and benzylamine in ethanol at room temperature gave a low yield of 2-benzyl-3-benzylaminopyrazolo-[4,3-*b*]pyridine instead of the expected 2-benzylamino-methyl-3-nitropyridine. Cyclisation under these mild conditions can be attributed to the strongly basic nature of the aliphatic amino-group. The yield of the pyrazolopyridine was not significantly improved when the reaction was carried out in boiling ethanol.

We previously showed [1] that treatment of the 2-aryl-aminomethyl-3-nitropyridines (IIIa and b) with the primary aromatic amines (IIa and b) in acetic acid on a steam-bath gave the 2-aryl-3-arylamino-2*H*-pyrazolo-[4,3-*b*]pyridines (IVa and b). In addition to these products the 2-arylpyrazolopyridones (XXIIIa and b) have now been obtained. On treatment of the 2-aryl-aminomethyl compounds (IIIc and d) under the foregoing conditions only the pyrazolopyridones (XXIIIc and d) were isolated. Addition of water to the anils (XX) followed by cyclodehydration of the adducts (XXI; R′ = OH) would give the hydroxypyrazolopyridines (XXII; R′ = OH) which are tautomeric with the pyrazolopyridones (XXIII). These compounds (XXIIIa—d) could also be formed by the addition of acetic acid across the –CH=N– group to give the 3-acetoxypyrazolopyridines (XXII; R′ = OAc) *via* the adducts (XXI; R′ = OAc). By analogy with 4-acetoxypyridine the ester group of the intermediate acetoxy-compounds (XXII; R′ = OAc) would be expected to be extremely sensitive towards nucleophiles.[8] Thus attack by water or the primary aromatic amine would again give the pyrazolopyridones (XXIIIa—d). Evidence for attack by the amine is provided by the isolation of ethyl *p*-acetamidobenzoate, in high yield, together with the pyrazolopyridone (XXIIIc), from the reaction of 2-*p*-ethoxycarbonylanilinomethyl-3-nitropyridine (IIIc) with ethyl *p*-aminobenzoate in acetic acid.

The use of 2-arylaminomethyl-3-nitropyridines in the preparation of 3-substituted 2-arylpyrazolo[4,3-*b*]-pyridines has been further extended. Thus treatment of compounds (IIIa—d) with ethanol saturated with hydrogen chloride gave the 3-chloropyrazolopyridines (XXIIa—d; R′ = Cl), presumably by addition of hydrogen chloride to the anils (XX) followed by cyclisation of the adducts (XXI; R′ = Cl).

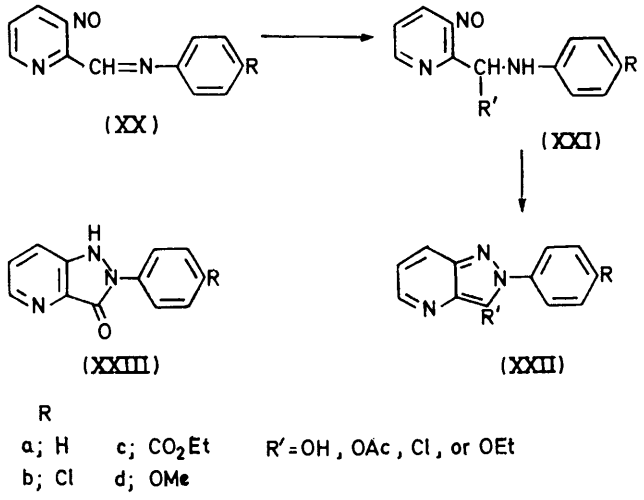
When the 2-arylaminomethyl-3-nitropyridines (IIIb and c) were heated under reflux in ethanol in the presence of toluene-*p*-sulphonic acid, addition of the weakly nucleophilic solvent to the anils (XXb and c) yielded the 3-ethoxypyrazolopyridines (XXIIb and c; R′ = OEt). We were unable to isolate the 3-ethoxypyrazolopyridines (XXIIa and d; R′ = OEt) from the corresponding aryl-aminomethyl compounds (IIIa and d) although t.l.c.

[6] G. W. Stacy, B. V. Ettling, and A. J. Papa, *J. Org. Chem.*, 1964, **29**, 1537.

