Pyrazolopyridines. Part 5.[1] Preparation and Reactions of Pyrazolo-[3,4-c]pyridines

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A series of pyrazolo[3,4-c]pyridines has been prepared by nitrosation of 3-acetamido-4-methylpyridines and subsequent rearrangement and cyclisation of the N-acetyl-N-nitroso-compounds produced. The reactions of the pyrazolo[3,4-c]pyridines have been investigated. 1- and 2-Acetyl and 1- and 2-benzyl compounds were obtained and their structures elucidated spectroscopically. The ring system readily undergoes electrophilic substitution in the 3-position. 7-Chloropyrazolo[3,4-c]pyridine has been shown to be more susceptible to nucleophilic substitution than the isomeric 5-chloro-compound.

FEW good methods are available for the synthesis of pyrazolo[3,4-c]pyridines. We have prepared pyrazolo-[4,3-b]pyridines by the cyclisation of N-acyl-N-nitroso-compounds derived from 3-amino-2-methylpyridines and pyrazolo[3,4-c]pyridine itself via 3-amino-4-methyl-pyridine.[2] This method is now extended to the synthesis of 5- and 7-substituted-pyrazolo[3,4-c]pyridines.

RESULTS AND DISCUSSION

Treatment of the 3-acetamido-4-methylpyridines (1a—d) with nitrosyl chloride gave the corresponding nitroso-compounds (2a—d), which were re-arranged without further purification. The pyrazolopyridines (5a and b) were isolated as the corresponding 1-acetyl derivatives (6a and b), whilst the pyrazolopyridines (5c and d) were obtained as a mixture of their 1- and 2-acetyl compounds (6c and d). The 3-azopyrazolopyridine (7) was also formed following treatment of the acetamide (1b), presumably by electrophilic attack of the intermediate diazonium salt (4b) at the 3-position of the 5-methoxy-compound (5b). The formation of by-products


(7)   (8)
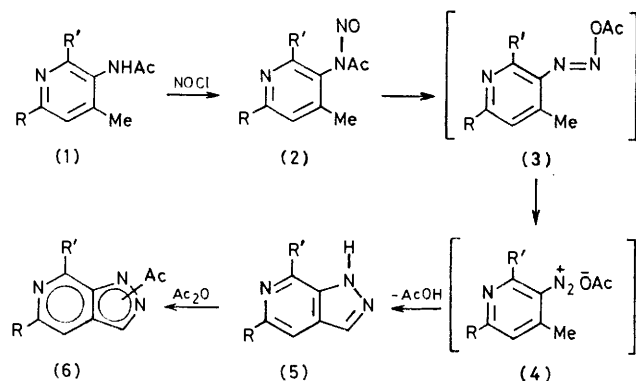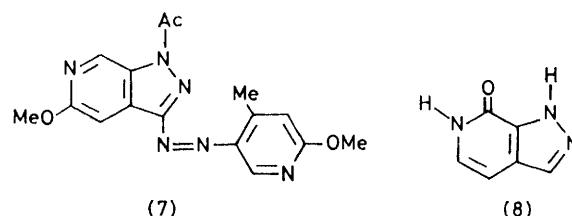
The parent pyrazolopyridines (5a—c) were readily prepared by hydrolysis of the corresponding acetyl compounds in aqueous acid. However, under these conditions the methoxy-group of compound (6d) is also hydrolysed to yield the pyrazolopyridone (8). The methoxy-compound (5d) was thus prepared by nitrosation of the acetamide (1d) in the absence of acetic anhydride.

The mechanism outlined for the formation of the pyrazolopyridines is analogous to that proposed for the formation of indazoles from N-acyl-N-nitroso-o-tolu-ides.[4] The intermediacy of an ion-pair was demonstrated by Suschitzky et al.[5] who obtained a mixture of 5-fluoro- and 5-benzoyloxy-indazole following the cyclis-ation of N-(4-fluoro-o-tolyl)-N-nitrosobenzamide. The benzoyloxy-compound is formed by nucleophilic displacement of the activated fluorine atom in the intermediate diazonium salt by benzoate ion. Similar displacements of fluorine were observed during the decomposition of N-(2-fluorophenyl)- and N-(4-fluoro-phenyl)-N-nitrosobenzamides.[5] No replacement of chlorine occurred in the analogous chloro-compounds. More recently, however, appreciable ionic displacement of chloride has been observed when reactions of the above type were carried out in the presence of 1,1-diphenyl-ethylene, which suppresses competing radical reactions.[6] In view of this, cyclisation of the acetamides (1c and e) is of interest since the chlorine atoms in the ion-pairs (4c and e) are activated to nucleophilic substitution by both the diazonium group and the pyridine nitrogen atom. Cyclisation of the acetamide (1c) gave the

(1)   (2)   (3)

(6)   (5)   (4)

a; R = Me, R′ = H
b; R = OMe, R′ = H
c; R = Cl, R′ = H
d; R = H, R′ = OMe
e; R = H, R′ = Cl

of this type has been reported in the analogous synthesis of indazoles.[3] Under the above conditions 3-acetamido-2-chloro-4-methylpyridine (1e) gave a dark oil from which none of the required 7-chloropyrazolopyridine

(6e) could be isolated. However, when the cyclisation was carried out in the absence of acetic anhydride the 7-chloro-compound (5e) was obtained in low yield together with small amounts of the pyrazolopyridone (8).

corresponding 5-chloropyrazolopyridine (6c) in good yield. No evidence for the replacement of chlorine by acetate ion was observed, indicating that cyclisation occurs more readily than an intermolecular nucleophilic substitution. However, cyclisation of the acetamide (1e) gave a dark oil from which only very low yields of the pyrazolopyridine (5e) and the pyrazolopyridone (8) were isolated. This may be due to an intramolecular nucleophilic replacement of the halogen in the ion-pair (4e) by acetate ion followed by further reactions to give other, as yet, unidentified products. An alternative explanation for the low yield may be difficulty in the nitrosation of the o-disubstituted-acetamide (1e). This is unlikely, however, since good yields have been obtained with other sterically hindered acetamides, e.g. (1d). A more detailed study of the cyclisation of the above chloro-acetamides (1c and e) will be carried out under closely controlled conditions.

