# Pyrazolo[3,4-*b*]pyridines. The Preparation of 1-Protected-1*H*-pyrazolo-[3,4-*b*]pyridines and Attempts to Remove the 1-Substituent. Some Reactions of 1-Benzyl-1*H*-pyrazolo[3,4-*b*]pyridine and its 7-Oxide

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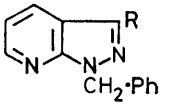
1-Protected-1*H*-pyrazolo[3,4-*b*]pyridines [*e.g.* (4)] and -1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-ones [*e.g.* 14)] have been obtained from 1-substituted-5-aminopyrazoles [*e.g.* (1)], and the removal of the protecting groups has been investigated. Cyclisation of 1-substituted-5-aminopyrazoles with ethyl acetoacetate under acidic conditions or of the β-aminopropionic acid derivative (19) under the same conditions gave only the 1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one isomer [*e.g.* (14) and (20), respectively]. *N*-Oxidation of 1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridine (4) gave the 7-oxide (21) which yielded (20) and the less usual β-substitution product (22) with acetic anhydride. Nitration of either (4) or (21) gave only substitution at the *para*-position of the 1-benzyl substituent, but bromination or chlorination gave substitution at the 3-position of the heterocycle.

Our investigations [1] of the alkylation and acylation of 3-aminopyrazole have shown that 5-amino-1-benzylpyrazole (1) is not readily obtained by these routes but is best prepared by a synthesis from 2-hydrazinoethyl

(1) R = $CH_2Ph$
(2) R = $CH_2 \cdot C_{10}H_7$-1
(3) R = Et

(4) R = $CH_2Ph$
(5) R = 1-$CH_2 \cdot C_{10}H_7$-1
(6) R = Et



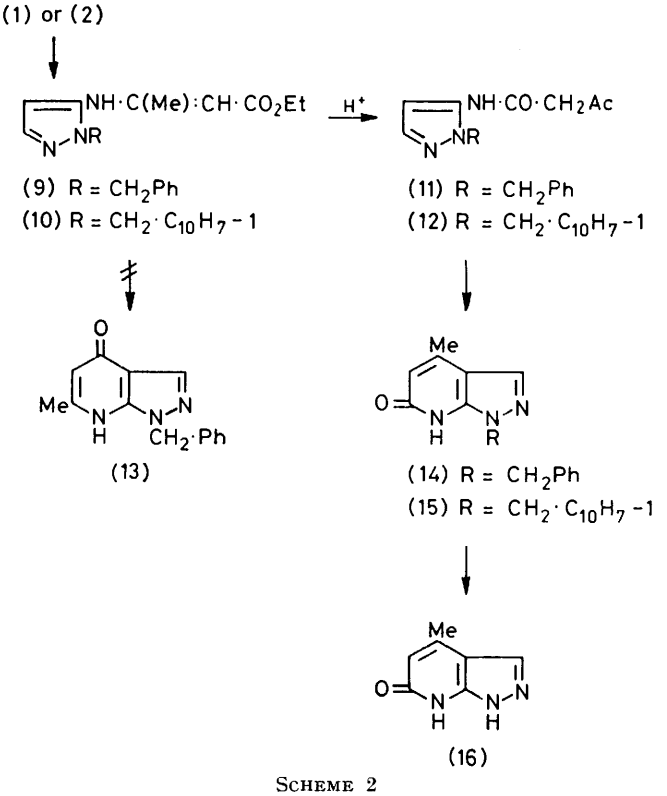
(7) R = Br
(8) R = Cl

Scheme 1

cyanide and benzaldehyde.[2] We next investigated the routes to 1-unsubstituted-pyrazolo[3,4-*b*]pyridine using (1) and other 1-substituted-5-aminopyrazoles, and also explored some reactions of the 1-benzyl derivative of the bicyclic system.

Previous workers [3] have obtained 1-substituted-pyrazolo[3,4-*b*]pyridines by applying the Skraup reaction to 1-substituted-5-aminopyrazoles, and this method was found to give 1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridine (4) in useful yield (Scheme 1). The 5-amino-1-benzylpyrazole (1) had been chosen as the reactant rather than the 1-phenyl or 1-alkyl derivative, which have been used frequently in earlier work, in the expectation [1] that the 1-benzyl substituent might be removable. However, attempted catalytic hydrogenolysis of (4) over palladium–charcoal or palladium black failed to yield any debenzylated product. These results were unexpected since Dorn and Zubek [4] have quoted the catalytic hydrogenolysis of what they reported as 1-benzyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-4(7*H*)-one (13) (Scheme 2). These workers also found that the use of sodium–liquid ammonia gave a higher yield of debenzylated product, but our attempts to use this method with (4) were unsuccessful. In the light of these unexpectedly different results reported by Dorn and Zubek on the one hand and found by ourselves on the other hand, we decided to re-investigate (i) the assignment of the structure (13) given by Dorn and Zubek, and (ii) the debenzylation of this compound.

