Pyrazolopyridines. Part IV.[1] Preparation and Tautomerism of 6-Cyano- and 6-Ethoxycarbonyl-1,4-dihydropyrazolo[4,3-*b*]pyridin-7-ones

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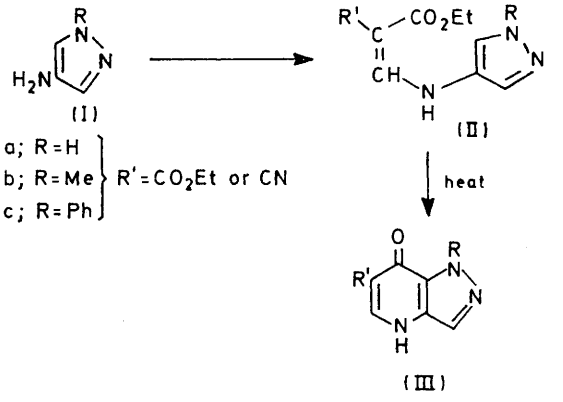
6-Cyano- and 6-ethoxycarbonyl-1,4-dihydropyrazolo[4,3-*b*]pyridin-7-ones have been prepared by cyclisation of pyrazol-4-ylaminomethylene-cyanoacetates and -malonates respectively. Cyclisation occurs preferentially at the 5-position of the pyrazole ring. The 6-ethoxycarbonyl compounds have been shown to exist in the pyridone form by comparison with model compounds.

PYRAZOLO[4,3-*b*]PYRIDINES have been prepared by the Skraup reaction from 4-amino-1-phenylpyrazole [2] and by cyclisation of the crotonate obtained on treatment of this amine with ethyl acetoacetate.[3] We have now prepared a series of 6-ethoxycarbonyl- and 6-cyano-1,4-dihydropyrazolo[4,3-*b*]pyridin-7-ones (IIIa—c) by cyclisation of the pyrazolylaminomethylene-malonates and -cyanoacetates (IIa—c) in boiling Dowtherm. The latter compounds were obtained by treatment of the 4-aminopyrazoles (Ia—c) with diethyl ethoxymethylenemalonate and ethyl cyano(ethoxymethylene)acetate respectively. The amines (Ia and b) are unstable and were used immediately after preparation without purification. Good yields were obtained on cyclisation of the aminomalonates (II; R′ = CO_2Et) but the cyanoacetates (II; R′ = CN) required a longer reflux period, yields were poorer, and purification of the products was more difficult. Similar problems have been reported in the preparation of quinolines [4] and pyridopyrimidines [5] from aminomethylenecyanoacetates.

Attempts to cyclise the cyanoacetates (IIa and c; R′ = CN) by using polyphosphoric acid were unsuccessful. Treatment at 100 °C gave the carboxamides (IIa and c; R′ = $CONH_2$); at higher temperatures intractable tars were obtained. Attempted cyclisations of the pentenone (IV), the nitropropenone (V), and the cinnamamide (VI)

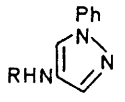


under acidic conditions also failed. The method of Tabak *et al.*[3] was extended to the preparation of compound (VIII).

In principle the above cyclisations could occur at the 5- or the 3-position of the pyrazole ring, to give the 1- or

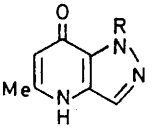
[1] Part III, H. E. Foster and J. Hurst, *J.C.S. Perkin I*, 1973, 2901.
[2] I. L. Finar and R. J. Hurlock, *J. Chem. Soc.*, 1958, 3259.
[3] S. V. Tabak, I. I. Grandberg, and A. N. Kost, *Khim. geterotsikl. Soedinenii*, 1965, **1**, 116.
[4] R. H. Baker, J. G. Van Oot, S. W. Tinsley, D. Butler, and B. Riegel, *J. Amer. Chem. Soc.*, 1949, **71**, 3060.
[5] W. J. Irwin and D. G. Wibberley, *J. Chem. Soc.* (*C*), 1967, 1745.

the 2-substituted pyrazolo[4,3-*b*]pyridine, respectively. Finar and Hurlock [2] assigned the structure of the product obtained by the Skraup reaction of 4-amino-1-phenylpyrazole as 1-phenylpyrazolo[4,3-*b*]pyridine by comparison of its u.v. spectrum with that of 3-methyl-1-phenylpyrazolo[4,3-*b*]pyridine. However they could not