Attempts to prepare the required 7-chloropyrazolopyridine (5e) by treatment of the pyrazolopyridone (8) with either phosphoryl chloride alone, or with a mixture of phosphoryl chloride and phosphorus pentachloride, were unsuccessful. However, conversion of the pyridone (8) to the corresponding thio-derivative (8; S for O), followed by treatment with chlorine in the presence of concentrated hydrochloric acid, gave the chloro-compound in good yield. This procedure has been used in the preparation of 6-chloropurines.[7]

Reactions of the pyrazolo[3,4-c]pyridine ring system, other than acetylation of the parent compound,[2] have


R

(9) Br
(10) Cl
(11) NO₂
(12) NH₂
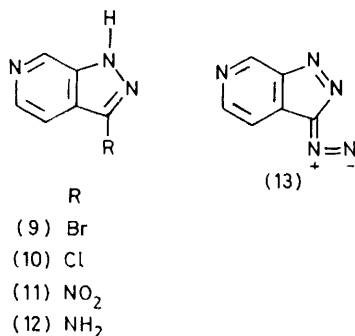
not been investigated. Electrophilic substitution occurs readily at the 3-position; thus treatment of pyrazolo-[3,4-c]pyridine with bromine water or sodium hypochlorite gave the corresponding 3-bromo- and 3-chloro-compounds [(9) and (10)]. The bromo-compound was also prepared by treatment of the diazopyrazolopyridine (13) with hydrobromic acid. The diazocompound was obtained by reduction of 3-nitropyrazolopyridine (11) to the amine (12) followed by diazotisation.[2,8] Nitration of pyrazolo[3,4-c]pyridine and 5-methylpyrazolo[3,4-c]pyridine gave the corresponding 3-nitro-compounds in excellent yield.

Acetylation of 5-methyl- and 5-methoxy-pyrazolo-[3,4-c]pyridine (5a and b) with acetic anhydride in boiling benzene gave the 1-acetyl compounds (6a and b). Under these conditions the 5-chloropyrazolopyridine (5c) also

gave a small amount of the 2-acetyl product; the 1-acetyl compound can be obtained exclusively on treatment with acetic anhydride in the absence of solvent. Acetylation of the 7-methoxy-compound (5d) in toluene at 100 °C gives mainly the 2-isomer, presumably due to steric hindrance by the peri-substituent. The proportion of the 1-acetyl-7-methoxypyrazolopyridine obtained can be increased to 80% by refluxing in acetic anhydride alone. A pair of isomers of this type can usually be distinguished by the carbonyl absorption in the i.r. spectrum, since the 2-acyl-compounds absorb 25—30 cm⁻¹ to higher wave number.[2] However this criterion is less reliable in 7-substituted-pyrazolopyridines since the substituent twists the 1-acetyl group out of the plane of the aromatic ring. This increases the wave number of the carbonyl absorption, and results in a difference of only 5 cm⁻¹ between the isomers. In such cases assignment of structure is more reliably based on n.m.r. evidence.[2,9]

We have investigated the benzylation of 5-chloro-(5c) and 3-nitro-pyrazolo[3,4-c]pyridine (11). Treatment of the anion of the 5-chloropyrazolopyridine with benzyl bromide gave a mixture of the 1- and 2-benzyl compounds which were separated chromatographically. The u.v. spectra of the isomers in ethanol were similar and assignment of structure is thus based on n.m.r. data. Elguero et al. have assigned the structures of many 1- and 2-alkylindazoles on the basis of shifts in the position of ¹H n.m.r. resonances in a range of solvents.[9] For the above 1- and 2-benzyl compounds, shifts in peak positions in deuteriochloroform as compared to [²H₆]acetone were identical in sign, although not in magnitude, to those recorded by Elguero for 1- and 2-methyl-6-nitroindazole. Furthermore, it has been reported [10] that in chloroform solution the 7-proton of 2-methylindazoles is deshielded by the lone pair of electrons at N-1 and occurs at a lower τ value than in the corresponding 1-isomers. Under these conditions the absorption due to the 7-proton occurs at τ 1.00 for the 2-benzylpyrazolopyridine and at τ 1.50 for the 1-benzyl compound.

Benzylation of 3-nitropyrazolo[3,4-c]pyridine (11)

(14)   (15)

(16)   (17)
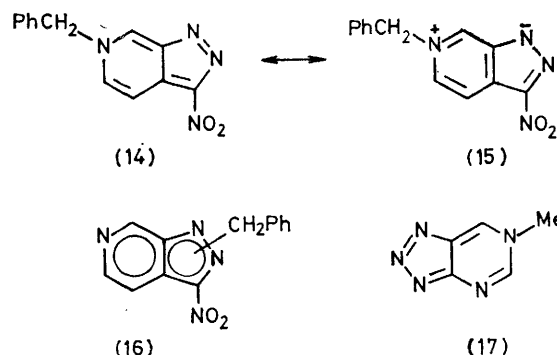
gave the 6-benzyl compound (14) as the major product together with smaller amounts of the 1- and 2-isomers (16). The structures of the latter compounds have been tentatively assigned, but a more detailed n.m.r. study

is required for confirmation. The 6-benzyl-3-nitro-pyrazolo[3,4-c]pyridine is much more polar than the other isomers, as shown by its higher melting point and reduced solubility in non-polar solvents. This may reflect the contribution of the charged structure (15) to the resonance hybrid. It has been reported that 1-methyl-8-azapurine(17) has much more polar character than its 7-, 8-, or 9-methyl isomers.[11]

The u.v. and n.m.r. spectrum of the 6-benzylpyrazolo-pyridine (14) also differs from the spectra of the 1- and 2-benzyl compounds (16). Protons 4-H and 7-H are markedly deshielded as would be expected for protons in a quaternised pyridine ring [see structure (15)]. However 5-H would also be expected to be deshielded but it is shifted to a higher τ-value. This could be due to shielding by the aromatic ring of the benzyl group at N-6. The n.m.r. spectra of 3-nitropyrazolo[3,4-c]pyr-idine (11) and 5-methyl-3-nitropyrazolo[3,4-c]pyridine in [$^2H_6$]dimethyl sulphoxide containing D$^+$, or in trifluoroacetic acid, show that protons 4-H, 5-H, and 7-H are all strongly deshielded when N-6 is protonated (see Experimental section).