The structure (13) assigned by Dorn and Zubek was in some doubt, since Tabak *et al.*[5] have given evidence that products obtained from 1-substituted-5-aminopyrazoles and ethyl acetoacetate in acetic acid solution (the method



(1) or (2)

(9) R = $CH_2Ph$
(10) R = $CH_2 \cdot C_{10}H_7$-1

(11) R = $CH_2Ph$
(12) R = $CH_2 \cdot C_{10}H_7$-1

(13)

(14) R = $CH_2Ph$
(15) R = $CH_2 \cdot C_{10}H_7$-1

(16)

Scheme 2

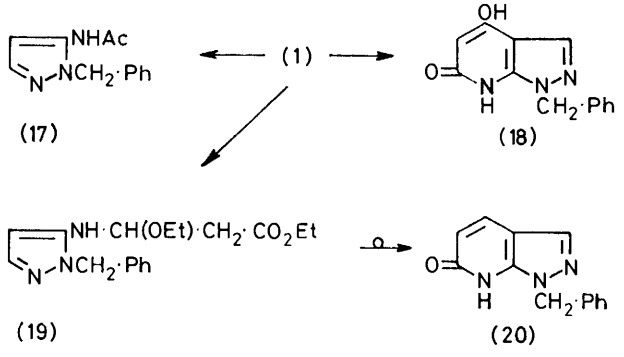
by which the compound was obtained by Dorn and Zubek) have the α-pyridone structure (*e.g.* 14), and have proposed that the intermediate crotonate (9) undergoes rearrangement to the acetoacetamide (11) prior to cyclisation. An analogous process has been shown to occur with benzenoid derivatives.[6] Very recently, Ratajczyk and Swett [7] have given additional chemical evidence to support the assignment made by Tabak *et al.* and have also provided evidence from $^{13}C$ n.m.r. spectra to support their assignment of structures to isomeric pyrazolo[3,4-*b*]pyridones. Thus, quinolones and the pyrazolopyridones containing the γ-pyridone system had δ(C:O) *ca.* 178 p.p.m., while the isomeric compounds having the α-pyridone system had δ(C:O) *ca.* 163 p.p.m. Our repetition of Dorn and Zubek's condensation of 5-amino-1-benzylpyrazole and ethyl acetoacetate gave a product identical to that reported, but the compound had δ(C:O) *ca.* 163 p.p.m. and is therefore 1-benzyl-4-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (14). We were able to repeat Dorn and Zubek's debenzylation of this compound. This confirms that the 1-benzyl group may be removed from some substituted pyrazolo[3,4-*b*]-pyridines (perhaps indicating that the 6-CO group is a prerequisite), but is particularly difficult to remove in the case of 1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridine.

Catalytic hydrogenolysis of the C–N bond has been shown [8] to occur $10^4$ times more rapidly with 1-naphthylmethylamines than for benzylamines. It thus seemed possible that the 1-naphthylmethyl group might provide a suitable 1-protecting group for the pyrazolo[3,4-*b*]-pyridine nucleus. Naphthalene-1-carbaldehyde and 2-hydrazinoethyl cyanide afforded 5-amino-1-(1-naphthylmethyl)pyrazole (2) and this was subjected to the Skraup reaction to give 1-(1-naphthylmethyl)-1*H*-pyrazolo[3,4-*b*]pyridine (5), but only in poor yield. Treatment of (2) with ethyl acetoacetate in glacial acetic acid gave the pyrazolo[3,4-*b*]pyridone (15), presumably *via* the intermediates (10) and (12). The structure of (15) was assigned on the basis of its $^{13}C$ n.m.r. spectrum [δ(C:O) 165.2 p.p.m.].

Other potential methods for the removal of the *N*-benzyl group were investigated. Attempts to cause oxidation of the methylene group with selenium dioxide or ceric ammonium nitrate were unsuccessful. Treatment of (4) with *N*-bromosuccinimide with either photochemical or peroxide initiation produced 1-benzyl-3-bromo-1*H*-pyrazolo[3,4-*b*]pyridine (7). Also, chlorination of (4) with chlorine in carbon tetrachloride gave only 1-benzyl-3-chloro-1*H*-pyrazolo[3,4-*b*]pyridine (8).

Recently, ready *N*-dealkylation of 1-alkylpyrazoles in the presence of anhydrous pyridine hydrochloride at reflux temperature has been reported.[9] When this reaction was tried on 1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridine (4) a 59% recovery of starting material was obtained together with a 58% [based on recovered (4)] yield of debenzylated material. Attempts to improve this yield by use of a longer reaction time, the use of pyridine hydrobromide, or the pyrolysis of the hydrochloride of (4) alone gave, respectively, more decomposition and only a maximum of a 40% yield of pyrazolo[3,4-*b*]-pyridine based on recovered (4), no significant difference in yield compared with that obtained with the hydrochloride, and quantitative recovery of (4). Hydriodic acid was also ineffective. Butler and De Wald's results [9] were quoted for 1-methyl- and 1-ethylpyrazole. 5-Amino-1-ethylpyrazole (3) was prepared and converted into 1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine (6). However, dealkylation with pyridine hydrochloride produced a result very similar to that obtained with (4).