[7] R. Marshall and D. M. Smith, *J. Chem. Soc.* (*C*), 1971, 3510; A. Kirpal and E. Reiter, *Ber.*, 1927, **60**, 664; S. Miyano, N. Abe, and A. Abe, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 511.

[8] H. Meislich, 'Heterocyclic Compounds, Pyridine and Its Derivatives,' Interscience, New York–London, vol. 14, part 3, p. 645.

indicated the presence of these compounds in the reaction mixtures. The $-CH=N-$ group of the intermediate anil (XXa) and, in particular, the *p*-methoxyanil (XXd), where the *para*-substituent is a powerful electron donor, would be expected to be less susceptible to nucleophilic attack than in the anils (XXb and c) which have electron withdrawing *para*-substituents. It has been shown [9] that in the addition of ethanol to anils



SCHEME 3

derived from heteroaromatic amines, an increase in electron withdrawal in the amine portion increases the rate of addition. In general we have found that the yield and the ease of isolation of the products from the *para*-substituted 2-anilinomethyl-3-nitropyridines (IIIa—d) is in the order *p*-$CO_2Et \sim$ *p*-Cl > *p*-H $\gtrsim$ *p*-OMe.

EXPERIMENTAL

I.r. spectra were recorded for Nujol mulls with a Unicam SP 200 spectrophotometer. N.m.r. spectra were recorded for solutions in deuteriochloroform (tetramethylsilane as internal standard) with a Perkin-Elmer R12 (60 MHz) instrument. Accurate mass measurements were made with an A.E.I. MS 902 spectrometer operating at 70 eV. Preparative t.l.c. was carried out on 100 × 20 cm plates with 1 mm Kieselgel PF_{254} (Merck) layers.

2-p-*Ethoxycarbonylanilinomethyl*-3-*nitropyridine* (IIIc).—2-Bromomethyl-3-nitropyridine (1·0 g), ethyl *p*-aminobenzoate (1·52 g), and ethanol (3 ml) were stirred at room temperature for 24 h to yield the *amine* (0·71 g, 51%) as yellow needles, m.p. 140—141° (from carbon tetrachloride) (Found: C, 59·85; H, 5·15; N, 13·9. $C_{15}H_{15}N_3O_4$ requires C, 59·8; H, 5·05; N, 13·95%), $\nu_{max.}$ ($CHCl_3$) 3400 (N–H), 1690 (C=O), 1600, 1530, and 1350 (NO_2), 1280 (C–O), 1180, and 1100 cm^{-1}.

2-p-*Methoxyanilinomethyl*-3-*nitropyridine* (IIId).—2-Bromomethyl-3-nitropyridine (0·5 g), *p*-anisidine (0·57 g), and ethanol (5 ml) were stirred at room temperature for 3 h to yield the *amine* (0·33 g, 55%) as orange needles, m.p. 92° (from ethanol) (Found: C, 60·2; H, 5·1; N, 16·45. $C_{13}H_{13}N_3O_3$ requires C, 60·2; H, 5·05; N, 16·2%), $\nu_{max.}$ 3400 (N–H), 1520 and 1350 (NO_2), 1230, 820, and 740 cm^{-1}.

3-p-*Ethoxycarbonylanilino*-2-p-*ethoxycarbonylphenyl*-2H-*pyrazolo*[4,3-b]*pyridine* (IVc).—(*a*) 2-Bromomethyl-3-nitropyridine (1·0 g), ethyl *p*-aminobenzoate (1·52 g), and ethanol (5 ml) were heated under reflux for 3 h. The solution was basified with 10% sodium carbonate solution and extracted with ether (3 × 20 ml). The extract was dried ($MgSO_4$) and evaporated to yield a brown oil which was triturated with boiling light petroleum (b.p. 60—80°) to yield the *pyrazolopyridine* (1·39 g, 70%). Crystallisation from ethanol gave yellow prisms, m.p. 189° (Found: C, 66·8; H, 5·25; N, 13·5. $C_{24}H_{22}N_4O_4$ requires C, 66·95; H, 5·15; N, 13·0%), $\nu_{max.}$ 3400 (NH), 1700 (C=O), 1600, 1280 (C–O), 1270, and 1210 cm^{-1}, τ 1·45 (1H, d, *J* 4 Hz, 5-H), 1·70 (1H, s, N–H), 1·6—2·5 (7H, m, 7-, 8-, 9-, 11-, 12-, 14-, and 16-H), 2·55—2·9 (1H, m, 6-H), 3·42 (2H, d, *J* 9 Hz, 13- and 17-H), 5·4—6·0 (4H, m, 2 × CH_2), and 8·5—8·8 (6H, m, 2 × CH_3).

