Pyrazolopyridines. Part III.[1] Preparation and Reactions of Pyrazolo-[4,3-*b*]pyridines

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A series of pyrazolo[4.3-*b*]pyridines have been prepared by nitrosation of 3-acetamido-2-methylpyridines and rearrangement and cyclisation of the *N*-acetyl-*N*-nitroso-compounds produced. The reactions of the pyrazolo-[4.3-*b*]pyridines have been investigated. 1- and 2-Acyl compounds were obtained: their structures were elucidated by i.r. and n.m.r. spectroscopy. The ring system readily undergoes electrophilic substitution at the 3-position.

PYRAZOLO[4,3-*b*]PYRIDINE itself (Va) and derivatives unsubstituted in the pyrazole ring have not been reported previously. The use of 3-amino-2-methylpyridines (1; R′ = H) appeared to be the most feasible route to these compounds since indazoles,[2] pyrazoloquinolines,[3] and pyrazolopyrimidines[4] have been prepared from *o*-methyl primary aromatic amines, either by direct diazotisation or by rearrangement and

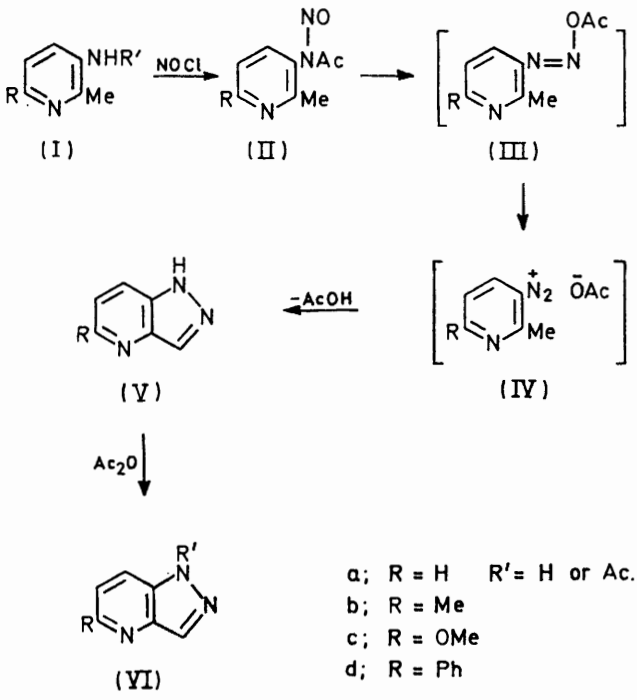
[1] Part II, H. E. Foster and J. Hurst, *J.C.S. Perkin I*, 1973, 319.

[2] L. C. Behr, 'Heterocyclic Compounds; Pyrazoles, Pyrazolones, Pyrazolidines, Indazoles, and Condensed Rings,' Interscience, New York–London, vol. 22, p. 295; C. Rüchardt and V. Hassmann, *Synthesis*, 1972, 375.

[3] D. W. Ockenden and K. Schofield, *J. Chem. Soc.*, 1953, 1915.

[4] F. L. Rose, *J. Chem. Soc.*, 1952, 3448; 1954, 4116.

cyclisation of their *N*-acyl-*N*-nitroso-derivatives. Pyrazolo[3,4-*c*]pyridines were obtained as by-products in the conversion of 3-amino-4-methylpyridines into the corresponding pyridinols.[5]



The 3-amino-2-methylpyridines (Ia—c; R′ = H) are known compounds. The 6-phenyl compound (Id; R′ = H) was obtained from the hydrazide of 2-methyl-6-phenylnicotinic acid by a Curtius rearrangement. Diazotisation of the amine (Ib; R′ = H) in sulphuric or acetic acid gave only 3-hydroxy-2,6-dimethylpyridine but the methoxy-amine (Ic; R′ = H) did afford the corresponding pyrazolopyridine (Vc), although in poor yield.

Treatment of the 3-acetamido-methylpyridines (Ia—d; R′ = Ac) with nitrosyl chloride gave the nitroso-compounds (IIa—d) as crude oils which were rearranged in boiling benzene without further purification. The pyrazolopyridines (Va, b, and d) were isolated as their 1-acetyl derivatives (VIa, b, and d; R′ = Ac) which were subsequently deacylated in aqueous acid. However under these conditions the methoxy-group of compound (VIc; R′ = Ac) was also hydrolysed, to yield 1*H*-pyrazolo[4,3-*b*]pyridin-5(4*H*)-one (VII). The 5-methoxypyrazolopyridine (Vc) was therefore prepared by nitrosation of the acetamide (Ic; R′ = Ac) in the absence of acetic anhydride. Pyrazolo[3,4-*c*]pyridine (XI) and its 1-acetyl derivative were obtained by the foregoing route from 3-acetamido-4-methylpyridine.

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

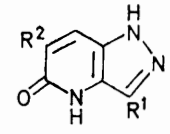
[6] M. Julia, H. Pinhas, and J. Igolen, *Bull. Soc. chim. France*, 1966, 2387.

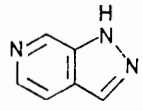
[7] R. Huisgen and R. Nakaten, *Annalen*, 1954, **586**, 84; H. Suschitzky, *Angew. Chem. Internat. Edn.*, 1967, **6**, 596; C. Rüchardt and C. C. Tan, *Chem. Ber.*, 1970, **103**, 1774; B. H. Klanderman, D. P. Maier, G. W. Clark, and J. A. Kampmeier, *Chem. Comm.*, 1971, 1003.