Halogen atoms α and γ to pyridine N-atoms are usually susceptible to attack by nucleophiles.[12] Thus treatment of 7-chloropyrazolo[3,4-c]pyridine (5e) with aniline and with piperidine gave the expected products (5; R = H, R^1 = anilino or piperidino). In contrast, on treatment with sodium methoxide, a stronger nucleophile, no reaction occurred and unchanged starting material was recovered. This is presumably due to deprotonation of the pyrazolopyridine to give the corresponding anion, which will be less reactive. The low reactivity of 2-chlorobenzimidazole towards powerful nucleophiles has been reported, whereas in its 1-methyl derivative, where deprotonation cannot occur, the halogen is readily replaced.[13] Treatment of 5-chloro-pyrazolo[3,4-c]pyridine (5c), or its 1- and 2-benzyl derivatives, with aniline, piperidine, or sodium meth-oxide, even under forcing conditions, failed to give the required substitution products. In all cases starting material was recovered almost quantitatively. The above observations are in agreement with the known differences in reactivity between 1-chloro- and 3-chloro-isoquinoline.[14] Similarly the 4-halogen atom in 4,6-dichloropyrazolo[4,3-c]pyridines is more reactive than the 6-substituent.[15]

The behaviour of the 5- and 7-methoxypyrazolo-pyridines (5b and d) mirrors that of the corresponding chloro-compounds. Thus treatment of the 7-methoxy-compound (5d) with hydrochloric acid gave the pyrazolo-pyridone (8) in good yield. Under similar conditions the 5-methoxy-group was unaffected. Prolonged treat-ment with hydrochloric or hydrobromic acid gave oily products which could not be identified. Attempted demethylation with boron tribromide in methylene chloride was also unsuccessful.[16] Frydman et al. have observed similar behaviour in methoxypyrrolopyr-idines.[17,18]

I.r. spectra were recorded for Nujol mulls with a Perkin-Elmer 157 or 157 G spectrophotometer. N.m.r. spectra were recorded with a Perkin-Elmer R12 (60 MHz) instru-ment with tetramethylsilane as internal standard. Accu-rate mass measurements were determined with an A.E.I. MS 902 spectrometer operating at 70 eV. Column chro-matography was carried out using Kieselgel 60 PF$_{254}$ (Merck). Preparative t.l.c. was carried out using 100 × 20 cm plates with 1-mm Kieselgel PF$_{254}$ (Merck) layers. Light petroleum (b.p. 60—80 °C) was used except where otherwise stated.

General Method for the Preparation of 3-Acetamido-4-methylpyridines (1).—The 3-amino-4-methylpyridine (1 g), acetic anhydride (1 g), and toluene (10 ml) were heated at 100 °C for 2 h. The solvent was removed under reduced pressure to yield the crude acetamide (See Table 1).

5-*Acetamido-2,4-dimethylpyridine* (1a). 5-Amino-2,4-dimethylpyridine [19] was treated as above, and distillation of the residue under reduced pressure yielded the acetamide (62%). This material was found to be hygroscopic and could not be purified further.

5-*Acetamido-2-methoxy-4-methylpyridine* (1b). 5-Amino-2-methoxy-4-methylpyridine [20] was treated as above; crystallisation from ethyl acetate gave the *acetamide* (92%).

5-*Acetamido-2-chloro-4-methylpyridine* (1c). The pro-cedure described below for the preparation of 3-acetamido-2-chloro-4-methylpyridine was used. Thus 2-chloro-4-methyl-5-nitropyridine [21] (6 g) gave crude 5-amino-2-chloro-4-methylpyridine which was treated by the general method. When cooled the reaction mixture yielded the acetamide [5.2 g, 77% (overall yield)].

3-*Acetamido-2-methoxy-4-methylpyridine* (1d). 3-Amino-2-methoxy-4-methylpyridine was treated as above; crystal-lisation from ethyl acetate–light petroleum yielded the *acetamide* (54%).

3-*Acetamido-2-chloro-4-methylpyridine* (1e). 2-Chloro-4-methyl-3-nitropyridine [21] (3 g) in ether (20 ml) was added dropwise to a stirred solution of tin(II) chloride (16 g) in concentrated hydrochloric acid (20 ml) and heated at 100 °C for 3 h. The reaction mixture was cooled and the pH adjusted to 12 by addition of 20% sodium hydroxide solution. The suspension obtained was extracted with chloroform (6 × 50 ml), the extract was dried (MgSO$_4$), and the solvent removed *in vacuo* to yield crude 3-amino-2-chloro-4-methylpyridine. The amino-compound was treated as above, and crystallisation from ethyl acetate–light petroleum gave the *acetamide* [2.1 g, 61% (overall yield)].

General Methods for the Preparation of 1- and 2-Acetyl-pyrazolo[3,4-c]pyridines (6) *from 3-Acetamido-4-methyl-pyridines* (1).—A stirred, cooled suspension of the 3-acetamido-4-methylpyridine (5 g) and anhydrous potassium acetate (5 g) in acetic anhydride (5 ml) and acetic acid (5 ml) was treated with a solution of nitrosyl chloride (5 g) in acetic anhydride (10 ml) during 15 min. After stirring for a further 15 min the suspension was added to a stirred suspension of anhydrous sodium carbonate (20 g) in dry benzene (150 ml). When the effervescence had ceased the suspension was filtered, the residue washed with dry benzene (100 ml), and the combined benzene solutions were refluxed for 2 h. Evaporation of the solution yielded a dark solid which on sublimation (110—120 °C at 0.5 mmHg) gave the acetylpyrazolopyridine.

1-*Acetyl*-5-*methyl*-1H-*pyrazolo*[3,4-c]*pyridine*   (1-Ac-6a).
5-Acetamido-2,4-dimethylpyridine was treated as before to
yield 1-*acetyl*-5-*methyl*-1H-*pyrazolo*[3,4-c]*pyridine* (82%).

1-*Acetyl*-5-*methoxy*-1H-*pyrazolo*[3,4-c]*pyridine*   (1-Ac-6b).
5-Acetamido-2-methoxy-4-methylpyridine was treated as
above to yield an orange solid which on crystallisation from
light petroleum yielded the *pyrazolopyridine* (69%).
Crystallisation of the residue from the sublimation from
dimethylformamide   yielded   1-*acetyl*-5-*methoxy*-1H-*pyr-
azolo*[3,4-c]*pyridine*-3-*azo*-3'-(6'-*methoxy*-4'-*methylpyridine*)
(7) (17%).