(*b*) 2-*p*-Ethoxycarbonylanilinomethyl-3-nitropyridine (0·2 g), ethyl *p*-aminobenzoate (0·11 g), toluene-*p*-sulphonic acid monohydrate (0·13 g), and ethanol (2 ml) were heated under reflux for 3 h. The pyrazolopyridine (0·22 g, 77%) was isolated as in (*a*). Crystallisation from ethanol gave yellow prisms, m.p. and mixed m.p. with product of (*a*) 189°.

3-p-*Methoxyanilino*-2-p-*methoxyphenyl*-2H-*pyrazolo*-[4,3-b]*pyridine* (IVd).—(*a*) 2-Bromomethyl-3-nitropyridine (1·0 g), *p*-anisidine (1·12 g), and ethanol (5 ml) were heated under reflux for 3 h. The solution was basified with 10% sodium carbonate solution and extracted with chloroform (3 × 20 ml). The extract was dried ($MgSO_4$) and evaporated to yield an oil. Preparative t.l.c. [benzene–ethyl acetate (1 : 1) as eluant] followed by extraction of the main yellow band with acetone yielded the *pyrazolopyridine* (0·77 g, 48%). Crystallisation from benzene–cyclohexane gave yellow prisms, m.p. 140° (Found: C, 69·1; H, 5·1; N, 16·5. $C_{20}H_{18}N_4O_2$ requires C, 69·35; H, 5·25; N, 16·2%), $\nu_{max.}$ 3400 (N–H), 1550, 1520, 1300, 1250, 1040, and 840 cm^{-1}, τ 1·55 (1H, d, *J* 4 Hz, 5-H), 2·00 (1H, d, *J* 9 Hz, 7-H), 2·40 (2H, d, *J* 9 Hz, 8- and 12-H), 2·75 (1H, q, 6-H), 3·0—3·4 (6H, m, 9-, 11-, 13-, 14-, 16-, and 17-H), 3·65 (1H, s, N–H), 6·25 (3H, s, 10- or 15-O·CH_3), and 6·33 (3H, s, 10- or 15-O·CH_3).

(*b*) 2-*p*-Methoxyanilinomethyl-3-nitropyridine (0·2 g), *p*-anisidine (0·095 g), toluene-*p*-sulphonic acid monohydrate (0·15 g), and ethanol (2 ml) were heated under reflux for 3 h. Isolation as in (*a*) followed by crystallisation from benzene–cyclohexane (charcoal) gave the pyrazolopyridine (0·1 g, 38%) as yellow prisms, m.p. and mixed m.p. with the product of (*a*) 140°.

Reaction of 2-p-*Chloroanilinomethyl*-3-*nitropyridine* (IIIb) *with* p-*Anisidine*.—2-*p*-Chloroanilinomethyl-3-nitropyridine (0·2 g), *p*-anisidine (0·094 g), toluene-*p*-sulphonic acid monohydrate (0·13 g), and ethanol (2 ml) were heated under reflux for 3 h. The solvent was removed and the residue was basified with 10% sodium carbonate solution and extracted with chloroform (3 × 20 ml). The dried ($MgSO_4$) extract was evaporated to give a black oil. Preparative t.l.c. [benzene–ethyl acetate (1 : 1) as eluant] followed by extraction of the main yellow band with acetone gave a yellow solid which contained the following compounds: 2-*p*-chlorophenyl-3-*p*-methoxyanilino-2*H*-pyrazolo[4,3-*b*]pyridine (IV; R^1 = Cl, R^2 = OMe) and 3-*p*-chloroanilino-2-*p*-methoxyphenyl-2*H*-pyrazolo[4,3-*b*]pyridine (IV; R^1 = OMe, R^2 = Cl), *m/e* 350 (base peak)

[9] J. Goerdeler and H. Ruppert, *Chem. Ber.*, 1963, **96**, 1630.