An attempt at formation of 1-benzyl-4-hydroxy-1*H*-pyrazolo[3,4-*b*]pyridin-6-one (18) by treatment of (1) with diethyl malonate in acetic acid gave only 5-acetamido-1-benzylpyrazole (17) (Scheme 3), but in the



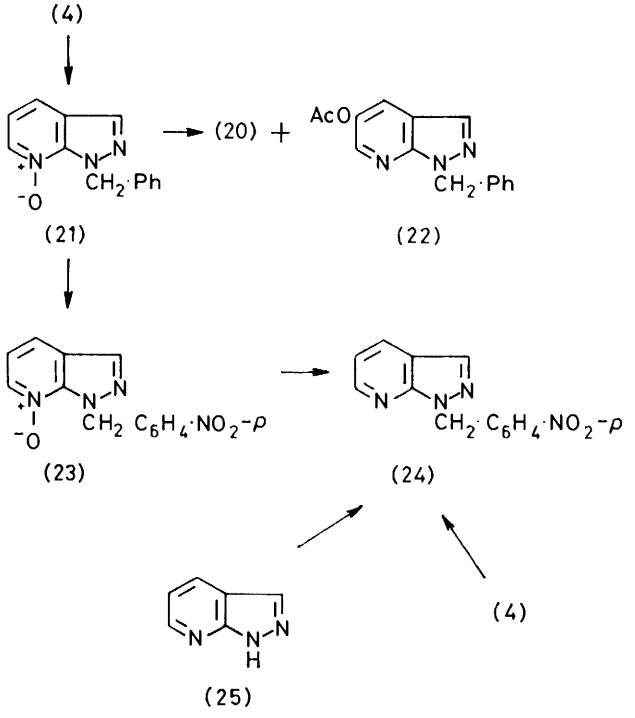

SCHEME 3

presence of base a product was obtained which had elemental analysis and i.r., mass, and $^1H$ n.m.r. spectra consistent with its formulation as a hydroxypyrazolo-[3,4-*b*]pyridone. The $^{13}C$ n.m.r. spectrum showed a peak due to the C:O group at δ 165.7 p.p.m., so indicating that the compound exists as the α-pyridone tautomer (18). Treatment of methyl propiolate with (1) in ethanolic sodium ethoxide yielded the double Michael reaction product (19), which underwent acid-catalysed elimination, rearrangement, and cyclisation to give 1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (20). The structure of (19) followed from its $^1H$ n.m.r. spectrum and the structure of (20) was deduced from the $^1H$ and, in particular, the $^{13}C$ n.m.r. spectrum, which showed δ(C:O) 163 p.p.m.

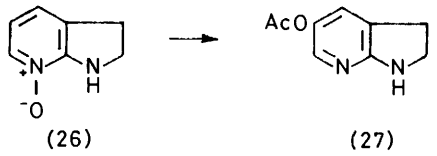
The first *N*-oxide of the pyrazolo[3,4-*b*]pyridine ring system was obtained by treatment of 1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridine with a mixture of glacial acetic acid and hydrogen peroxide or (better) with *m*-chloroperbenzoic acid. The product was shown to be the mono-*N*-oxide and was thought to be 1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridine 7-oxide (21) (Scheme 4), rather than the isomeric 2-oxide, on the basis of the $^1H$ n.m.r. spectral evidence that the 3-H (particular) and the 5-H were little shifted from their positions in the spectrum of (4), but the 4-H and, to a lesser extent, the 6-H showed marked shifts to higher field. We are unaware of any instance where *N*-oxidation of a 5 : 6-bicyclic system has occurred in the 5-membered ring when the heterocycle contains oxidisable nitrogen atoms in both the five- and

six-membered rings. Hydrogenolysis of a compound having both an *O*-benzyl and an *N*-oxide group may occur with [10] or without [11] retention of the *N*-oxide group. It was hoped that the presence of the *N*-oxide function might facilitate hydrogenolysis of the *N*-benzyl group; however, hydrogenolysis of (21) yielded only (4).

Rearrangement of the 7-oxide (21) in the presence of acetic anhydride and sodium acetate yielded two oxygen-containing products, and the minor one was 1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (20). The major product (53%) was shown from its elemental analysis and mass and n.m.r. spectra to contain an acetoxy-group, and the chemical shifts and small coupling constants of the pyridine-ring protons showed the compound to be 5-acetoxy-1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridine (22). The formation of this compound is unusual, since nucleophilic substitution β to the pyridine-ring nitrogen atom is rare, though isolated cases have been reported. Interestingly, the related 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-pyridine 7-oxide (26) is stated [12] to give the 5-acetoxy-derivative (27) though in poor yield. Photochemical rearrangement of the pyrazolopyridine 7-oxide (21) gave only (20) in high yield.