R

(IV) MeCO·CH : CMe
(V) OHC · C(NO$_2$) : CH
(VI) PhCH : CH·CO
(VII) EtO$_2$C · CH : CMe

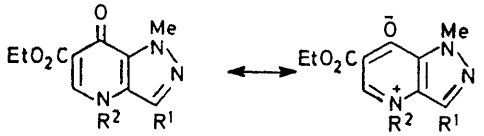


(VIII) R = H
(IX) R = Ph

obtain a 2-phenyl compound for reference. Cyclisation of the crotonate (VII) gave the 1-substituted pyrazolo-[4,3-*b*]pyridine (IX). In this case the product was identified by comparison of its u.v. spectrum with those of closely related pyrazolo[5,4-*b*]pyridines.[3] We have found that cyclisation of the aminomethylenemalonates (II; R′ = CO_2Et) also yields 1-substituted pyrazolopyridines, by a comparison of the spectroscopic properties of the products with those of the model compounds (XII) and (XV). Although the u.v. curves are similar, the spectrum of the product from the cyclisation of 1-methylpyrazol-4-ylaminomethylenemalonate (IIb; R′ = CO_2Et) more closely resembles that of the 1-substituted compound (XII) than that of the 2-substituted pyrazolo-[4,3-*b*]pyridine (XV) (Figure 1).* It has been observed, in related compounds, that the maxima of 2-substituted derivatives are also displaced to longer wavelength.[3] Furthermore the carbonyl stretching frequencies in the i.r. spectra indicate that cyclisation occurs into the 5-position. In the case of the 1-methyl compounds (X) and (XII) and their *N*-ethyl derivatives (XI) and (XIII) the ester C=O absorption occurs at a much higher wavenumber, and the ring C=O absorption at a much lower wavenumber, than in the corresponding 2-methyl compounds (XV) and (XVI). In compounds (X)—(XIII), structures such as (XIV) would be expected to make a significant contribution to the resonance hybrid. The analogous structures (XVII) in the 2-methyl compounds are *o*-quinonoid and would make a smaller contribution. In this case the lone pair on N-4 may be delocalised through the 6-ethoxycarbonyl group (XVIII) thus accounting for the observed positions of the carbonyl absorptions.

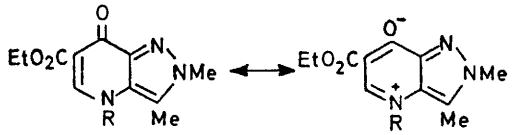
The tautomerism of the 1-methyl-, 1,3-dimethyl-, and 2,3-dimethyl-pyrazolopyridines [(X), (XII), and (XV)] has been investigated by use of model compounds. The *N*-ethyl derivatives [(XI), (XIII), and (XVI)] were prepared by treatment of the sodium salts with ethyl iodide, and the *O*-ethyl derivatives [(XIX)—(XXI)] were obtained *via* the corresponding 7-chloro-compounds [(XIX)—(XXI); Cl for OEt] by the action of sodium ethoxide.

Spectral evidence indicates that the 1,4-dihydropyrazolo[4,3-*b*]pyridin-7-one form predominates in each case. The u.v. spectrum of the 1,3-dimethylpyrazolopyridine (XII) is almost identical with that of its *N*-ethyl derivative but differs markedly from that of its *O*-ethyl derivative (Figure 2). Similar results were obtained for the 1-methyl compound (X) and its *N*- and *O*-ethyl derivatives. However the 7-ethoxy-compounds (XIX) and (XX) may not be completely satisfactory models for the hydroxy-tautomers since the substituents in the 1- and 6-positions of the ring may twist the ethoxy-group out of plane. In the 2-methyl compound (XXI) the ethoxy-group is more likely to be in the ring plane and in this case the difference between the u.v. curves of the *N*- and *O*-ethyl compounds [(XVI) and (XXI)] is less marked (Figure 3). The argument is substantiated by the observation that the ester carbonyl group in the 2-methyl-7-ethoxypyrazolopyridine (XXI) absorbs *ca.* 35 cm^{-1} to



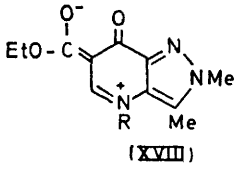
(XIV)

	R^1	R^2
(X)	H	H
(XI)	H	Et
(XII)	Me	H
(XIII)	Me	Et



(XV) R = H
(XVI) R = Et

(XVII)



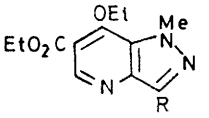
(XVIII)

lower wavenumber than that in the 1-methyl-7-ethoxy-compounds (XIX) and (XX). This is due to the powerful +*M* effect of the 7-OEt group [see structure (XXII)], which is maximal when the group is in the plane of the ring. I.r. spectra (Nujol) indicate that the pyridone structures also predominate in the solid phase. Ring carbonyl stretching frequencies occur in the region 1 615—1 635 cm^{-1}, and the broad absorptions at 2 400—3 300 cm^{-1} can be attributed to intermolecularly bonded N–H groups.