(Found: *M*, 350·0927. Calc. for $C_{19}H_{15}ClN_4O$: 350·0935), 3-*p*-chloroanilino-2-*p*-chlorophenyl-2*H*-pyrazolo[4,3-*b*]-pyridine (IVb), *m/e* 354 (98% of base peak) (Found: *M*, 354·0435. Calc. for $C_{18}H_{12}Cl_2N_4$: 354·0440), 3-*p*-methoxyanilino-2-*p*-methoxyphenyl-2*H*-pyrazolo[4,3-*b*]pyridine (IVd), *m/e* 346 (53% of base peak) (Found: *M*, 346·1425. Calc. for $C_{20}H_{18}N_4O_2$: 346·1430), τ 1·55—3·73 (m, aromatic protons), 6·17 (s, 10- or 15-O·CH_3), and 6·29 (s, 10- or 15-O·CH_3).

2-o-*Aminoanilinomethyl*-3-*nitropyridine* (XVII).—2-Bromomethyl-3-nitropyridine (0·6 g), *o*-phenylenediamine (0·6 g), and ethanol (5 ml) were stirred at room temperature for 3 h to yield the *amine* (0·46 g, 68%) as red needles, m.p. 156—157° (from ethanol) (Found: C, 59·0; H, 5·05; N, 23·0. $C_{12}H_{12}N_4O_2$ requires C, 59·0; H, 5·0; N, 22·95%), $\nu_{max.}$ 3400 and 3300 (N–H), 1600, 1570, 1520, and 1340 (NO_2), and 730 cm^{-1}.

Pyrido[3′,2′:3,4]*pyrazolo*[1,5-a]*benzimidazole* (XIX).—2-*o*-Aminoanilinomethyl-3-nitropyridine (0·2 g), toluene-*p*-sulphonic acid monohydrate (0·17 g), and ethanol (5 ml) were heated under reflux for 3 h. Evaporation of the solvent followed by basification of the residue with 10% sodium carbonate solution gave a buff solid which on crystallisation from dimethylformamide gave the *tetracyclic compound* (0·1 g, 59%) as yellow needles, m.p. 325—330° (Found: *M*, 208·0752. $C_{12}H_8N_4$ requires *M*, 208·0749), $\nu_{max.}$ 2650br (N–H), 1610, 1580, 1530, 1330, 1310, 1240, 1120, 830, 785, and 740 cm^{-1}.

2-*Benzyl*-3-*benzylamino*-2H-*pyrazolo*[4,3-b]*pyridine*.— 2-Bromomethyl-3-nitropyridine (0·5 g), benzylamine (0·5 g), and ethanol (5 ml) were stirred at room temperature for 3 h. The solution was basified with 10% sodium carbonate solution and extracted with ether (3 × 20 ml). The extract was dried ($MgSO_4$) and the solvent and unchanged benzylamine were removed under reduced pressure. The residual oily solid was crystallised from benzene–cyclohexane to yield the *pyrazolopyridine* (0·13 g, 18%) as cream prisms, m.p. 123—124° (Found: C, 76·65; H, 5·85; N, 17·9. $C_{20}H_{18}N_4$ requires C, 76·4; H, 5·8; N, 17·8%), $\nu_{max.}$ 3200 (N–H), 1590, 1580, 1370, 1120, and 720 cm^{-1}, τ 1·66 (1H, d, *J* 4 Hz, 5-H), 2·16 (1H, d, *J* 9 Hz, 7-H), 2·5—3·0 (11H, m, 6-H and 2 × C_6H_5), 3·4br (1H, s, N–H), 4·55 (2H, s, 2-CH_2Ph), and 5·05 (2H, s, NH·CH_2Ph).

General Method for the Preparation of 2-*Arylpyrazolo*[4,3-b]*pyridin*-3(2H)-*ones*.—The stated amounts of the 2-arylaminomethyl-3-nitropyridine, the corresponding arylamine, and acetic acid were heated on a steam-bath for 4 h. The solvent was removed under reduced pressure to yield an oily solid which on trituration with acetone gave the pyrazolopyridone. Crystallisation was from 2-ethoxyethanol.