SCHEME 4




Nitration of 1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridine (4) with a mixture of concentrated sulphuric and concentrated nitric acids yielded a nitro-derivative and the n.m.r. spectrum indicated that substitution had occurred at the 4-position of the phenyl ring to give (24). This assignment was confirmed by the preparation of (24) from the pyrazolopyridine (25) and *p*-nitrobenzyl chloride in the presence of the base. A by-product was 4,4'-dinitrostilbene and this is known [13] to be formed from *p*-nitrobenzyl chloride in the presence of certain bases. Nitration of the pyrazolopyridine 7-oxide (21) gave only the corresponding product (23) formed by nitration in the phenyl nucleus even under forcing conditions. The structure of (23) was proved by its deoxygenation to give (24) in the presence of phosphorus trichloride.

## EXPERIMENTAL

I.r. and $^1$H n.m.r. spectra were measured as described previously.[14] $^{13}$C N.m.r. spectra were measured on a Varian CFT 20 spectrometer with tetramethylsilane as internal standard. Mass spectra were obtained on a Hitachi–Perkin-Elmer RMS 4 spectrometer operated at 70 eV.

1-*Benzyl*-1H-*pyrazolo*[3,4-b]*pyridine* (4).—5-Amino-1-benzylpyrazole [2] (70 g), glycerol (160 g), nitrobenzene (68 g), and concentrated sulphuric acid (96 g) were heated to 130 °C for 6 h with continuous stirring. The cold mixture was poured into water (500 cm$^3$), basified to pH 10 by addition of sodium hydroxide solution, and extracted with chloroform (4 × 250 cm$^3$). The extract yielded a black gum which was distilled to yield 5-amino-1-benzylpyrazole (12 g), b.p. 176—178 °C at 0.5 mmHg and the lower boiling 1-*benzyl*-1H-*pyrazolo*[3,4-b]*pyridine* (4) (35 g, 50% with allowance for recovered starting material), b.p. 146—148 °C at 0.5 mmHg (Found: C, 74.8; H, 5.3; N, 20.3. $C_{13}H_{11}N_3$ requires C, 74.6; H, 5.3; N, 20.1%), δ ($CDCl_3$) 8.42 (1 H, dd, *J* 2 and 4 Hz, 6-H), 7.83 (1 H, s, 3-H), 7.80 (1 H, dd, *J* 2 and 8 Hz, 4-H), 7.10 (5 H, m, Ph), 6.86 (1 H, dd, *J* 4 and 8 Hz, 5-H), and 5.67 (2 H, s, $CH_2$).

1-*Benzyl*-3-*bromo*-1H-*pyrazolo*[3,4-b]*pyridine* (7).—1-Benzyl-1*H*-pyrazolo[3,4-*b*]pyridine (4) (0.5 g) and freshly recrystallised *N*-bromosuccinimide (1.1 g) were dissolved in dioxan (9 cm) and a suspension of calcium carbonate (0.5 g) in water (1 cm$^3$) added. The mixture was stirred for 2.5 h at 70 °C whilst it was irradiated with a 100-W tungsten filament lamp. The mixture was poured into water (10 cm$^3$) and extracted with chloroform (3 × 50 cm$^3$). The extracts yielded a residue which was triturated with carbon tetrachloride. The soluble fraction was crystallised from benzene–light petroleum (b.p. 60—80 °C) to give 1-*benzyl*-3-*bromopyrazolo*[3,4-b]*pyridine* (7) (0.15 g), m.p. 88—90 °C (Found: C, 54.2; H, 3.5; N, 14.7. $C_{13}H_{10}N_3Br$ requires C, 54.2; H, 3.5; N, 14.6%), δ ($CDCl_3$) 8.82 (1 H, dd, *J* 2 and 5 Hz, 6-H), 8.18 (1 H, dd, *J* 2 and 9 Hz, 4-H), 7.46 (6 H, m, Ph and 5-H), and 5.85 (2 H, s, $CH_2$).

The same compound was obtained (14%) when benzoyl peroxide was employed as the initiator, in the absence of calcium carbonate, and the mixture heated under reflux for 6 h.

1-*Benzyl*-3-*chloro*-1H-*pyrazolo*[3,4-b]*pyridine* (8).—Chlorine was bubbled through a solution of 1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridine (5 g) in carbon tetrachloride (20 cm$^3$) for 25 min. The mixture was washed with aqueous sodium hydroxide and the organic layer evaporated to give a viscous oil. G.l.c. showed only one product which was purified by preparative g.l.c. (20% OV-17 at 220 °C) to give 1-*benzyl*-

3-*chloro*-1H-*pyrazolo*[3,4-b]*pyridine* (8), m.p. 54—55 °C (Found: C, 64.3; H, 4.1; N, 17.5. $C_{13}H_{10}N_3Cl$ requires C, 64.1; H, 4.1; N, 17.2%), δ ($CDCl_3$) 8.53 (1 H, dd, *J* 1.5 and 4 Hz, 6-H), 7.95 (1 H, dd, *J* 1.5 and 8 Hz, 4-H), 7.27 (5 H, m, Ph), 7.10 (1 H, q, 5-H), and 5.63 (2 H, s, $CH_2$).