Cyclisation of the nitroso-derivative of 3-acetamido-2,4,6-trimethylpyridine, which can occur through the 2- or the 4-methyl group, afforded a yellow diacetyl compound, the structure of which is under investigation. Rearrangement of the *N*-nitroso-compound (IIa) in benzene has been carried out previously but 3-phenyl-2-methylpyridine was the only product recorded.[6]

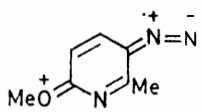
The mechanism for the formation of indazoles from *N*-acyl-*N*-nitroso-*o*-toluides has been discussed.[7] By analogy the formation of the pyrazolopyridines would be expected to involve the diazoester (III) and the ion-pair (IV). Tarry by-products were obtained in the preparation of compounds (VIa and b) but the 5-phenyl- and 5-methoxy-pyrazolopyridines (VIc and d) were obtained in excellent yield. This may be due to the +*M* effect of the phenyl and the methoxy-group, which would hinder nitrogen loss from the intermediates (III) and (IV) and thus retard competing side reactions [see structure (XII)]. *para*-Substituents of this type are known to retard the decomposition of benzenediazonium salts in water.[8]

Reactions of the pyrazolo[4,3-*b*]pyridine ring system with electrophiles have not been reported previously. Treatment of 5-methylpyrazolo[4,3-*b*]pyridine (Vb) with acetic anhydride, with benzoyl chloride, and with toluene-*p*-sulphonyl chloride under forcing conditions gave the 1-substituted compounds (VIb; R′ = Ac, Bz, or *p*-$MeC_6H_4{\cdot}SO_2$). Under milder conditions the 2-substituted derivatives (XIII; R = Me or Ph) were obtained. The structures of the products were determined by n.m.r. spectroscopy; a 1-acyl group causes a marked deshielding of the 7-proton whereas a 2-acyl





(XI)



(XII)

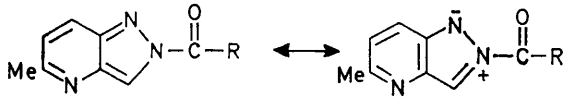
	R^1	R^2
(VII)	H	H
(VIII)	Br	H
(IX)	Br	Br
(X)	NO_2	NO_2

group deshields the 3-proton. Elguero *et al.* have used this technique to elucidate the structure of *N*-acylindazoles.[9] I.r. spectroscopy also distinguishes between a pair of isomers since the carbonyl group of a 2-acylpyrazolopyridine absorbs 25—30 cm^{-1} to higher wavenumber than that of the corresponding 1-acyl compound. Structure (XIV) would be expected to make a significant contribution to the resonance hybrid of the 2-acyl compound, as the six-membered ring is fully aromatic. Electron withdrawal by the positively charged nitrogen atom at the 2-position would thus account for the observed shift in the carbonyl absorption band.

[8] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' Cornell University Press, New York, 1953, p. 801.

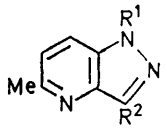
[9] J. Elguero, A. Fruchier, and R. Jacquier, *Bull. Soc. chim. France*, 1966, 2075.

5-Methylpyrazolo[4,3-*b*]pyridine (Vb) also undergoes electrophilic substitution at the 3-position. Thus the 3-bromo- and 3-nitro-compounds, (XV) and (XVI),

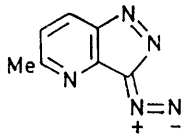


(XIII) (XIV)

were obtained in excellent yield. The pyrazolopyridone (VII) gives a 3-bromo- and a 3,6-dibromo-compound [(VIII) and (IX)] on treatment with bromine water, but on nitration only the dinitro-derivative (X) was isolated.



	R^1	R^2
(XV)	H	Br
(XVI)	H	NO_2
(XVII)	Me	NO_2
(XVIII)	H	NH_2
(XIX)	Ac	NHAc
(XX)	Ac	NAc_2



(XXI)

Methylation of 5-methyl-3-nitropyrazolo[4,3-*b*]pyridine (XVI) gave a mixture of the 1- and 2-methyl compounds. Recrystallisation from ethanol gave the 1-methyl isomer (XVII), the structure of which was assigned on the basis of the close similarity of its u.v. spectrum with that of the starting material.[10] Reduction of the nitro-group of compound (XVI) gave the amine (XVIII), which was subsequently acetylated to give a di- and a tri-acetyl derivative, (XIX) and (XX). Diazotisation of the amine (XVIII) in mineral acid followed by basification of the solution gave the diazopyrazolopyridine (XXI), as is characteristic of azoles which can be deprotonated.[11] Addition of hydrobromic acid to the diazo-compound regenerated the diazonium salt, and on heating the 3-bromo-compound (XV) was obtained.

Treatment of the pyrazolopyridone (VII) with phosphoryl chloride yielded the 5-chloro-compound (V; R = Cl), which was then converted into the 5-hydrazinopyrazolopyridine (V; R = NH·NH_2). The preparation of 7-chloro-3,5-dimethylpyrazolo[4,3-*b*]pyridine from the corresponding pyrazolopyridone has been reported.[12]

EXPERIMENTAL

I.r. spectra were recorded for Nujol mulls, except where stated, with a Unicam SP 200 spectrophotometer. U.v. data were obtained by using Unicam SP 800 and SP 500 spectrophotometers. N.m.r. spectra were recorded for solutions in deuteriochloroform, with tetramethylsilane as internal standard, with a Perkin-Elmer R12 (60 MHz) instrument. Preparative t.l.c. was carried out on 100 × 20 cm plates with 1 mm Kieselgel PF_{254} (Merck) layers. The light petroleum used had b.p. 60—80° except where stated otherwise.

3-Amino-2-methylpyridine and 3-amino-4-methylpyridine were prepared by hydrogenation of 6-chloro-2-methyl-3-nitropyridine [13] and 2-chloro-4-methyl-5-nitropyridine,[14] respectively, over palladium–charcoal. 3-Amino-6-methoxy-2-methylpyridine was obtained by the method of Besly,[15] and 3-amino-2,6-dimethylpyridine is available commercially.

2-Methyl-6-phenylnicotinohydrazide.—Ethyl 2-methyl-6-phenylnicotinate (48 g) and 100% hydrazine hydrate (48 ml) were heated under reflux for 15 min. The solution was clarified by addition of ethanol (60 ml) and was heated under reflux for a further 1 h. The solvent was evaporated off to yield the *hydrazide* (45 g, 98%). Crystallisation from ethanol gave prisms, m.p. 143° (Found: C, 68·85; H, 6·0; N, 18·7. $C_{13}H_{13}N_3O$ requires C, 68·7; H, 5·8; N, 18·5%), $\nu_{max.}$ 3300 and 3200 (N–H), 1640 (C=O), 1585, 1550 1510 (aryl), 1320, 1300, 730, and 680 cm^{-1}.