1-*Acetyl*-5-*chloro*-1H-*pyrazolo*[3,4-c]*pyridine* (1-Ac-6c).   5-
Acetamido-2-chloro-4-methylpyridine was treated as above
to yield a mixture of the 1- and 2-acetyl-5-chloropyrazolo-
[3,4-c]pyridines (66%); $\nu_{max.}$ 1 730 and 1 760 cm^{-1}. Re-
peated crystallisation from cyclohexane yielded the 1-
acetyl-compound.

2-*Acetyl*-7-*methoxy*-2H-*pyrazolo*[3,4-c]*pyridine* (2-Ac-6d).
3-Acetamido-2-methoxy-4-methylpyridine was treated as
above to yield a mixture of the 1- and 2-acetylpyrazolo-
pyridines (94%). Repeated crystallisation from light
petroleum yielded 2-*acetyl*-7-*methoxy*-2H-*pyrazolo*[3,4-c]-
pyridine.

General Method for the Preparation of 1H-*Pyrazolo*[3,4-c]-
pyridines (5).—The acetylpyrazolopyridine (3 g) and 10%

and 2-acetyl-7-methoxypyrazolopyridines (1.0 g) and dilute
hydrochloric acid were refluxed for 30 min; dissolution of
the solid was followed by precipitation of the product.
The reaction mixture was cooled, basified, and then neutral-
ised with acetic acid.   The solid obtained was collected and
crystallised from dimethylformamide to give the *pyrazolo-
pyridone* (0.7 g, 99%).

7-*Methoxy*-1H-*pyrazolo*[3,4-c]*pyridine*   (5d).—3-Acet-
amido-2-methoxy-4-methylpyridine (5 g), phosphorus penta-
oxide (0.4 g), and potassium acetate (5 g) were added to
acetic acid (15 ml).   The mixture was cooled and stirred
whilst nitrosyl chloride was passed in for 15 *min*, after
which stirring was continued for a further 15 min.   The
reaction mixture was added to a stirred suspension of
sodium carbonate (40 g) in benzene (250 ml) and stirred until
effervescence ceased.   The filtered benzene solution was
refluxed for 2 h, and evaporation of the solvent under
reduced pressure yielded the crude pyrazolopyridine.
Sublimation (130—140 °C at 0.5 mmHg) and crystallisation
from toluene yielded 7-*methoxy*-1H-*pyrazolo*[3,4-c]*pyridine*
(3.3 g, 82%).

7-*Chloro*-1H-*pyrazolo*[3,4-c]*pyridine*   (5e).—(*a*)   3-Acet-
amido-2-chloro-4-methylpyridine was treated in a similar
manner to the methoxy-compound in the previous synthesis
to yield a mixture on removal of the benzene.   The mixture

TABLE 1

Physical and analytical data for the 3-acetamido-4-methylpyridines (1)

Compound	M.p. (°C)	¹H n.m.r. (τ) [a]	$\nu_{max.}$/cm^{-1} (Nujol)	Molecular formulae	Analysis Found (required) (%)			
					C	H	N	Other
(1a) [b]	192—196 [c]	1.6 (1 H, s, 6-H), 1.6—1.9 (1 H, s, NH), 3.05 (1 H, s, 3-H), 7.55 (3 H, s, Me), 7.84 and 7.86 (6 H, 2 s, Me and COMe)	3 250 (N—H), 1 670 (C=O), 1 620, 1 380					
(1b)	138—139	1.98 (1 H, s, 6-H), 2.25—2.55 (1 H, s, NH), 3.45 (1 H, s, 3-H), 6.10 (3 H, s, OMe), 7.86 (6 H, s, 4-Me and COMe)	3 250 (N—H), 1 640 (C=O), 1 605, 1 520	$C_9H_{12}N_2O_2$	60.05 (60.0)	6.7 (6.65)	15.6 (15.55)	
(1c)	155—156	1.6 (1 H, s, 6-H) 2.3—2.5 (1 H, s, NH), 2.9 (1 H, s, 5-H), 7.8 (3 H, s, Me), 7.85 (3 H, s, COMe)	3 200 (N—H), 1 650 (C=O), 1 600, 1 580	$C_6H_6ClNO_2$	52.05 (52.0)	4.9 (4.9)	15.25 (15.2)	18.95 (Cl) (19.25)
(1d)	110—112	2.05 (1 H, d, J 6 Hz, 6-H), 2.70—3.00 (1 H, s, NH), 3.20 (1 H, d, J 6 Hz, 5-H), 6.00 (3 H, s, OMe), 7.70—7.75 (6 H, 2 s, Me and COMe)	3 275 (N—H), 1 670 (C=O), 1 610, 1 400	$C_9H_{12}N_2O_2$	60.05 (60.0)	6.65 (6.65)	15.75 (15.55)	
(1e)	119—120	2.05 (1 H, d, J 6 Hz, 6-H), 2.2—2.4 (1 H, s, NH), 3.0 (1 H, d, J 6 Hz, 5-H), 7.78 (3 H, s, Me), 7.82 (3 H, s, COMe)	3 250 (N—H), 1 660 (C=O), 1 510, 1 390	$C_6H_6ClNO_2$	52.05 (52.0)	4.9 (4.9)	15.25 (15.2)	18.95 (Cl) (19.25)

[a] Solvent CDCl$_3$.   [b] See ref. 19.   [c] B.p. at 4 mmHg.

hydrochloric acid (10 ml) were refluxed for 30 min.   The
reaction mixture was adjusted to pH 7 with 20% sodium
hydroxide solution and the crude product was obtained
either directly by filtration, or by extraction with chloro-
form (3 × 50 ml).

5-*Methyl*-1H-*pyrazolo*[3,4-c]*pyridine*   (5a).   The   acetyl
compound gave 5-methyl-1*H*-pyrazolo[3,4-c]pyridine (98%)
from toluene.[19]

5-*Methoxy*-1H-*pyrazolo*[3,4-c]*pyridine*   (5b).   1-Acetyl-5-
methoxy-1*H*-pyrazolo[3,4-c]pyridine   gave   the   *pyrazolo-
pyridine* (92%) from toluene.