5-*Amino*-1-*ethylpyrazole* (3).—(2-Cyanoethyl)hydrazine (25.5 g), acetaldehyde (13.2 g), and ethanol (50 cm³) were refluxed for 1 h. The solvent was removed and the residue poured into a vigorously stirred solution of sodium (6.9 g) in t-butyl alcohol (250 cm³). The mixture was heated under reflux for 16 h and then poured into water (500 cm³), and the solution extracted with ether (4 × 100 cm³). The extract yielded 5-amino-1-ethylpyrazole (3) (12.4 g, 37%), b.p. 106—108 °C at 4 mmHg (lit.,[2] 75 °C at 0.25 mmHg), δ ($CDCl_3$) 7.42 (1 H, d, *J* 2 Hz, 3-H), 5.63 (1 H, d, *J* 2 Hz, 4-H), 4.06 (2 H, q, *J* 8 Hz, $CH_2$), 4.10 (2 H, s, exchanged in $D_2O$, $NH_2$), and 1.40 (3 H, t, *J* 8 Hz, Me).

1-*Ethyl*-1H-*pyrazolo*[3,4-b]*pyridine* (6).—5-Amino-1-ethylpyrazole (3) (5.6 g) in a mixture of glycerol (21.0 g), nitrobenzene (4.3 g), and concentrated sulphuric acid (11.25 g), and by a procedure similar to that described for the preparation of the 1-benzyl analogue, afforded a fraction, b.p. 62—68 °C at 4 mmHg. This fraction was added to dilute hydrochloric acid (10 cm³) and extracted with chloroform. The aqueous phase was basified with sodium hydroxide and extracted with chloroform to give 1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine (6) (3 g, 41%) as an oil with a strong mouse-like odour. The compounds was converted into its less troublesome hydrochloride and crystallisation from ethanol gave 1-*ethyl*-1H-*pyrazolo*[3,4-b]*pyridine hydrochloride*, m.p. 125—126 °C (Found: C, 51.9; H, 5.4; N, 22.7; Cl, 19.05. $C_8H_{10}N_3Cl$ requires C, 52.3; H, 5.45; N, 22.9; Cl, 19.35%), δ [$(CD_3)_2SO$] 9.85 (1 H, s, exchanged in $D_2O$, $\overset{+}{N}H$), 8.35 (1 H, dd, *J* 2 and 4.5 Hz, 6-H), 8.08 (1 H, dd, *J* 2 and 8 Hz, 4-H), 7.98 (1 H, s, 3-H), 7.05 (1 H, dd, *J* 4.5 and 8 Hz, 5-H), 4.42 (2 H, q, *J* 7 Hz, $CH_2$), and 1.40 (3 H, t, *J* 7 Hz, Me).

5-*Amino*-1-(1-*naphthylmethyl*)*pyrazole* (2).—1-Naphthaldehyde (5.4 g) and (2-cyanoethyl)hydrazine (3.0 g) were treated as described earlier for the preparation of the ethyl analogue to yield 5-*amino*-1-(1-*naphthylmethyl*)*pyrazole* (3.0 g, 38%), b.p. 182—186 °C at 0.5 mmHg, m.p. 93—94 °C (Found: C, 75.1; H, 6.1; N, 19.0. $C_{14}H_{13}N_3$ requires C, 75.3; H, 5.8; N, 18.8%), $\nu_{max.}$ (liquid film) 3 300 and 3 200 $cm^{-1}$ ($NH_2$), δ ($CDCl_3$) 7.66 (7 H, m, $C_{10}H_7$), 7.45 (1 H, d, *J* 2 Hz, 3-H), 5.70 (2 H, s, $CH_2$), 5.63 (1 H, d, *J* 2 Hz, 4-H), and 3.67 (2 H, s, exchanged in $D_2O$, $NH_2$).

1-(1-*Naphthylmethyl*)-1H-*pyrazolo*[3,4-b]*pyridine* (5).—The aforementioned 5-amino-1-(1-naphthylmethyl)pyrazole (2) (3.0 g) afforded a distillate 0.6 g), b.p. 160—180 °C at 0.1 mmHg by a method similar to that described for the benzyl analogue. The oil was chromatographed [silica gel; chloroform–ether (50 : 50 v/v)] to give 1-(1-*naphthylmethyl*)-1H-*pyrazolo*[3,4-b]*pyridine* (0.35 g, 10%), m.p. 63—65 °C (Found: C, 79.0; H, 5.25; N, 16.4. $C_{17}H_{13}N_3$ requires C, 78.8; H, 5.0; N, 16.2%), δ ($CDCl_3$) 8.83 (1 H, dd, *J* 2 and 5 Hz, 6-H), 8.33 (1 H, dd, *J* 2 and 8 Hz, 4-H), 8.30 (1 H, s, 3-H), 7.85 (7 H, m, $C_{10}H_7$), 7.35 (1 H, dd, *J* 5 and 8 Hz, 5-H), and 6.37 (2 H, s, $CH_2$).