Ethyl N-(*2-Methyl-6-phenyl-3-pyridyl*)*carbamate.*—A solution of sodium nitrite (35 g) in water (35 ml) was added dropwise to a stirred, cooled solution of 2-methyl-6-phenylnicotinohydrazide (35 g) in 10% hydrochloric acid (280 ml) so that the temperature of the mixture did not rise above 10°. The mixture was stirred for a further 15 min, then overlaid with ether (100 ml), and the excess of nitrous acid was decomposed with urea. The mixture was basified with sodium carbonate and extracted with ether (3 × 200 ml). Absolute ethanol (100 ml) was added to the dried ($MgSO_4$) extract, the ether was evaporated off, and the ethanolic solution was heated under reflux for 1 h. Evaporation gave a buff solid which was extracted with boiling cyclohexane. Evaporation of the extract to low bulk yielded the *carbamate* (20 g, 51%), which crystallised from benzene as needles, m.p. 122—123° (Found: C, 70·1; H, 6·5; N, 11·15. $C_{15}H_{16}N_2O_2$ requires C, 70·35; H, 6·3; N, 10·95%), $\nu_{max.}$ 3250 (N–H), 1690br (C=O), 1540, 1290, 1270, 1240, 1060, 840, 780, 740, and 690 cm^{-1}. The cyclohexane-insoluble residue was crystallised from dimethylformamide to yield 1,3-*bis*-(*2-methyl-6-phenyl-3-pyridyl*)*urea* (0·39 g, 3·5%) as needles, m.p. 284—286° (Found: C, 76·0; H, 5·8; N, 14·35. $C_{25}H_{22}N_4O$ requires C, 76·05; H, 5·65; N, 14·2%), $\nu_{max.}$ 3450 (N–H), 1640 (C=O), 1605, 1595, and 1570 (aryl), 1275, 785, 740, 690, and 670 cm^{-1}.

3-Amino-2-methyl-6-phenylpyridine Monohydrate (Id; R′ = H).—Ethyl *N*-(2-methyl-6-phenyl-3-pyridyl)carbamate (1 g), 50% potassium hydroxide solution (10 ml), and ethanol (10 ml) were heated under reflux for 4 h. The ethanol was evaporated off, and the mixture was cooled and extracted with ether (3 × 40 ml). The dried ($MgSO_4$) extract was evaporated to give the *amine* (0·61 g, 77%). Crystallisation from aqueous ethanol gave prisms, m.p. 86—87° (Found: C, 71·0; H, 6·8; N, 13·5. $C_{12}H_{14}N_2O$ requires C, 71·3; H, 7·0; N, 13·85%), $\nu_{max.}$ 3500, 3400, and 3300 (NH_2), 1640, 1620, 1580, 1250, 840, 740, and 695 cm^{-1}.

General Method for the Preparation of the 3-Acetamido-2-methylpyridines (I; R′ = Ac).—The 3-amino-2-methylpyridine (0·05 mol), acetic anhydride (0·06 mol), and

[10] V. Rousseau and H. G. Lindwall, *J. Amer. Chem. Soc.*, 1950, **72**, 3047.
[11] J. M. Tedder, *Adv. Heterocyclic Chem.*, 1967, **8**, 1.
[12] E. Ajello, *J. Heterocyclic Chem.*, 1971, **8**, 1035.
[13] H. E. Baumgarten and H. Chien-Fan Su, *J. Amer. Chem. Soc.*, 1952, **74**, 3828.
[14] W. Herz and D. R. K. Murty, *J. Org. Chem.*, 1960, **25**, 2242.
[15] D. M. Besly and A. A. Goldberg, *J. Chem. Soc.*, 1954, 2448.

benzene (50 ml) were heated under reflux for 1 h. The solvent was removed under reduced pressure.

3-*Acetamido*-2-*methylpyridine* (Ia; R′ = Ac). The residual oil was distilled to yield the *amide* (71%), b.p. 132—136° at 0·5 mmHg. Crystallisation from ethyl acetate–light petroleum gave needles, m.p. 85° (Found: C, 63·8; H, 6·9; N, 18·4. $C_8H_{10}N_2O$ requires C, 63·95; H, 6·7; N, 18·65%), $\nu_{max.}$ ($CHCl_3$) 3450 and 3300 (N–H), 1700 (C=O), 1540, 1470, and 1300 cm^{-1}.

3-*Acetamido*-2-*methyl*-6-*phenylpyridine* (Id; R′ = Ac). The residual buff solid was crystallised from toluene to give the *amide* (90%) as needles, m.p. 140—141° (Found: C, 74·6; H, 6·55; N, 12·5. $C_{14}H_{14}N_2O$ requires C, 74·3; H, 6·25; N, 12·4%), $\nu_{max.}$ 3400 (N–H), 1660 (C=O), 1600, 1580, 1505, 1290, 1280, 845, 785, 740, and 700 cm^{-1}.

General Method for the Preparation of 1-*Acetyl*-1H-*pyrazolo*[4,3-b]*pyridines* (VI; R′ = Ac) *from* 3-*Acetamido*-2-*methylpyridines* (I; R′ = Ac).—A stirred, cooled suspension of the 3-acetamido-2-methylpyridine (3 g) and anhydrous potassium acetate (3 g) in acetic acid (5 ml) and acetic anhydride (5 ml) was treated with a solution of nitrosyl chloride (3 g) in acetic anhydride (10 ml) during 10 min. The suspension was stirred for a further 10 min and was then added to 25% sodium carbonate solution (200 ml) and stirred for 5 min. The solution was extracted with benzene (3 × 50 ml); the extract was dried ($MgSO_4$), heated under reflux for 1 h, and evaporated to low bulk. Acetic anhydride (10 ml) was added, and heating was continued for a further 30 min. Evaporation of the mixture under reduced pressure gave the product.

1-*Acetyl*-1H-*pyrazolo*[4,3-b]*pyridine* (VIa; R′ = Ac). 3-Acetamido-2-methylpyridine gave a black oil which was extracted with boiling light petroleum. The solvent was evaporated off to give a red solid which, on sublimation (80° and 0·5 mmHg), gave the *pyrazolopyridine* (1·48 g, 48%). Crystallisation from cyclohexane gave needles, m.p. 87—88° (Found: C, 59·05; H, 4·3; N, 26·15. $C_8H_7N_3O$ requires C, 59·25; H, 4·35; N, 25·9%), $\nu_{max.}$ ($CHCl_3$) 1715 (C=O), 1420, 1380, 1350, 1270, 1170, 1125, 945, and 920 cm^{-1}, τ 1·1—1·4 (2H, m, 5- and 7-H), 1·64 (1H, s, 3-H), 2·3—2·7 (1H, m, 6-H), and 7·17 (3H, s, CH_3).