5-*Chloro*-1H-*pyrazolo*[3,4-c]*pyridine*   (5c).   The   acetyl
compounds gave 5-*chloro*-1H-*pyrazolo*[3,4-c]*pyridine* (92%)
from toluene.

1H-*Pyrazolo*[3,4-c]*pyridin*-7(6H)-*one* (8).   The mixed 1-

was extracted with acetone, and the solvent removed under
reduced pressure to yield the crude chloro-compound.
Crystallisation from toluene gave 7-*chloro*-1H-*pyrazolo*-
[3,4-c]*pyridine* (9%).   Crystallisation of the residue from
the acetone extraction from dimethylformamide yielded
1*H*-pyrazolo[3,4-c]pyridin-7(6*H*)-one   (8)   (2%),   m.p.
>300 °C, identical to an authentic sample.

(*b*) Chlorine was bubbled into a cooled, stirred suspension
of 1*H*-pyrazolo[3,4-c]pyridine-7(6*H*)-thione (2.8 g) in con-
centrated hydrochloric acid (20 ml) for 20 min.   The result-
ing solution was neutralised with aqueous sodium hydroxide
to yield the chloro-compound (2 g, 71%), identical to
previously prepared material.

1H-*Pyrazolo*[3,4-c]*pyridin*-7(6H)-*thione* (8, S *for* O).—The
pyrazolopyridone (8) (5 g), phosphorus pentasulphide (10 g),

Table 2

Physical and analytical data for the pyrazolo[3,4-c]pyridines

Compound	M.p. (°C)	^{1}H N.m.r. (τ) ^{a}	$\nu_{max.}/$ cm^{-1} (Nujol)	Molecular formulae	Analysis Found (required)(%)			
					C	H	N	Other
(5a) ^{b}	171—172	−0.5 (1 H, br, NH), 1.0 (1 H, s, 7-H), 1.95 (1 H, s, 3-H), 2.55 (1 H, s, 4-H), 7.3 (3 H, s, Me)	3 400—2 500 (N–H) 1 590, 1 460, 1 150	$C_7H_7N_3$	62.85 (36.15)	5.3 (5.3)	31.7 (31.55)	
(5b)	169—170	1.4 (1 H, s, 7-H), 2.0 (1 H, s, 3-H), 3.0 (1 H, s, 4-H), 6.0 (3 H, s, Me)	3 400—2 500 (N–H), 1 480, 1 310, 1 240	$C_7H_7N_3O$	56.1 (56.4)	4.7 (4.7)	28.45 (28.2)	
(5c)	184—185	−0.5 (1 H, br, NH), 1.12 (1 H, s, 7-H), 1.8 (1 H, s, 3-H), 2.15 (1 H, s, 4-H) ^{e}	3 300—2 300 (N–H), 1 470, 1 390, 1 250	$C_6H_4ClN_3$	46.6 (46.9)	2.5 (2.6)	27.5 (27.35)	
(1-Benzyl-5c)	80—81	1.5 (1 H, d, J 1 Hz, 7-H), 2.1 (1 H, s, 3-H), 2.5 (1 H, d, J 1 Hz, 4-H), 2.8 (5 H, s, Ph), 4.45 (2 H, s, −CH₂−)	1 600, 1 560, 1 200, 1 150, 1 070, 865	$C_{13}H_{10}ClN_2$	64.0 (64.1)	4.3 (4.15)	17.15 (17.25)	14.3 (Cl) (14.55)
(2-Benzyl-5c)	113—114	1.0 (1 H, d, J 1 Hz, 7-H), 2.15 (1 H, s, 3-H), 2.55 (1 H, d, J 1 Hz, 4-H), 2.7 (5 H, s, Ph), 4.4 (2 H, s, −CH₂−)	1 610, 1 540, 1 450, 1 370, 1 160, 1 140	$C_{13}H_{10}ClN_3$	63.9 (64.1)	4.3 (4.15)	17.3 (17.25)	14.5 (Cl) (14.55)
(5d)	153—154	1.9 (1 H, s, 3-H), 2.18 (1 H, d, J 6 Hz, 5-H), 2.75 (1 H, d, J 6 Hz, 4-H), 5.8 (3 H, s, OMe)	3 250—2 400 (N–H), 1 580, 1 500, 1 300	$C_7H_7N_3O$	56.0 (56.35)	4.5 (4.7)	28.5 (28.2)	
(5e)	161—163	3.2 (1 H, br, NH), 1.82 (1 H, s, 3-H), 1.96 (1 H, d, J 6 Hz, 5-H), 2.25 (1 H, d, J 6 Hz, 4-H) ^{c}	3 300—2 600 (N–H), 1 570, 1 335, 1 260	$C_6H_4ClN_3$	47.3 (46.9)	2.75 (2.6)	27.2 (27.35)	
(5; R = H, R′ = anilino)	189—191	1.95 (1 H, s, 3-H), 2.0—2.3 (3 H, m, Ar-H), 2.4—3.1 (4 H, m, 4-H, 5-H, and Ar-H) ^{c}	3 400—2 600, 3 375 (N–H), 1 640, 1 580	$C_{12}H_{10}N_4$	68.35 (68.85)	5.0 (4.8)	26.85 (26.65)	