1H-*Pyrazolo*[3,4-b]*pyridine* (25).—(*a*) Pyridine (7.9 g) and an excess of concentrated hydrochloric acid were mixed and the mixture distilled until the temperature in the flask rose to 210 °C. 1-Benzyl-1*H*-pyrazolo[3,4-*b*]pyridine (4) (0.85 g) was then added, and the mixture heated under reflux for 6 h. The mixture was poured into water (100 cm³) and extracted with chloroform (5 × 35 cm³) to yield unchanged 1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridine (0.5 g). The aqueous phase was basified with aqueous ammonia and extracted with chloroform (4 × 30 cm³). Evaporation of the extract and distillation of the residue gave 1*H*-pyrazolo[3,4-*b*]-pyridine (25) (0.12 g, 58% with allowance for recovered starting material), b.p. 110—120 °C at 0.1 mmHg, identical with an authentic sample.

(*b*) Under identical conditions to those described, 1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine (6) (0.92 g) gave 1*H*-pyrazolo-[3,4-*b*]pyridine (25) (0.13 g, 56%) and starting material (0.45 g).

1-*Benzyl*-4-*methyl*-1H-*pyrazolo*[3,4-b]*pyridin*-6(7H)-*one* (14).—This compound was prepared by the method of Dorn and Zubek [4] who wrongly assigned its structure as 1-benzyl-6-methylpyrazolo[3,4-*b*]pyridin-4(7*H*)-one (13). 5-Amino-1-benzylpyrazole (0.85 g) gave 1-benzyl-4-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (0.6 g, 51%), m.p. 225—227 °C (lit.,[4] 227—228 °C) (Found: C, 70.5; H, 5.6. Calc. for $C_{14}H_{13}N_3O$: C, 70.3; H, 5.4%), $\nu_{max.}$ 3 450 (NH) and 1 660 $cm^{-1}$ (CO), δ [$(CD_3)_2SO$] 11.60 (1 H, s, exchanged in $D_2O$, NH), 8.32 (1 H, d, *J* 1 Hz, 3-H), 7.43 (5 H, m, Ph), 6.42 (1 H, d, *J* 1 Hz, 5-H), 6.18 (2 H, s, $CH_2$), and 2.43 (3 H, s, Me), $\delta_C$ [$(CD_3)_2SO$] 163.6 (CO).

4-*Methyl*-1-(1-*naphthylmethyl*)-1H-*pyrazolo*[3,4-b]*pyridin*-6(7H)-*one* (15).—5-Amino-1-(1-naphthylmethyl)pyrazole (2) (1.1 g), ethyl acetoacetate (0.72 g), and glacial acetic acid (10 cm³) were refluxed for 16 h. Removal of the acetic acid gave a residue which was crystallised from ethanol as the *substituted pyrazolopyridone* (15) (0.8 g, 55%), m.p. 259—260 °C (Found: C, 74.7; H, 5.4; N, 14.4. $C_{18}H_{15}N_3O$ requires C, 74.7; H, 5.2; N, 14.5%), $\nu_{max.}$ 3 450 (NH) and 1 650 (CO) $cm^{-1}$, δ [$(CD_3)_2SO$] 11.80 (1 H, s, exchanged in $D_2O$, NH), 8.17 (1 H, d, *J* 1 Hz, 3-H), 7.95 (7 H, m, $C_{10}H_7$), 6.38 (1 H, d, *J* 1 Hz, 5-H), 6.12 (2 H, s, $CH_2$), and 2.50 (3 H, s, Me), and $\delta_C$ [$(CD_3)_2SO$] 165.2 (α-pyridone).

1-*Benzyl*-4-*hydroxy*-1H-*pyrazolo*[3,4-b]*pyridin*-6(7H)-*one* (18).—5-Amino-1-benzylpyrazole (1.75 g) was added to sodium (0.92 g) in ethanol (25 cm³) and, when solution was complete, diethyl malonate (3.5 g) was added. The mixture was refluxed for 20 h and then the ethanol was removed. Water (3 cm³) was added to the residue, the mixture acidified to pH 6 with acetic acid, and the solid filtered off. Crystallisation from methanol–chloroform gave the *hydroxyketone* (18) (0.8 g, 33%), m.p. 178—178.5 °C (Found: C, 65.05; H, 4.25; N, 17.3. $C_{13}H_{11}N_3O_2$ requires C, 64.7; H, 4.6; N, 17.4%), $\nu_{max.}$ 3 250 (NH) and 1 670 $cm^{-1}$ (CO), δ [$(CD_3)_2SO$] 7.63 (1 H, d, *J* 1.5 Hz, 3-H), 7.47 (6 H, m, became 5 H on addition of $D_2O$, Ph, and NH), 6.47 (1 H, d, *J* 1.5 Hz, 5-H), 5.43 (2 H, s, $CH_2$), and 3.67 (1 H, s, exchanged in $D_2O$, OH), $\delta_C$ [$(CD_3)_2SO$] 165.7 (α-pyridone).