1-*Acetyl*-5-*methyl*-1H-*pyrazolo*[4,3-b]*pyridine* (VIb; R′ = Ac). 3-Acetamido-2,6-dimethylpyridine gave a black semi-solid which was extracted with boiling light petroleum. The solvent was evaporated off to give a red solid which, on sublimation (95° and 3 mmHg), gave the *pyrazolopyridine* (1·63 g, 51%). Crystallisation from cyclohexane gave needles, m.p. 99—100° (Found: C, 61·65; H, 5·05; N, 23·8. $C_9H_9N_3O$ requires C, 61·75; H, 5·15; N, 24·0%), $\lambda_{max.}$ (cyclohexane) 234 (log ε 4·31), 285 (3·46), 291 (3·53), 296 (3·57), and 303 nm (3·49), $\nu_{max.}$ ($CHCl_3$) 1710 (C=O), 1410, 1390, 1350, 1260, 940, and 830 cm^{-1}, τ 1·48 (1H, d, *J* 9 Hz, 7-H), 1·76 (1H, s, 3-H), 2·69 (1H, d, *J* 9 Hz, 6-H), 7·22 (3H, s, 1-Ac), and 7·30 (3H, s, 5-CH_3).

1-*Acetyl*-5-*methoxy*-1H-*pyrazolo*[4,3-b]*pyridine* (VIc; R′ = Ac). 3-Acetamido-6-methoxy-2-methylpyridine gave the *pyrazolopyridine* (2·6 g, 82%). Crystallisation from cyclohexane gave needles, m.p. 145—146° (Found: C, 56·8; H, 4·5; N, 22·0. $C_9H_9N_3O_2$ requires C, 56·55; H, 4·75; N, 22·0%), $\nu_{max.}$ 1715 (C=O), 1515, 1405, 1385, 1365, 1345, 1315, 1165, 1025, 940, and 830 cm^{-1}, τ 1·45 (1H, d, *J* 9 Hz, 7-H), 1·85 (1H, s, 3-H), 3·08 (1H, d, *J* 9 Hz, 6-H), 5·99 (3H, s, OCH_3), and 7·23 (3H, s, Ac).

1-*Acetyl*-5-*phenyl*-1H-*pyrazolo*[4,3-b]*pyridine* (VId; R′ = Ac). 3-Acetamido-2-methyl-6-phenylpyridine gave the *pyrazolopyridine* (2·69 g, 86%). Crystallisation from cyclohexane gave prisms, m.p. 129—130° (Found: C, 70·85; H, 4·7; N, 17·7. $C_{14}H_{11}N_3O$ requires C, 71·1; H, 4·85; N, 17·6%), $\nu_{max.}$ ($CHCl_3$) 1720 (C=O), 1560, 1530, 1510 (aryl), 1425, 1395, 1365, 1330, 1165, and 945 cm^{-1}, τ 1·30 (1H, d, *J* 9 Hz, 7-H), 1·64 (1H, s, 3-H), 1·8—2·7 (6H, s, 6-H and Ph), and 7·25 (3H, s, CH_3).

1-*Acetyl*-1H-*pyrazolo*[3,4-c]*pyridine*. 3-Acetamido-4-methylpyridine gave a brown solid which, on sublimation (100° and 0·2 mmHg), gave the *pyrazolopyridine* (1·71 g, 55%). Crystallisation from cyclohexane gave needles, m.p. 104—105° (Found: C, 59·35; H, 4·2; N, 25·65. $C_8H_7N_3O$ requires C, 59·25; H, 4·35; N, 25·9%), $\nu_{max.}$ 1705 (C=O), 1420, 1350, 1200, and 950 cm^{-1}, τ 0·22 (1H, s, 7-H), 1·44 (1H, d, *J* 5 Hz, 5-H), 1·82 (1H, s, 3-H), 2·37 (1H, d, *J* 5 Hz, 4-H), and 7·20 (3H, s, CH_3).

General Method for the Preparation of the Pyrazolopyridines (Va, b, and d) *and* (XI) *from their* 1-*Acetyl Derivatives*.—The 1-acetyl compound (0·5 g) and 15% hydrochloric acid (5 ml) were heated under reflux for 30 min. The solution was cooled and basified with ammonium hydroxide solution (*d* 0·88).

1H-*Pyrazolo*[4,3-b]*pyridine* (Va). The mixture was extracted with chloroform (3 × 20 ml); the extract was dried ($MgSO_4$) and evaporated to yield the *pyrazolopyridine* (0·34 g, 90%). Crystallisation from benzene gave needles, m.p. 105—106° (Found: C, 60·55; H, 4·05; N, 35·35. $C_6H_5N_3$ requires C, 60·5; H, 4·25; N, 35·3%), $\lambda_{max.}$ (EtOH) 282 nm (log ε 3·85), $\nu_{max.}$ 3500—2500 (N–H), 1680, 1425, 1120, 960, 950, 920, 855, 790, and 780 cm^{-1}, τ (Me_2SO) −3·3br (1H, s, NH), 1·45 (1H, d, *J* 4 Hz, 5-H), 1·67 (1H, s, 3-H), 1·95 (1H, d, *J* 9 Hz, 7-H), and 2·15 (1H, q, *J* 4 and 9 Hz, 6-H).

5-*Methyl*-1H-*pyrazolo*[4,3-b]*pyridine* (Vb). The *pyrazolopyridine* (0·34 g, 89%) was collected. Crystallisation from ethyl acetate gave needles, m.p. 203° (Found: C, 63·05; H, 5·3; N, 31·25. $C_7H_7N_3$ requires C, 63·15; H, 5·3; N, 31·55%), $\lambda_{max.}$ (EtOH) 288 nm (log ε 3·74), $\lambda_{max.}$ (cyclohexane) 258 (3·60), 294 (3·68), 298 (3·68), and 306 nm (3·57), $\nu_{max.}$ 3300—2500 (N–H), 1580, 1500, 1410, 1295, 1140, 940, 865, and 830 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 1·00 (1H, d, *J* 9 Hz, 7-H), 1·20 (1H, s, 3-H), 1·94 (1H, d, *J* 9 Hz, 6-H), and 6·85 (3H, s, CH_3).