2-*Phenylpyrazolo*[4,3-b]*pyridin*-3(2H)-*one* (XXIIIa) (22%) (0·5 g; 0·25 g; 5 ml), m.p. 226—227° (decomp.) (Found: C, 68·2; H, 4·5; N, 19·6. $C_{12}H_9N_3O$ requires C, 68·25; H, 4·3; N, 19·9%), $\nu_{max.}$ 3300—2500 (N–H), 1680 (C=O), 1600, 1500, 1340, 1160, and 760 cm^{-1}, τ [$(CD_3)_2SO$] −1·0br (1H, s, N–H), 1·46 (1H, d, *J* 4 Hz, 5-H), 1·9—2·2 (3H, m, 7-, 2′-, and 6′-H), and 2·3—2·9 (4H, m, 6-, 3′-, 4′-, and 5′-H). The acetone was evaporated off and the residue extracted with boiling cyclohexane. Evaporation of the extract gave a solid which on crystallisation from ethanol afforded 3-anilino-2-phenyl-2*H*-pyrazolo[4,3-*b*]pyridine (IVa) (0·15 g, 24%) as lemon-yellow prisms, m.p. and mixed m.p. 198—199°, identical (i.r. spectrum) with a previously prepared sample.[1]

2-p-*Chlorophenylpyrazolo*[4,3-b]*pyridin*-3(2H)-*one* (XXIIIb) (43%) (1 g; 0·55 g; 10 ml), m.p. 245—246° (decomp.) (Found: C, 58·65; H, 3·5; Cl, 14·7; N, 17·0. $C_{12}H_8ClN_3O$ requires C, 58·65; H, 3·3; Cl, 14·4; N, 17·1%), $\nu_{max.}$ 3200—2500 (N–H), 1650 (C=O), 1590, 1490, and 1340 cm^{-1}, τ [$(CD_3)_2SO$] 1·48 (1H, d, *J* 4 Hz, 5-H), 1·8—2·3 (3H, m, 7-, 2′-, and 6′-H), and 2·3—2·6 (3H, m, 6-, 3′-, and 5′-H). Evaporation of the acetone and crystallisation of the residue from ethanol gave 3-*p*-chloroanilino-2-*p*-chlorophenyl-2*H*-pyrazolo[4,3-*b*]pyridine (IVb) (0·39 g, 29%) as lemon-yellow prisms, m.p. and mixed m.p. 201—202°, identical (i.r. spectrum) with a previously prepared sample.[1]

2-p-*Ethoxycarbonylphenylpyrazolo*[4,3-b]*pyridin*-3(2H)-*one* (XXIIIc) (47%) (0·5 g; 0·28 g; 5 ml), m.p. 220—222° (decomp.) (Found: C, 63·35; H, 4·55; N, 14·9. $C_{15}H_{13}N_3O_3$ requires C, 63·6; H, 4·6; N, 14·85%), $\nu_{max.}$ 3200—2500 (N–H), 1700 (ester C=O), 1650 (ring C=O), 1600, 1520, 1420, 1350, 1280 (C–O), and 770 cm^{-1}, τ [$(CD_3)_2SO$] 1·46 (1H, d, *J* 4 Hz, 5-H), 1·88 (4H, s, 2′-, 3′-, 5′-, and 6′-H), 2·10 (1H, d, *J* 8 Hz, 7-H), 2·40 (1H, q, *J* 4 and 8 Hz, 6-H), 5·65 (2H, q, CH_2), and 8·66 (3H, t, CH_3). The acetone was evaporated off and the residue was extracted with boiling cyclohexane. Evaporation of the extract gave an oil which on trituration with light petroleum gave ethyl *p*-acetamidobenzoate (0·3 g, 85%). Crystallisation from benzene–cyclohexane (charcoal) gave prisms, m.p. and mixed m.p. 104°, identical (i.r. spectrum) with an authentic sample.[10]

Ethyl *p*-acetamidobenzoate was obtained in only 20% yield when ethyl *p*-aminobenzoate and acetic acid were heated on a steam-bath for 4 h.