*Ethyl* 3-(1-*Benzylpyrazol*-5-*ylamino*)-3-*ethoxypropionate* (19).—5-Amino-1-benzylpyrazole (1.75 g) was dissolved in a mixture of sodium (0.92 g) and ethanol (30 cm³), and ethyl propiolate (2.0 g) was added dropwise. After the exothermic reaction had moderated, the mixture was refluxed for 8 h and left to stand overnight. The mixture was filtered, the filtrate evaporated, and water (20 cm³) added to the residue. Acidification with acetic acid to pH 6 gave a precipitate, which was removed, dried, and purified by addition of light petroleum (b.p. 40—60 °C) to its solution in benzene. Sublimation (130 °C at 0.1 mmHg) of the solid gave the *ester* (19) (2.5 g, 79%), m.p. 96—97 °C (Found: C, 64.5; H, 7.5; N, 13.0. $C_{17}H_{23}N_3O_3$ requires C, 64.35; H,

7.3; N, 13.25%), $\nu_{max.}$ 3 230 (NH), 1 660 (CO), and 1 060 $cm^{-1}$ (C–O–C), δ ($CDCl_3$) 8.10 (1 H, s, exchanged on addition of $D_2O$, NH), 7.37 (1 H, d, *J* 2 Hz, 3-H), 7.13 (5 H, m, Ph), 6.27 (1 H, d, *J* 2 Hz, 4-H), 5.18 (2 H, s, PhC$H_2$), 4.65 (1 H, t, *J* 5 Hz, CH), 3.55 (2 H, q, *J* 7 Hz, $CH_2$), 3.48 (2 H, q, *J* 7 Hz, $CH_2$), 2.63 (2 H, d, *J* 5 Hz, C·$CH_2$·C), and 1.12 (6 H, t, *J* 7 Hz, 2 × Me).

1-*Benzyl*-1H-*pyrazolo*[3,4-b]*pyridin*-6(7H)-*one* (20).—(*a*) The aforementioned ester (0.5 g) in glacial acetic acid (10 $cm^3$) was refluxed for 4 h. The acid was removed and the residue crystallised from aqueous ethanol. The solid was sublimed (200 °C at 0.1 mmHg) to yield 1-*benzyl*-1H-*pyrazolo*[3,4-b]*pyridin*-6(7H)-*one* (0.23 g, 65%), m.p. 186—188 °C (Found: C, 68.9; H, 5.1; N, 18.2. $C_{13}H_{11}N_3O$ requires C, 69.3; H, 4.9; N, 18.7%), $\nu_{max.}$ 3 300 (NH) and 1 670 $cm^{-1}$ (CO), δ [$(CD_3)_2SO$] 8.40 (1 H, br s, exchanged in $D_2O$, NH), 7.60 (1 H, d, *J* 8.5 Hz, 4-H), 7.58 (1 H, s, 3-H), 7.12 (5 H, s, Ph), 6.23 (1 H, d, *J* 8.5 Hz, 5-H), and 5.42 (2 H, s, $CH_2$).

(*b*) A degassed solution of 1-benzyl-1*H*-pyrazolo[3,4-*b*]-pyridine 7-oxide (21) (0.85 g) in dry benzene (800 $cm^3$) was irradiated for 4 h with a Hanovia medium-pressure mercury lamp. Evaporation of the solution gave the ketone (20) (0.41 g, 48%), identical with the sample previously obtained.

1-*Benzyl*-1H-*pyrazolo*[3,4-b]*pyridine* 7-*Oxide* (21).—A mixture of *m*-chloroperbenzoic acid (2.7 g), 1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridine (1.6 g), and dichloromethane (10 $cm^3$) was allowed to stand for 6 days. Solid was removed and the solution washed with sodium carbonate solution. Evaporation of the organic phase and sublimation (110 °C at 4 mmHg) gave the N-*oxide* (21) (1.4 g, 81%), m.p. 75—76.5 °C (Found: C, 69.7; H, 5.05; N, 18.5. $C_{13}H_{11}N_3O$ requires C, 69.3; H, 4.9; N, 18.7%), $\nu_{max.}$ 1 240 $cm^{-1}$ ($\overset{+}{N}$–$\overset{-}{O}$), δ ($CCl_4$) 7.87 (1 H, d, *J* 6 Hz, 6-H), 7.70 (1 H, s, 3-H), 7.17 (6 H, m, Ph and 4-H), 6.72 (1 H, dd, *J* 6 and 8 Hz, 5-H), and 6.00 (2 H, s, $CH_2$).