5-*Phenyl*-1H-*pyrazolo*[4,3-b]*pyridine* (Vd). The precipitated solid was collected and extracted with boiling ethyl acetate. Evaporation of the extract gave the *pyrazolopyridine* (0·36 g, 85%), which crystallised from ethyl acetate as needles, m.p. 198—199° (Found: C, 74·0; H, 4·45; N, 21·25. $C_{12}H_9N_3$ requires C, 73·85; H, 4·65; N, 21·55%), $\nu_{max.}$ 3500—2300 (N–H), 1590, 1490, 1280, 960, 835, 780, 755, 715, and 700 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 0·86 (1H, d, *J* 9 Hz, 7-H), 1·12 (1H, s, 3-H), 1·53 (1H, d, *J* 9 Hz, 6-H), and 1·7—2·3 (5H, m, Ph).

1H-*Pyrazolo*[3,4-c]*pyridine* (XI).—The mixture was extracted with chloroform (3 × 20 ml); the extract was dried ($MgSO_4$) and evaporated to dryness to yield the *pyrazolopyridine* (0·31 g, 82%). Crystallisation from benzene–cyclohexane gave needles, m.p. 102° (Found: C, 60·25; H, 4·15; N, 35·0. $C_6H_5N_3$ requires C, 60·5; H, 4·25; N, 35·3%), $\lambda_{max.}$ (EtOH) 235 (log ε 3·37), 298 (3·75), and 309 nm (3·63), $\nu_{max.}$ 3400—2300 (N–H), 1340, 1330, 1250, 1160, 1030, 950, 885, 845, 810, 790, and 785 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 0·18 (1H, s, 7-H), 1·00 (1H, s, 3-H), and 1·31 (2H, s, 4- and 5-H).

5-*Methoxy*-1H-*pyrazolo*[4,3-b]*pyridine* (Vc).—(*a*) Nitrosyl

chloride (2 g) was passed into a cooled suspension of 3-acetamido-6-methoxy-2-methylpyridine (2 g), phosphorus pentoxide (0·4 g), and anhydrous potassium acetate (2 g) in acetic acid (10 ml) during 10 min. The suspension was stirred for a further 10 min and was added to a stirred suspension of sodium carbonate (20 g) in benzene (200 ml). The mixture was filtered; the solution was dried ($MgSO_4$), heated under reflux for 2 h, then evaporated under reduced pressure to yield the *pyrazolopyridine* (1·48 g, 86%). Sublimation (140° and 0·5 mmHg) followed by crystallisation from ethyl acetate gave needles, m.p. 186—187° (Found: C, 56·65; H, 4·95; N, 28·1. $C_7H_7N_3O$ requires C, 56·35; H, 4·75; N, 28·15%), $\nu_{max.}$ 3400—2500 (N–H), 1600, 1525, 1310, 1295, 1250, 1180, 1120, 1025, 960, 885, 835, and 830 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 1·00 (1H, s, *J* 9 Hz, 7-H), 1·40 (1H, s, 3-H), 2·29 (1H, d, *J* 9 Hz, 6-H), and 5·45 (3H, s, CH_3).

(*b*) A cooled solution of 3-amino-6-methoxy-2-methylpyridine (1·0 g) in acetic acid (40 ml) was treated with a solution of sodium nitrite (0·5 g) in water (0·5 ml). After 3 days at room temperature the solvent was removed *in vacuo*. Extraction of the residual semi-solid with boiling benzene and evaporation of the extract *in vacuo* gave an oil. Preparative t.l.c. (ethyl acetate as eluant) followed by extraction of the main fluorescent band with acetone and evaporation of the solution gave the pyrazolopyridine (0·06 g, 5·5%), m.p. and mixed m.p. with the product of (*a*) 186—187°.

1H-*pyrazolo*[4,3-b]*pyridin*-5(4H)-*one* (VII).—1-Acetyl-5-methoxy-1*H*-pyrazolo[4,3-*b*]pyridine (4 g) and 15% hydrochloric acid (20 ml) were heated under reflux for 1 h. The mixture was cooled and on basification with ammonium hydroxide solution (*d* 0·88) gave the *pyridone* (2·7 g, 96%). Crystallisation from water gave needles, m.p. 251—252° (Found: C, 53·1; H, 3·75; N, 31·4. $C_6H_5N_3O$ requires C, 53·35; H, 3·75; N, 31·1%), $\nu_{max.}$ 3400—2500 (N–H), 1655 (C=O), 1600, 1575, 1190, 1130, 965, 850, and 825 cm^{-1}, τ (Me_2SO) 2·20 (1H, d, *J* 9 Hz, 7-H), 2·47 (1H, s, 3-H), and 3·65 (1H, d, *J* 9 Hz, 6-H).

1-*Benzoyl*-5-*methyl*-1H-*pyrazolo*[4,3-b]*pyridine* (VIb; R′ = Bz).—(*a*) A boiling solution of 5-methyl-1*H*-pyrazolo-[4,3-*b*]pyridine (0·2 g) in dry pyridine (2 ml) was treated with benzoyl chloride (0·25 g). The solution was heated under reflux for 15 min, cooled, and added to water to give the 1-*benzoyl compound* (0·35 g, 97%). Crystallisation from cyclohexane gave needles, m.p. 114—115° (Found: C, 71·1; H, 4·65; N, 17·85. $C_{14}H_{11}N_3O$ requires C, 70·85; H, 4·7; N, 17·7%), $\lambda_{max.}$ (cyclohexane) 256 (log ε 4·39) and 303 nm (3·61), $\nu_{max.}$ 1685 (C=O), 1475, 1420, 1385, 1140, 915, and 685 cm^{-1}, τ 1·26 (1H, d, *J* 9 Hz, 7-H), 1·61 (1H, s, 3-H), 1·7—2·0 (2H, m, 2′- and 6′-H), 2·25—2·6 (4H, m, 6-, 3′-, 4′-, and 5′-H), and 7·25 (3H, s, CH_3).