2-p-*Methoxyphenylpyrazolo*[4,3-b]*pyridin*-3(2H)-*one* (XXIIId) (29%) (0·6 g; 0·3 g; 6 ml), m.p. 218—220° (decomp.) (Found: C, 64·05; H, 4·9; N, 17·2. $C_{13}H_{11}N_3O_2$ requires C, 64·7; H, 4·6; N, 17·4%), $\nu_{max.}$ 3200—2500 (N–H), 1650 (C=O), 1520, 1260, 1175, and 830 cm^{-1}, τ [$(CD_3)_2SO$] 1·47 (1H, d, *J* 4 Hz, 5-H), 1·98—2·65 (4H, m, 6-, 7-, 2′-, and 6′-H), 2·89 (2H, d, *J* 9 Hz, 3′- and 5′-H), and 6·17 (3H, s, CH_3).

General Method for the Preparation of 2-*Aryl*-3-*chloro*-2H-*pyrazolo*[4,3-b]*pyridines*.—A solution of the 2-arylaminomethyl-3-nitropyridine (0·5 g) in ethanol (50 ml) which had been saturated with hydrogen chloride was heated under reflux for 3 h. The solution was evaporated to low bulk (5 ml) and basified with 10% sodium carbonate solution.

3-*Chloro*-2-*phenyl*-2H-*pyrazolo*[4,3-b]*pyridine* (XXIIa; R′ = Cl). The mixture was extracted with chloroform (3 × 20 ml). The extract was dried ($MgSO_4$) and evaporated to yield a waxy solid which was extracted with boiling light petroleum (b.p. 40—60°). Evaporation of the extract to low bulk gave the *chloro-compound* (46%) as needles, m.p. 68—69° [from light petroleum (b.p. 40—60°)] (Found: C, 62·9; H, 3·6; Cl, 15·15; N, 18·5. $C_{12}H_8ClN_3$ requires C, 62·7; H, 3·5; Cl, 15·4; N, 18·3%), $\nu_{max.}$ 1510, 1380, 1265, 1045, 810, 770, and 695 cm^{-1}, τ 1·25 (1H, d, *J* 4 Hz, 5-H), 1·85 (1H, d, *J* 8 Hz, 7-H), 2·0—2·5 (5H, m, C_6H_5), and 2·62 (1H, q, *J* 4 and 8 Hz, 6-H).

3-*Chloro*-2-p-*chlorophenyl*-2H-*pyrazolo*[4,3-b]*pyridine* (XXIIb; R′ = Cl). The *chloro-compound* (83%) was filtered off. Crystallisation from ethyl acetate gave needles, m.p. 190—191° (Found: C, 54·55; H, 2·55; Cl, 27·1; N, 16·1. $C_{12}H_7Cl_2N_3$ requires C, 54·6; H, 2·7; Cl, 26·8; N,

[10] A. J. Hill and M. V. Cox, *J. Amer. Chem. Soc.*, 1926, **48**, 3214.

15·9%), $\nu_{max.}$ 1500, 1090, 830, 800, and 770 cm^{-1}, τ 1·30 (1H, q, *J* 4 and 1·5 Hz, 5-H), 1·92 (1H, q, *J* 9 and 1·5 Hz, 7-H), 2·26 (2H, d, *J* 9 Hz, 2′- and 6′-H), 2·48 (2H, d, *J* 9 Hz, 3′- and 5′-H), and 2·68 (1H, q, *J* 4 and 9 Hz, 6-H).

3-*Chloro*-2-p-*ethoxycarbonylphenyl*-2H-*pyrazolo*[4,3-b]-*pyridine* (XXIIc; R′ = Cl). The *chloro-compound* (80%) was collected. Sublimation (120° and 2 mmHg) followed by crystallisation from cyclohexane gave needles, m.p. 145—147° (Found: C, 59·45; H, 4·1; Cl, 11·55; N, 13·6. $C_{15}H_{12}ClN_3O_2$ requires C, 59·7; H, 4·0; Cl, 11·75; N, 13·95%), $\nu_{max.}$ 1730 (C=O), 1420, 1280 (C–O), 1100, and 770 cm^{-1}, τ 1·32 (1H, q, *J* 4 and 1·5 Hz, 5-H), 1·75 (2H, d, *J* 9 Hz, 3′- and 5′-H), 1·83 (1H, q, *J* 9 and 1·5 Hz, 7-H), 2·13 (2H, d, *J* 9 Hz, 2′- and 6′-H), 2·64 (1H, q, *J* 4 and 9 Hz, 6-H), 5·54 (2H, q, CH_2), and 7·54 (3H, t, CH_3).