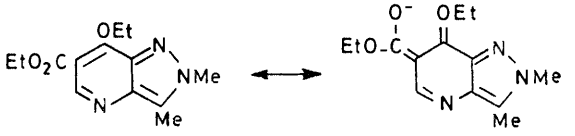
In the n.m.r. spectra (solvent deuteriochloroform) the

* Figures 1—3 are available as Supplementary Publication No. SUP 26132 (4 pp.). For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

5-proton signal of the *O*-ethyl compounds (XIX)—(XXI) occurs *ca.* 0.6 p.p.m. downfield in comparison with the *N*-ethylpyrazolopyridines (XI), (XIII), and (XVI). The parent compounds [(X), (XII), and (XV)] are too insoluble to give satisfactory spectra in this solvent. In



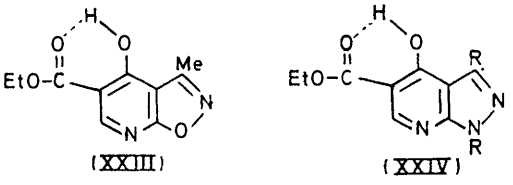
(XIX) R = H
(XX) R = Me



(XXI) (XXII)

$(CD_3)_2SO$ the resonances of the 5-protons of the *O*- and *N*-ethyl compounds are less widely separated and are less diagnostic. However the absorption due to the 5-proton in the parent compounds is closer to that of the *N*-ethyl derivatives, which again indicates that the pyridone form is predominant.

The closely related isoxazolo[5,4-*b*]pyridines (XXIII) [6] and pyrazolo[3,4-*b*]pyridines (XXIV) [7,8] have been shown by n.m.r. and i.r. spectroscopy to exist as the hydroxy-tautomers in which the 4-hydroxy-group is intramolecularly hydrogen bonded with the adjacent ester carbonyl group. The pyrazolo[3,4-*b*]pyridines (XXIV) have relatively low m.p.s and are soluble in non-polar solvents. In contrast the pyrazolo[4,3-*b*]-pyridines (X), (XII), and (XV) have high m.p.s and are



(XXIII) (XXIV)

insoluble in most organic solvents. This indicates that these compounds are intermolecularly H-bonded and further supports their assignment as the pyridones.

The tautomeric equilibria of dimethyl 4-hydroxypyridine-2,6-dicarboxylate and a number of other 4-hydroxypyridines have been discussed by Katritzky *et al.*[9]

EXPERIMENTAL

I.r. spectra were recorded for Nujol mulls with a Unicam SP 200 or Perkin-Elmer 157 G 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, except where stated otherwise, with tetramethylsilane as internal standard, with a Perkin-Elmer R12 (60 MHz) instrument. Accurate mass measurements were determined with an A.E.I. MS 902 spectrometer operating at 70 eV. Light petroleum of b.p. 60—80° was used except where stated otherwise.

1-Methyl-4-nitropyrazole.—A solution of methylhydrazine (5.52 g) in ethanol (30 ml) was acidified with concentrated hydrochloric acid and was then treated with sodiomalonaldehyde monohydrate (18.96 g) during 10 min. The mixture was heated under reflux for 30 min and was diluted with water (100 ml) to yield a brown solid. Continuous extraction of the solid with light petroleum afforded the *nitro-compound* (9.9 g, 65%). Crystallisation from carbon tetrachloride gave spars, m.p. 92° (Found: C, 37.75; H, 3.8; N, 33.3. $C_4H_5N_3O_2$ requires C, 37.8; H, 3.95; N, 33.05%), $\nu_{max.}$ 1 520br (NO_2), 1 460, 1 400br, 1 320br (NO_2), 1 000, 820, and 760 cm^{-1}.

General Method for the Preparation of Diethyl Pyrazol-4-ylaminomethylenemalonates (II; R′ = CO_2Et) *and Ethyl Cyano(pyrazol-4-ylaminomethylene)acetates* (II; R′ = CN) *from 4-Nitropyrazoles.*—The 4-nitropyrazole (0.01 mol),[10] 10% palladium–charcoal (0.1 g), and methanol (40 ml) were shaken together with hydrogen at 5 atm for 3 h. The catalyst was filtered off and diethyl ethoxymethylenemalonate (0.011 mol) or ethyl cyano(ethoxymethylene)-acetate (0.011 mol) was added to the filtrate. Evaporation gave an oil which was heated on a steam-bath for 15 min. The excess of diethyl ethoxymethylenemalonate was removed *in vacuo*. Trituration of the residual oil with light petroleum gave the crude product (see Table).