(*b*) A warm solution (50°) of 5-methyl-1*H*-pyrazolo-[4,3-*b*]pyridine (0·2 g) in 5% sodium hydroxide solution (2 ml) was treated with benzoyl chloride (0·25 g); the mixture was stirred for 10 min, then cooled to yield the 1-benzoyl compound (0·2 g, 56%), m.p. and mixed m.p. with the sample prepared by method (*a*) 114—115°.

5-*Methyl*-1-p-*tolylsulphonyl*-1H-*pyrazolo*[4,3-b]*pyridine* (VIb; R′ = *p*-$MeC_6H_4{\cdot}SO_2$).—5-Methyl-1*H*-pyrazolo[4,3-*b*]-pyridine (0·5 g), toluene-*p*-sulphonyl chloride (0·72 g), and dry pyridine (5 ml) were heated under reflux for 20 min. The solution was cooled and added to water to yield the *pyrazolopyridine* (0·86 g, 79%). Crystallisation from carbon tetrachloride gave needles, m.p. 134—135° (Found: C, 58·4; H, 4·4; N, 14·55; S, 11·3. $C_{14}H_{13}N_3SO_2$ requires C, 58·5; H, 4·55; N, 14·6; S, 11·15%), $\nu_{max.}$ 1380, 1280, 1175, 1060, 825, and 760 cm^{-1}, τ 1·58 (1H, d, *J* 9 Hz, 7-H), 1·66 (1H, s, 3-H), 2·10 (2H, d, *J* 8 Hz, 2′- and 6′-H), 2·65 (1H, d, *J* 9 Hz, 6-H), 2·73 (2H, d, *J* 8 Hz, 3′- and 5′-H), 7·31 (3H, s, 5-CH_3), and 7·65 (3H, s, 4′-CH_3).

2-*Acetyl*-5-*methyl*-2H-*pyrazolo*[4,3-b]*pyridine* (XIII: R = Me).—A warm solution of 5-methyl-1*H*-pyrazolo[4,3-*b*]-pyridine (0·1 g) in ethanol (2 ml) was treated with a solution of silver nitrate (0·13 g) in water (0·2 ml). The precipitated silver salt was collected, dried, and heated under reflux with a solution of acetyl chloride (0·055 g) in dry ether (10 ml) for 5 h. The mixture was filtered and the filtrate was evaporated to yield the 2-*acetyl compound* (0·06 g, 45%). Crystallisation from benzene–cyclohexane gave needles, m.p. 145—146° (Found: C, 61·5; H, 5·15; N, 24·15. $C_9H_9N_3O$ requires C, 61·75; H, 5·15; N, 24·0%). $\lambda_{max.}$ (cyclohexane) 2·14 (log ε 4·19) and 296 nm (3·81), $\nu_{max.}$ 1740 (C=O), 1400, 1380, 1335, 1210, 1195, and 940 cm^{-1}, τ 1·15 (1H, s, 3-H), 2·07 (1H, d, *J* 9 Hz, 7-H), 2·85 (1H, d, *J* 9 Hz, 6-H), 7·10 (3H, s, 2-Ac), and 7·35 (3H, s, 5-CH_3).

2-*Benzoyl*-5-*methyl*-2H-*pyrazolo*[4,3-b]*pyridine* (XIII; R = Ph).—A cooled, stirred suspension of 5-methyl-1*H*-pyrazolo[4,3-*b*]pyridine (0·25 g) in dry pyridine (2 ml) was treated with benzoyl chloride (0·3 g) during 5 min. The suspension was stirred for a further 1 h and diluted with water (20 ml) to yield a mixture of the 1- and 2-benzoyl compounds (0·36 g, 82%). Crystallisation from benzene–cyclohexane gave the 2-*benzoyl compound* (0·1 g, 22%) as needles, m.p. 135° (Found: C, 70·8; H, 4·95; N, 17·6. $C_{14}H_{11}N_3O$ requires C, 70·85; H, 4·7; N, 17·7%), $\lambda_{max.}$ (cyclohexane) 254 (log ε 4·80) and 302 nm (4·07), $\nu_{max.}$ 1710 (C=O), 1360, 1240, 1105, 890, 700, and 670 cm^{-1}, τ 0·93 (1H, s, 3-H), 1·75 (2H, d, 2′- and 6′-H), 1·98 (1H, d, *J* 9 Hz, 7-H), 2·2—2·6 (3H, m, 3′-, 4′-, and 5′-H), and 2·85 (1H, d, *J* 9 Hz, 6-H).

3-*Bromo*-5-*methyl*-1H-*pyrazolo*[4,3-b]*pyridine* (XV).—(*a*) 5-Methyl-1*H*-pyrazolo[4,3-*b*]pyridine (0·25 g), bromine (0·33 g), and water (10 ml) were stirred at room temperature for 1 h. Basification of the suspension with 10% sodium carbonate solution gave the *bromo-compound* (0·39 g, 97%). Crystallisation from ethanol gave needles, m.p. 291—293° (Found: C, 39·8; H, 2·9; Br, 37·8; N, 19·9. $C_7H_6BrN_3$ requires C, 39·65; H, 2·85; Br, 37·7; N, 19·8%), $\nu_{max.}$ 3300—2500 (N–H), 1420, 1285, 1210, 995, 940, 825, and 810 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 1·14 (1H, d, *J* 9 Hz, 7-H), 2·03 (1H, d, *J* 9 Hz, 6-H), and 7·87 (3H, s, CH_3).

(*b*) 3-Diazo-5-methyl-3*H*-pyrazolo[4,3-*b*]pyridine (0·1 g) and 60% hydrobromic acid (0·5 ml) were heated under reflux for 20 min. The mixture was basified with 10% sodium carbonate solution to yield the bromo-compound (0·13 g, 97%), identical with sample prepared by method (*a*).

5-*Methyl*-3-*nitro*-1H-*pyrazolo*[4,3-b]*pyridine* (XVI).—A mixture of concentrated nitric acid (4 ml) and concentrated sulphuric acid (4 ml) was added dropwise to a cooled solution of 5-methyl-1*H*-pyrazolo[4,3-*b*]pyridine (1·0 g) in concentrated sulphuric acid (4 ml) during 5 min. The solution was heated at 110—120° for 3 h, poured on ice, and basified with ammonium hydroxide solution (*d* 0·88) to yield the *nitro-compound* (1·32 g, 98%). Crystallisation from dimethylformamide gave pale yellow prisms which did not melt below 320° (Found: C, 47·35; H, 3·35; N, 31·55. $C_7H_6N_4O_2$ requires C, 47·2; H, 3·4; N, 31·45%), $\lambda_{max.}$ (EtOH) 250 (log ε 3·80) and 295 nm (3·96), $\nu_{max.}$ 3200—2400 (N–H), 1580, 1535 (NO_2), 1490, 1425, 1380, 1320

(NO_2), 1200, 940, and 820 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 0·97 (1H, d, *J* 9 Hz, 7-H), 1·87 (1H, d, *J* 9 Hz, 6-H), and 6·75 (3H, s, CH_3).