3-*Chloro*-2-p-*methoxyphenyl*-2H-*pyrazolo*[4,3-b]*pyridine* (XXIId; R′ = Cl). Preparative t.l.c. of the precipitated solid [benzene–ethyl acetate (9 : 1) as eluant] followed by extraction of the main yellow band with acetone yielded the *pyrazolopyridine* (32%). Crystallisation from cyclohexane gave needles, m.p. 125—126° (Found: C, 60·25; H, 4·05; Cl, 14·1; N, 15·95. $C_{13}H_{10}ClN_3O$ requires C, 60·1; H, 3·9; Cl, 13·7; N, 16·2%), $\nu_{max.}$ 1620, 1250, and 840 cm^{-1}, τ 1·32 (1H, q, *J* 4 and 1·5 Hz, 5-H), 1·92 (1H, q, *J* 9 and 1·5 Hz, 7-H), 2·36 (2H, d, *J* 9 Hz, 2′- and 6′-H), 2·71 (1H, m, 6-H), 2·90 (2H, d, *J* 9 Hz, 3′- and 5′-H), and 6·07 (3H, s, CH_3).

2-p-*Chlorophenyl*-3-*ethoxy*-2H-*pyrazolo*[4,3-b]*pyridine* (XXIIb; R′ = OEt). 2-*p*-Chloroanilinomethyl-3-nitropyridine (0·2 g), toluene-*p*-sulphonic acid monohydrate (0·15 g), and absolute ethanol (8 ml) were heated under reflux for 5 h. The solvent was removed and the residue was basified with 10% sodium carbonate solution and extracted with chloroform (3 × 20 ml). The dried ($MgSO_4$) extract was evaporated and the residue was extracted with boiling light petroleum (b.p. 60—80°). Evaporation of the light petroleum solution gave the *ethoxy-compound* (0·13 g, 62%), as plates, m.p. 99—100° (from ethanol) (Found: C, 61·2; H, 4·6; Cl, 13·3; N, 15·55. $C_{14}H_{12}ClN_3O$ requires C, 61·45; H, 4·4; Cl, 12·95; N, 15·35%), $\nu_{max.}$ (CCl_4) 1560, 1520, 1505, 1495, 1470, 1410, 1135, 1125, 1100, 1020, and 840 cm^{-1}, τ 1·57 (1H, q, *J* 4 and 1·5 Hz, 5-H), 1·9—2·2 (1H, m, 7-H), 2·1 (2H, d, *J* 9 Hz, 2′- and 6′-H), 2·51 (2H, d, *J* 9 Hz, 3′- and 5′-H), 2·84 (1H, q, *J* 4 and 9 Hz, 6-H), 4·88 (2H, q, CH_2), and 8·5 (3H, t, CH_3).

3-*Ethoxy*-2-p-*ethoxycarbonylphenyl*-2H-*pyrazolo*[4,3-b]-*pyridine* (XXIIc; R′ = OEt).—2-*p*-Ethoxycarbonylanilinomethyl-3-nitropyridine (0·1 g), toluene-*p*-sulphonic acid monohydrate (0·063 g), and absolute ethanol (3 ml) were heated under reflux for 5 h. The solvent was removed; basification of the residue with 10% sodium carbonate solution gave the *ethoxy-compound* (0·073 g, 70%). Crystallisation from ethanol gave prisms, m.p. 120—122° (Found: C, 65·75; H, 5·4; N, 13·25. $C_{17}H_{17}N_3O_3$ requires C, 65·6; H, 5·5; N, 13·5%), $\nu_{max.}$ 1700 (C=O), 1610, 1560, 1520, 1395, 1310, 1280br (C–O), 1120, 1105, and 995 cm^{-1}, τ 1·64 (1H, d, *J* 4 Hz, 5-H), 1·78 (2H, d, *J* 9 Hz, 3′- and 5′-H), 2·00 (2H, d, *J* 9 Hz, 2′- and 6′-H), 2·14 (1H, d, *J* 9 Hz, 7-H), 2·87 (1H, q, *J* 4 and 9 Hz, 6-H), 4·86 (2H, q, 3-O·CH_2·CH_3), 5·58 (2H, q, CO_2·CH_2·CH_3), and 8·2—8·8 (6H, m, 2 × CH_3).

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