(5; R = H, R′ = piperidino)	172—174	1.95 (1 H, s, 3-H), 2.25 (1 H, d, J, 6 Hz, 5-H), 2.95 (1 H, d, J 6 Hz, 4-H), 6.2 (4 H, m, −CH₂−), 8.3 (6 H, m, −CH₂−) ^{c}	3 200—2 200, (N–H), 1 600, 1 570, 1 480	$C_{11}H_{14}N_4$	65.3 (65.25)	7.0 (6.9)	27.7 (27.55)	
(1-Ac-6a)	127—128	0.40 (1 H, s, 7-H), 1.95 (1 H, s, 3-H), 2.6 (1 H, s, 4-H), 7.2 (3 H, s, Me), 7.3 (3 H, s, COMe)	1 710 (C=O), 1 460, 1 360, 1 275, 1 210	$C_9H_9N_3O$	61.8 (61.7)	5.2 (5.1)	24.2 (24.2)	
(1-Ac-6b)	115—116	0.82 (1 H, s, 7-H), 2.08 (1 H, s, 3-H), 3.14 (1 H, s, 4-H), 6.08 (3 H, s, OMe), 7.40 (3 H, s, COMe)	1 700 (C=O), 1 620, 1 575, 1 500, 1 320	$C_9H_9N_3O_2$	56.5 (56.4)	4.7 (4.4)	22.0 (22.3)	
(1-Ac-6c)	133—133.5	0.60 (1 H, s, 7-H), 1.95 (1 H, s, 3-H), 2.40 (1 H, s, 4-H), 7.20 (3 H, s, COMe)	1 730 (C=O), 1 570, 1 470, 1 375, 1 275	$C_8H_6ClN_3O$	49.0 (49.1)	3.2 (3.1)	21.5 (21.5)	
(1-Ac-6d)	127—128	1.95 (1 H, s, 3-H), 2.0 (1 H, d, J 6 Hz, 5-H), 2.9 (1 H, d, J 6 Hz, 4-H), 5.85 (3 H, s, OMe), 7.2 (3 H, s, COMe)	1 745 (C=O), 1 580, 1 500, 1 400, 1 380	$C_9H_9N_3O_2$	56.2 (56.4)	4.65 (4.4)	22.3 (22.3)	
(2-Ac-6d)	120—121	1.4 (1 H, s, 3-H), 2.4 (1 H, d, J 8 Hz, 5-H), 3.0 (1 H, d, J 8 Hz, 4-H), 5.85 (3 H, s, OMe), 7.1 (3 H, s, COMe)	1 750 (C=O), 1 520, 1 300, 1 200, 1 140	$C_9H_9N_3O_2$	56.2 (56.4)	4.6 (4.4)	22.3 (22.3)	
(7)	269—270	0.16 (1 H, s, 7-H), 1.02 (1 H, s, 6′-H), 1.7 (1 H, s, 3′-H), 2.3 (1 H, s, 4-H), 5.6 (3 H, s, OMe), 5.65 (3 H, s, OMe), 6.8 (3 H, s, Me), 6.9 (3 H, s, COMe) ^{d}	1 720 (C=O), 1 610 (N=N), 1 560, 1 485, 1 400, 1 305	$C_{16}H_{16}N_6O_3$	56.7 (56.5)	4.9 (4.7)	24.6 (24.7)	
(8)	>320	−1.2 (1 H, br, NH), 2.0 (1 H, s, 3-H), 2.2 (1 H, br, NH), 3.0 (1 H, d, J 6 Hz, 5-H), 3.4 (1 H, d, J 6 Hz, 4-H) ^{c}	3 500—2 500, 3 400 and 3 150 (N–H) 1 695 (C=O)	$C_6H_5N_3O$	53.1 (53.3)	3.7 (3.7)	31.4 (31.1)	
(8; S for O)	258—260	−3.5 (1 H, br, NH), 1.95 (1 H, s, 3-H), 2.75 (1 H, d, J 6 Hz, 5-H), 2.95 (1 H, d, J 6 Hz, 4-H) ^{c}	3 200—2 500 (N–H), 1 570, 1 460, 1 380	$C_6H_5N_3S$	47.4 (47.7)	3.3 (3.3)	28.0 (27.8)	21.3 (S) (21.2)
(9)	208—210	0.85 (1 H, d, $J_{4,7}$ 1 Hz, 7-H), 1.55 (1 H, d, J 6 Hz, 6-H), 2.35 (1 H, q, J 6 Hz and 1 Hz, 4-H) ^{c}	3 200—2 100 (N–H), 1 460, 1 250, 1 040	$C_6H_4BrN_3$	36.2 (36.4)	2.2 (2.0)	21.35 (21.2)	40.1 (Br) (40.3)
(10)	212—212.5	0.80 (1 H, d, $J_{4,7}$ 1 Hz, 7-H), 1.55 (1 H, d, J 6 Hz, 5-H), 2.30 (1 H, q, J 6 Hz and 1 Hz, 4-H) ^{c}	3 250—2 200 (N–H), 1 460, 1 275, 1 050	$C_6H_4ClN_3$	46.8 (46.9)	2.65 (2.65)	27.2 (27.35)	23.0 (Cl) (23.1)
(11)	272—274	0.70 (1 H, s, 7-H), 1.45 (1 H, d, 5-H), 1.95 (1 H, d, 4-H); ^{e}, 0.05 (1 H, s, 7-H), 1.10 (2 H, s, 4- and 5-H); ^{e} 0.07 (1 H, s, 7-H), 0.93 (1 H, d, J 6 Hz, 4-H), 1.13 (1 H, d, J 6 Hz, 5-H)	2 550(br) (N–H), 1 490, (NO₂), 1 390, 1 360 (NO₂)	$C_6H_4N_4O_2$	43.9 (43.9)	2.6 (2.55)	34.1 (34.15)	