3-*Bromo*-1H-*pyrazolo*[4,3-b]*pyridin*-5(4H)-*one Monohydrate* (VIII).—1*H*-Pyrazolo[4,3-*b*]pyridin-5(4*H*)-one (1 g), bromine (1·3 g), and water (10 ml) were stirred at room temperature for 1 h. Basification of the suspension with 10% sodium carbonate solution gave the *bromo-compound* (1·13 g, 63%) as needles, m.p. 283—284° (from water) (Found: C, 31·2; H, 2·35; Br, 34·7; N, 18·05. $C_6H_6BrN_3O_2$ requires C, 31·05, H, 2·6; Br, 34·45; N, 18·1%), $\nu_{max.}$ 3500—2500 (N–H), 1650 (C=O), 1585, 1030, and 740 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 1·55 (1H, d, *J* 9 Hz, 7-H) and 2·66 (1H, d, *J* 9 Hz, 6-H).

3,6-*Dibromo*-1H-*pyrazolo*[4,3-b]*pyridin*-5(4H)-*one* (IX). —(*a*) 1*H*-Pyrazolo[4,3-*b*]pyridin-5(4*H*)-one (0·25 g), bromine (0·65 g), and water (10 ml) were heated on a steam-bath for 30 min. The suspension was cooled and on basification with 10% sodium carbonate solution gave the *dibromo-compound* (0·29 g, 54%). Crystallisation from dimethylformamide–water gave prisms which did not melt below 320° (Found: C, 24·6; H, 1·2; Br, 54·1; N, 14·2. $C_6H_3Br_2N_3O$ requires C, 24·6; H, 1·05; Br, 54·55; N, 14·35%), $\nu_{max.}$ 3400—2500 (N–H), 1650 (C=O), 1595, 1580, 1200, 1020, and 770 cm^{-1}.

(*b*) 3-Bromo-1*H*-pyrazolo[4,3-*b*]pyridin-5(4*H*)-one (0·5 g), bromine (0·45 g), and water (5 ml) were heated on a steam-bath for 1 h. The suspension was cooled and on basification with sodium carbonate gave the dibromo-compound (0·48 g, 70%), identical with the sample prepared by method (*a*).

3,6-*Dinitro*-1H-*pyrazolo*[4,3-b]*pyridin*-5(4H)-*one Monohydrate* (X).—A mixture of concentrated nitric acid (2 ml) and concentrated sulphuric acid (2 ml) was added dropwise to a cooled solution of 1*H*-pyrazolo[4,3-*b*]pyridin-5(4*H*)-one (0·5 g) in concentrated sulphuric acid (2 ml) during 5 min. The solution was heated at 110—120° for 3 h, poured on ice, and basified with ammonium hydroxide solution (*d* 0·88) to yield the ammonium salt of 3,6-*dinitro*-1H-*pyrazolo*[4,3-b]*pyridin*-5(4H)-*one* (0·6 g, 73%). Crystallisation from water gave bright yellow needles, m.p. 262—264° (Found: C, 29·7; H, 2·45; N, 34·9. $C_6H_6N_6O_5$ requires C, 29·75; H, 2·5; N, 34·7%), $\nu_{max.}$ 3300—2500 (N–H), 1640 (C=O), 1520 and 1320 (NO_2), 1290, 1275, 1160, 880, and 820 cm^{-1}.

The ammonium salt (0·5 g) was acidified with dilute hydrochloric acid and the precipitated solid was collected. Crystallisation from water gave the *dinitro-compound* (0·38 g, 76%) as yellow needles, m.p. 284—285° (Found: C, 29·8; H, 2·1; N, 28·45. $C_6H_5N_5O_6$ requires C, 29·65; H, 2·1; N, 28·8%), $\nu_{max.}$ 3600—2400 (N–H), 1660 (C=O), and 1520br and 1320br (NO_2) cm^{-1}. When the reaction was carried out at 20°, only unchanged starting material was isolated.

1,5-*Dimethyl*-3-*nitro*-1H-*pyrazolo*[4,3-b]*pyridine* (XVII). —A solution of methyl iodide (0·36 g) in ether (1 ml) was added to a suspension of 5-methyl-3-nitro-1*H*-pyrazolo-[4,3-*b*]pyridine (0·45 g) and sodium hydroxide (0·14 g) in boiling aqueous 90% ethanol (2 ml) and the mixture was heated under reflux for 3 h. The solvent was evaporated off and the residue was extracted with boiling chloroform. Evaporation of the extract gave a mixture of 2,5-dimethyl- and 1,5-dimethyl-3-nitropyrazolo[4,3-*b*]pyridine (0·33 g, 64%). Crystallisation from ethanol gave the 1,5-*dimethyl compound* as pale yellow needles, m.p. 206—208° (Found: C, 49·95; H, 4·13; N, 28·95. $C_8H_8N_4O_2$ requires C, 50·0; H, 4·2; N, 29·15%), $\lambda_{max.}$ (C_2H_5OH) 250 (log ε 3·87) and 307 nm (4·00), $\nu_{max.}$ 1630, 1495 (NO_2), 1430, 1320 (NO_2), 1280, 1220, 825, and 805 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 1·02 (1H, d, *J* 9 Hz, 7-H), 1·87 (1H, d, *J* 9 Hz, 6-H), 5·50 (3H, s, 1-CH_3), 6·75 (3H, s, 5-CH_3).