1-*Benzyl*-5-*acetoxy*-1H-*pyrazolo*[3,4-b]*pyridine* (22).—The *N*-oxide (21) (1.0 g), acetic anhydride (25 $cm^3$), and sodium acetate (0.25 g) were refluxed for 5 h. The volatile material was removed under reduced pressure, water (10 $cm^3$) added, and the mixture extracted with ether (3 × 25 $cm^3$). The extract yielded an oil which was distilled to give a liquid (0.7 g), b.p. 150—160 °C at 0.1 mmHg. The distillate contained three major components (in the ratio 3 : 5 : 9.6 in order of retention time), which were separated by preparative g.l.c. (7 ft column of 20% Apiezon L on Diatomite C with $N_2$ at 700 $cm^3$ $min^{-1}$) with temperature programming at 4° $min^{-1}$ in the range 100—180 °C. The first and second components (retention times 11 and 18 min) were 1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridine (4) and 1-benzyl-1*H*-pyrazolo-[3,4-*b*]pyridin-6(7*H*)-one (20), respectively, and were identified by comparison with authentic samples. The third component (retention time 25 min) was 1-*benzyl*-5-*acetoxy*-1H-*pyrazolo*[3,4-b]*pyridine*, m.p. 95.5—96.5 °C (Found: C, 67.4; H, 5.0; N, 16.0. $C_{15}H_{13}N_3O_2$ requires C, 67.4; H, 4.9; N, 15.7%), $\nu_{max.}$ 1 770 $cm^{-1}$ (ester CO), δ ($CDCl_3$) 8.22 (2 H, d, *J* 2 Hz, 6-H), 7.88 (1 H, s, 3-H), 7.68 (1 H, d, *J* 2 Hz, 4-H), 7.18 (5 H, s, Ph), 5.63 (2 H, s, $CH_2$), and 2.33 (3 H, s Me).

1-(4-*Nitrobenzyl*)-1H-*pyrazolo*[3,4-b]*pyridine* 7-*Oxide* (23).—A mixture of 1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridine 7-oxide (21) (0.45 g), concentrated nitric acid (0.4 g), and concentrated sulphuric acid (0.9 g) was stirred at 80—85 °C for 5 h. The cooled solution was then added to ice, and the solid filtered off and washed with sodium carbonate solution. Crystallisation of the solid from ethyl acetate gave the *nitro-derivative* (23) (0.24 g, 44%), m.p. 188—190 °C (Found: C, 57.5; H, 3.8; N, 20.6. $C_{13}H_{10}N_4O_3$ requires C, 57.8; H, 3.8; N, 20.6%), $\nu_{max.}$ 1 520 and 1 340 $cm^{-1}$ ($NO_2$) and 1 248 $cm^{-1}$ ($\overset{+}{N}$–$\overset{-}{O}$), δ [$(CD_3)_2SO$] 8.62 (1 H, d, *J* 6 Hz, 6-H), 8.49 (1 H, s, 3-H), 8.28 (2 H, d, *J* 9 Hz, 3′- and 5′-H), 7.98 (1 H, d, *J* 8 Hz, 4-H), 7.58 (2 H, d, *J* 9 Hz, 2′- and 6′-H), 7.28 (1 H, dd, *J* 6 and 8 Hz, 5-H), and 6.42 (2 H, s, $CH_2$).

1-(4-*Nitrobenzyl*)-1H-*pyrazolo*[3,4-b]*pyridine* (24).—(*a*) In a similar way to that described for the 7-oxide (23), 1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridine (4) (0.6 g) in concentrated nitric acid (0.6 g) and concentrated sulphuric acid (2.0 g) yielded 1-(4-*nitrobenzyl*)-1H-*pyrazolo*[3,4-b]*pyridine* (24) (0.36 g, 49%), m.p. 114—116 °C [from benzene–light petroleum (b.p. 60—80 °C)] (Found: C, 61.2; H, 4.0; N, 22.0. $C_{13}H_{10}N_4O_2$ requires C, 61.4; H, 4.0; N, 22.0%), $\nu_{max.}$ 1 538 and 1 350 $cm^{-1}$ ($NO_2$), δ ($CDCl_3$) 8.58 (1 H, dd, *J* 1.5 and 4.5 Hz, 6-H), 8.09—8.23 (3 H, m, 4-, 3′-, and 5′-H), 8.09 (1 H, s, 3-H), 7.46 (2 H, d, *J* 9 Hz, 2′- and 6′-H), 7.17 (1 H, dd, *J* 4 and 8 Hz, 5-H), and 5.81 (2 H, s, $CH_2$). The use of fuming nitric acid (*d* 1.5) and concentrated sulphuric gave only the same product.

(*b*) A mixture of 1*H*-pyrazolo[3,4-*b*]pyridine (25) (0.24 g) and sodium ethoxide [from sodium (0.06 g)] was refluxed in ethanol (25 $cm^3$) for 2 h. *p*-Nitrobenzyl chloride (0.34 g) in ethanol (10 $cm^3$) was added to the cold solution and the mixture refluxed for 0.5 h. Water was added to the cold solution and the solid (0.08 g) was filtered off and crystallised from a large volume of acetic acid as 4,4′-dinitrostilbene, m.p. 288—292 °C (lit.,[13] 292—294 °C). The aqueous ethanolic filtrate was evaporated to dryness and the residue extracted with chloroform. Preparative g.l.c. (15% SE52 column at 245 °C) of the extract yielded a product which, on crystallisation from benzene–light petroleum (b.p. 60—80 °C) gave the nitro-compound (24), identical with that obtained previously.

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