TABLE 2 (Continued)

Compound	M.p. (°C)	¹H N.m.r. (τ)	$\nu_{max.}$/cm⁻¹ (Nujol)	Molecular formulae	Analysis Found (required)(%)			
					C	H	N	Other
(5-Me-11)	284—285	0.85 (1 H, s, 7-H), 2.1 (1 H, s, 4-H), 7.3 (3 H, s, Me),^{c} 0.05 (1 H, s, 7-H), 1.20 (1 H, s, 4-H) ^{e}	3 125—2 200 (N–H), 2 075, 1 640, 1 500	$C_7H_6N_4O_2\cdot$ $0.5H_2O$	44.95 (44.9)	4.0 (3.8)	30.1 (30.0)	
(12)	213—214	1.30 (1 H, d, $J_{4,7}$ 1 Hz, 7-H), 2.0 (1 H, d, $J_{4,5}$ 6 Hz, 5-H), 2.35 (1 H, q, J 6 Hz and 1 Hz, 4-H), 4.2—5.5 (2 H, br, NH₂) ^{c}	3 400, 3 350— 2 100 (NH₂ and NH), 1 610	C_6H_6N	43.5 (53.7)	4.6 (4.5)	41.85 (41.8)	
(13)	145 (decomp.)	0.45 (1 H, s, 7-H), 1.45 (1 H, d, J 6 Hz, 5-H), 2.37 (1 H, d, J 6 Hz, 4-H)	2 200 (=N⁺=N⁻), 1 600, 1 460, 1 120, 920	$C_6H_3N_5$	M^+, 145.0395 (145.0389)			
(14)	228—230	0.0 (1 H, d, $J_{4,7}$ 1 Hz, 7-H), 1.5 (1 H, q, J 1 and 6 Hz, 4-H), 1.7 (1 H, d, $J_{4,5}$ 6 Hz, 5-H), 2.55 (5 H, s, Ph), 4.1 (2 H, s, CH₂) ^{e}	1 610, 1 480, 1 380, 1 180, 1 140, 1 080	$C_{13}H_{10}N_4O_2$	61.2 (61.4)	4.3 (3.95)	21.95 (22.0)	
(1-Benzyl-16)	110—112	0.7 (1 H, d, $J_{4,7}$ 1 Hz, 7-H), 1.55 (1 H, d, $J_{4,5}$ 6 Hz, 5-H), 2.15 (1 H, q, J 1 and 6 Hz, 4-H), 2.7 (5 H, s, Ph), 3.8 (2 H, s, CH₂) ^{c}	1 520, 1 410. 1 380, 1 360, 1 250, 1 180	$C_{13}H_{10}N_4O_2$	M^+, 254.0808 (254.0808)			
(2-Benzyl-16)	159—160	0.55 (1 H, d, $J_{4,7}$ 1 Hz, 7-H), 1.45 (1 H, d, $J_{4,5}$ 6 Hz, 5-H), 2.0 (1 H, q, J 1 and 6 Hz, 4-H), 2.65 (5 H, s, Ph), 4.0 (2 H, s, CH₂) ^{e}	1 610, 1 510, 1 400, 1 340, 1 275, 840	$C_{13}H_{10}N_4O_2$	61.1 (61.4)	4.1 (3.95)	22.0 (22.0)	

^{a} Solvent CDCl₃ except where stated otherwise. ^{b} See ref. 19. ^{c} Solvent (CD₃)₂SO. ^{d} Solvent CF₃CO₂H. ^{e} Solvent (CH₃)₂SO + D⁺.

and pyridine (100 ml) were refluxed for 4.5 h. The solvent was removed under reduced pressure to yield a dark tar. The tar was digested with 5% sodium hydroxide solution (100 ml), the pH was then adjusted to 6 with concentrated hydrochloric acid, and the solid which was obtained filtered off. Crystallisation from ethanol gave the thione (3.8 g, 67%), m.p. 258—260 °C.

3-Bromo-1H-pyrazolo[3,4-c]pyridine (9).—(a) 1H-pyrazolo[3,4-c]pyridine (1 g), bromine (1.33 g), and water (40 ml) were stirred for 1 h. Basification with 20% sodium hydroxide solution, and adjustment to pH 7 by addition of acetic acid, yielded the bromo-compound (1.1 g, 67%).

(b) 3-Diazo-3H-pyrazolo[3,4-c]pyridine (0.5 g) and 60% hydrobromic acid (0.5 ml) were refluxed for 20 min. The mixture was basified with 20% sodium hydroxide solution and neutralised with acetic acid to yield the bromo-compound (0.6 g, 94%), identical with the sample prepared earlier.

3-Chloro-1H-pyrazolo[3,4-c]pyridine (10).—1H-Pyrazolo[3,4-c]pyridine (2 g) was stirred in an aqueous solution of sodium hypochlorite (40 ml, technical grade) for 1 h. The solution was neutralised with acetic acid to yield the chloro-compound (0.9 g, 40%). Sublimation yielded needles, m.p. 212—212.5 °C.

3-Nitro-1H-pyrazolo[3,4-c]pyridine (11).—A mixture of concentrated sulphuric acid (1 ml) and concentrated nitric acid (1 ml) was added dropwise to a stirred, cooled solution of 1H-pyrazolo[3,4-c]pyridine (1 g) in concentrated sulphuric acid (3 ml) over 5 min. The solution was heated on a boiling water-bath for 1 h, cooled, and neutralised with aqueous ammonia solution (d 0.88) to yield the nitro-compound (1.1 g, 80%). Crystallisation from butanol gave yellow prisms.

5-Methyl-3-nitro-1H-pyrazolo[3,4-c]pyridine (5-Me-11).—Under the above conditions 5-methyl-1H-pyrazolo[3,4-c]pyridine yielded the nitro-compound (1.1 g, 83%) from ethanol.

3-Amino-1H-pyrazolo[3,4-c]pyridine (12).—A solution of 3-nitro-1H-pyrazolo[3,4-c]pyridine (3 g), palladium–charcoal (10%, 0.3 g), and ethanol (100 ml) was shaken together with hydrogen (2 atm.) until no further uptake of hydrogen occurred. The catalyst was filtered off and the solvent removed in vacuo to yield the crude amino-compound. Crystallisation from ethanol yielded pale yellow needles (1.5 g, 61%).

3-Diazo-3H-pyrazolo[3,4-c]pyridine (13).—Sodium nitrite (0.6 g) was slowly added to a cooled, stirred solution of 3-amino-1H-pyrazolo[3,4-c]pyridine (1 g) in aqueous sulphuric acid (1.5 ml in 10 H₂O), the solution being stirred for 30 min. Neutralisation with aqueous ammonia solution (d 0.88) yielded the diazo-compound (1.05 g, 97%).

1-Acetyl-7-methoxy-1H-pyrazolo[3,4-c]pyridine (1-Ac-6d).—7-Methoxy-1H-pyrazolo[3,4-c]pyridine (0.5 g) and acetic anhydride (5 ml) were refluxed for 3 h. The solvent was removed in vacuo to yield a mixture of the 1- and 2-acetyl compounds which on repeated crystallisation from cyclohexane yielded the 1-acetylpyrazolopyridine (0.2 g, 31%).

The Benzylation of 5-Chloropyrazolo[3,4-c]pyridine.—(a) The 5-chloro-compound (5c) (0.5 g) and sodium methoxide [from sodium (0.08 g) and methanol (10 ml)] were refluxed for 15 min. Benzyl bromide (0.67 g) was added and the mixture was refluxed for 2 h. The solvent was removed in vacuo, water was added, and the pH adjusted to 6.5 with dilute hydrochloric acid. The mixture was extracted with ethyl acetate (3 × 50 ml), and the extract was dried (MgSO₄) and evaporated to yield a mixture of the 1- and 2-benzyl compounds.