3-*Amino*-5-*methyl*-1H-*pyrazolo*[4,3-b]*pyridine* (XVIII).— 5-Methyl-3-nitro-1*H*-pyrazolo[4,3-*b*]pyridine (3 g), 10% palladium–charcoal (0·3 g), and ethanol (100 ml) were heated under reflux, and 100% hydrazine hydrate (10 ml) was added in portions during 30 min. The mixture was heated under reflux for a further 30 min, filtered, and evaporated under reduced pressure to yield the *amine* (2·29 g, 92%). Crystallisation from ethyl acetate gave prisms, m.p. 159—160° (Found: C, 56·35; H, 5·15; N, N, 37·7. $C_7H_8N_4$ requires C, 56·7; H, 5·45; N, 37·8%), $\nu_{max.}$ 3250br (N–H), 1620, 1525, 1490, 1435, 1275, and 820 cm^{-1}, τ (Me_2SO) 2·35 (1H, d, *J* 9 Hz, 7-H) and 2·85 (1H, d, *J* 9 Hz, 6-H).

3-*Acetamido*-1-*acetyl*-5-*methyl*-1H-*pyrazolo*[4,3-b]*pyridine* (XIX).—3-Amino-5-methyl-1*H*-pyrazolo[4,3-*b*]pyridine (0·2 g) and acetic anhydride (1 ml) were heated under reflux for 10 min. The solvent was evaporated off under reduced pressure to yield the *acetamido-compound* (0·29 g, 93%). Crystallisation from benzene–cyclohexane gave needles, m.p. 166—168° (Found: C, 56·85; H, 5·25; N, 23·9. $C_{11}H_{12}N_4O_2$ requires C, 56·9; H, 5·2; N, 24·15%), $\nu_{max.}$ 3300 (N–H), 1715 and 1680 (C=O), 1540, 1410, 1380br, 1220, and 940 cm^{-1}, τ 1·2br (1H, s, N–H), 1·45 (1H, d, *J* 9 Hz, 7-H), 2·63 (1H, d, *J* 9 Hz, 6-H), 7·25 (3H, s, 1-Ac), 7·33 (3H, s, 5-CH_3), and 7·48 (3H, s, NHAc).

1-*Acetyl*-3-*diacetylamino*-5-*methyl*-1H-*pyrazolo*[4,3-b]-*pyridine* (XX).—3-Amino-5-methyl-1*H*-pyrazolo[4,3-*b*]-pyridine (0·3 g) and acetic anhydride (1 ml) were heated under reflux for 2 h. The mixture was cooled and diluted with water (10 ml) to yield the *diacetylamino-compound* (0·25 g, 45%). Crystallisation from benzene–cyclohexane gave needles, m.p. 156—157° (Found: C, 56·75; H, 5·1; N, 20·4. $C_{13}H_{14}N_4O_3$ requires C, 56·9; H, 5·15; N, 20·45%), $\nu_{max.}$ 1715 (C=O), 1410, 1370, 1340, 1315, 1270, 1225, 1215, 1115, and 940 cm^{-1}, τ 1·37 (1H, d, *J* 9 Hz, 7-H), 2·59 (1H, d, *J* 9 Hz, 6-H), 7·25 (3H, s, 1-Ac), 7·32 (3H, s, 5-CH_3), and 7·60 (6H, s, NAc_2).

3-*Diazo*-5-*methyl*-3H-*pyrazolo*[4,3-b]*pyridine* (XXI).—A cooled solution (0°) of 3-amino-5-methyl-1*H*-pyrazolo-[4,3-*b*]pyridine (0·6 g) in water (20 ml) and concentrated sulphuric acid (3 ml) was treated with sodium nitrite (0·6 g) in water (3 ml). The mixture was stirred for 30 min and basified with sodium carbonate. The precipitated solid was collected and the solution extracted with chloroform (3 × 20 ml). The dried ($MgSO_4$) extract was evaporated to yield a further crop of product. The solids were bulked to yield the *diazo-compound* (0·4 g, 63%) which, on crystallisation from cyclohexane, gave fawn needles, m.p. 155° (decomp.) (Found: *M*, 159·0545. $C_7H_5N_5$ requires *M*, 159·0545), $\nu_{max.}$ 2100 ($\overset{+}{N}{=}\overset{-}{N}$), 1400, 1340, 1140, 1115, 1090, 1025, 825, and 770 cm^{-1}, τ 1·62 (1H, d, *J* 8 Hz, 7-H), 2·70 (1H, d, *J* 8 Hz, 6-H), and 7·25 (3H, s, CH_3).

5-*Chloro*-1H-*pyrazolo*[4,3-b]*pyridine* (V; R = Cl).—1*H*-Pyrazolo[4,3-*b*]pyridin-5(4*H*)-one (4 g) and phosphoryl chloride (10 ml) were heated under reflux for 2 h. The solvent was evaporated off under reduced pressure and the residue was basified with an aqueous paste of sodium carbonate and extracted with boiling toluene. The dried

($MgSO_4$) extract was evaporated to low bulk and on cooling gave the *chloro-compound* (3·17 g, 70%) as prisms, m.p. 201—202° (from toluene) (Found: C, 47·0; H, 2·85; Cl, 23·15; N, 27·65. $C_6H_4ClN_3$ requires C, 46·9; H, 2·65; Cl, 23·1; N, 27·35%), $\nu_{max.}$ 3500—2500 (N–H), 1680, 1425, 1120, 960, 950, 935, 845, and 820 cm^{-1}, τ (Me_2SO) 1·72 (1H, s, 3-H), 1·87 (1H, d, *J* 9 Hz, 7-H), and 2·60 (1H, d, *J* 9 Hz, 6-H).

5-Hydrazino-1H-pyrazolo[4,3-b]pyridine (V; R = $NH{\cdot}NH_2$).—5-Chloro-1*H*-pyrazolo[4,3-*b*]pyridine (1 g) and 100% hydrazine hydrate (10 ml) were heated under reflux for 2 h. The mixture was cooled and the precipitated *hydrazino-compound* (0·88 g, 90%) was collected. Crystallisation from dimethylformamide gave buff prisms, m.p. 258—260° (Found: C, 48·6; H, 4·95; N, 46·5. $C_6H_7N_5$ requires C, 48·3; H, 4·75; N, 46·95%), $\nu_{max.}$ 3500—2500 (N–H), 1610, 1595, 1520, 1410, 1300, 940, 830, and 800 cm^{-1}, τ (Me_2SO) 2·20 (1H, s, 3-H), 2·31 (1H, d, *J* 9 Hz, 7-H), and 3·29 (1H, d, *J* 9 Hz, 6-H).

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