The mixture was separated on a 12-in silica column by elution with toluene. The polarity of the solvent was gradually increased by the addition of ethyl acetate. Elution with ethyl acetate–toluene (1 : 19) gave the 1-benzyl-compound (1-benzyl-5c) (0.15 g, 20%). Elution with ethyl acetate–toluene (1 : 9) yielded the 2-benzyl compound (2-benzyl-5c) (0.284 g, 36%).

(b) The chloro-compound (0.5 g), sodium hydroxide (0.13 g), and 90% ethanol (2 ml) were heated on a boiling water-bath for 15 min. Benzyl bromide (0.57 g) was added and the mixture was refluxed for 2 h. A mixture of 1- and 2-benzyl compounds was obtained by the above

procedure. Preparative t.l.c. [ethyl acetate–toluene (1 : 3) as eluant] followed by extraction of the band at higher R_F gave the 1-benzyl compound (0.2 g, 25%). The 2-benzyl compound (0.2 g, 25%) was obtained from the band at lower R_F.

The Benzylation of 3-*Nitro*-1H-*pyrazolo*[3,4-c]*pyridine.*— The 3-nitro-compound (11) (5 g), sodium methoxide (from 0.8 g sodium), and methanol (100 ml) were refluxed for 30 min. Benzyl bromide (5.7 g) was added and refluxing was continued for a further 3 h. The solvent was removed *in vacuo* and the residue was extracted with boiling cyclohexane (3 × 100 ml). The cyclohexane-insoluble solid was washed with chloroform (50 ml) and crystallised from ethanol to yield 6-*benzyl*-3-*nitro*-6H-*pyrazolo*[3,4-c]*pyridine* (14) (3.2 g, 41%). Preparative t.l.c. on the cyclohexane extract [benzene–ethyl acetate (1 : 1) as eluant] followed by extraction of the band at higher R_F gave 1-*benzyl*-3-*nitro*-2H-*pyrazolo*[3,4-c]*pyridine* (1-benzyl-16) (0.07 g, 0.9%). Extraction of the lower R_F band yielded 2-*benzyl*-3-*nitro*-1H-*pyrazolo*[3,4-c]*pyridine* (2-benzyl-16) (0.185 g, 2.4%).

7-*Anilino*-1H-*pyrazolo*[3,4-c]*pyridine* (5; R = H, R' = anilino).—7-Chloro-1H-pyrazolo[3,4-c]pyridine (1 g) and aniline (10 ml) were heated at 100 °C for 3 h. The solvent was removed *in vacuo* and the residue was treated with sodium carbonate solution. The mixture was extracted with chloroform (3 × 50 ml), and the extract was dried (MgSO₄) and evaporated. Crystallisation from toluene yielded the *anilino-compound* (0.47 g, 24%).

7-*Piperidino*-1H-*pyrazolo*[3,4-c]*pyridine* (5; R = H, R' = *piperidino*).— 7-Chloro-1H-pyrazolo[3,4-c]pyridine (1 g) and piperidine (10 ml) were heated under reflux for 3 h. The solvent was removed *in vacuo* and the residue was extracted with boiling chloroform. Evaporation of the chloroform gave a solid which on crystallisation from toluene yielded the *piperidino-compound* (0.8 g, 60%).

REFERENCES

[1] Part 4, H. E. Foster and J. Hurst, *J.C.S. Perkin I*, 1976, 507.

[2] H. E. Foster and J. Hurst, *J.C.S. Perkin I*, 1973, 2901.

[3] L. C. Behr, R. Fusco, and C. H. Jarboe, ' Heterocyclic Compounds; Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings,' Interscience, New York and London, 1967, vol. 22, p. 295.

[4] R. Huisgen and R. Nakaten, *Annalen*, 1954, **586**, 84; H. Suschitzky, *Angew. Chem. Internat. Edn.*, 1967, **6**, 596; C. Rüchardt and C. C. Tan, *Chem. Ber.*, 1970, **103**, 1774; B. H. Klanderman, D. P. Maier, G. W. Clark, and J. A. Kampmeier, *Chem. Comm.*, 1971, 1003; F. Tröndlin, R. Werner, and C. Rüchardt, *Chem. Ber.*, 1978, **111**, 367.

[5] I. K. Barben and H. Suschitzky, *J. Chem. Soc.*, 1960, 2735.

[6] J. Brennan, J. I. G. Cadogan, and J. T. Sharp, *J.C.S. Perkin I*, 1977, 1844.

[7] W. A. Nasutavicus and J. Love, *J. Heterocyclic Chem.*, 1974, **11**, 77.

[8] J. M. Tedder, *Adv. Heterocyclic Chem.*, 1967, **8**, 1.

[9] J. Elguero, A. Fruchier, and R. Jacquier, *Bull. Soc. chim. France*, 1966, 2075.

[10] M. H. Palmer, R. H. Findlay, S. M. F. Kennedy, and P. S McIntyre, *J.C.S. Perkin II*, 1975, 1695.

[11] A. Albert, *J.C.S. Perkin I*, 1978, 513.

[12] H. E. Mertel, ' Heterocyclic Compounds; Pyridine and Its Derivatives,' Interscience, New York and London, 1961, vol. 14, part 2, p. 299.

[13] D. Harrison and J. T. Ralph, *J. Chem. Soc.*, 1965, 236.

[14] N. B. Chapman and D. Q. Russell-Hill, *J. Chem. Soc.*, 1956, 1563.

[15] M. D. Nair, S. R. Mehta, and S. M. Kalbag, *Indian J. Chem.*, 1967, **5**, 464.

[16] J. F. W. McOmie and M. L. Watts, *Chem. and Ind.*, 1963, 1658.

[17] B. Frydman, S. J. Reil, J. Boned, and H. Rapoport, *J. Org. Chem.*, 1968, **33**, 3762.

[18] B. Frydman, S. J. Reil, M. E. Despuy, and H. Rapoport, *J. Amer. Chem. Soc.*, 1969, **91**, 2338.

[19] S. Furukawa, *J. Pharm. Soc. Japan*, 1956, **76**, 900.

[20] D. M. Besley and A. A. Goldberg, *J. Chem. Soc.*, 1954, 2448.

[21] A. Roe and R. B. Seligman, *J. Org. Chem.*, 1955, **20**, 1729.