General Method for the Preparation of Ethyl 4,7-Dihydro-7-oxo-1H-pyrazolo[4,3-b]pyridine-6-carboxylates from Diethyl Pyrazol-4-ylaminomethylenemalonates.—The diethyl pyrazol-4-ylaminomethylenemalonate was added to boiling Dowtherm (50 ml g^{-1}). The mixture was heated under reflux for 15 min, then cooled, and on dilution with light petroleum gave the product.

Ethyl 4,7-dihydro-7-oxo-1H-pyrazolo[4,3-b]pyridine-6-carboxylate (IIIa; R′ = CO_2Et) Diethyl pyrazol-4-ylaminomethylenemalonate (1.5 g) gave the *pyrazolopyridine* (0.87 g, 71%), prisms, m.p. 295—298° (from dimethylformamide) (Found: M^+, 207.0641. $C_9H_9N_3O_3$ requires *M*, 207.0644), $\lambda_{max.}$ (EtOH) 225 (log ε 4.33) and 293 nm (4.07), $\nu_{max.}$ 3 500—2 500 (N–H), 1 690 (ester C=O), 1 605, 1 575, 1 435, 1 380, 1 365, 1 285 (C–O), 1 180, 1 105, and 935 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 0.74 (1 H, s, 5-H), 1.32 (1 H, s, 3-H), 5.28 (2 H, q, CH_2), and 8.44 (3 H, t, CH_3).

Ethyl 4,7-dihydro-7-oxo-1-phenyl-1H-pyrazolo[4,3-b]-pyridine-6-carboxylate (IIIc; R′ = CO_2Et). Diethyl 1-phenylpyrazol-4-ylaminomethylenemalonate (0.75 g) gave the *pyrazolopyridine* (0.58 g, 88%), needles, m.p. 278—280° (from dimethylformamide) (Found: C, 63.75; H, 4.75; N, 14.95. $C_{15}H_{13}N_3O_3$ requires C, 63.6; H, 4.65; N, 14.85%), $\lambda_{max.}$ (EtOH) 227 (log ε 4.44) and 301 nm (4.19), $\nu_{max.}$ 3 300—2 500 (N–H), 1 700 (ester C=O), 1 610, 1 575, 1 360, and 1 280 cm^{-1} (C–O), τ ($CF_3{\cdot}CO_2H$) 0.65 (1 H, s, 5-H), 1.18 (1 H, s, 3-H), 2.31 (5 H, s, Ph), 5.27 (2 H, q, CH_2), and 8.43 (3 H, t, CH_3).

Ethyl 4,7-dihydro-1-methyl-7-oxo-1H-pyrazolo[4,3-b]-pyridine-6-carboxylate (X). Diethyl 1-methylpyrazol-4-ylaminomethylenemalonate (0.75 g) gave the *pyrazolopyridine*

[6] T. Denzel and H. Höhn, *Arch. Pharm.*, 1972, **305**, 833.
[7] H. Höhn, T. Denzel, and W. Janssen, *J. Heterocyclic Chem.*, 1972, **9**, 235.
[8] T. Denzel, *Arch. Pharm.*, 1974, **307**, 177.
[9] A. Gordon, A. R. Katritzky, and S. K. Roy, *J. Chem. Soc.* (*B*), 1968, 556.
[10] R. H. Wiley, L. C. Behr, R. Fusco, and C. H. Jarboe, 'Heterocyclic Compounds; Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles, and Condensed Rings,' Interscience, New York–London, 1967, vol. 22, p. 673.

(0.51 g, 84%), prisms, m.p. 295—296° (from dimethylformamide) (Found: C, 54.25; H, 5.2; N, 19.1. $C_{10}H_{11}N_3O_3$ requires C, 54.3; H, 5.0; N, 19.0%), $\lambda_{max.}$ (EtOH) 227 (log ε 4.29) and 298 nm (4.06), $\nu_{max.}$ 3 300—2 500 (N–H), 1 690 (ester C=O), 1 615 (ring C=O), 1 600, 1 515, 1 380, 1 280 (C–O), 1 250, 1 195, 1 125, 935, and 800 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 0.73 (1 H, s, 5-H), 1.41 (1 H, s, 3-H), 5.23 (2 H, q, CH_2), 5.35 (3 H, s, 1-CH_3), and 8.41 (3 H, t, CH_2CH_3), τ [$(CD_3)_2SO$] 1.64 (1 H, s, 5-H).

Ethyl 4,7-*dihydro*-1,3-*dimethyl*-7-*oxo*-1H-*pyrazolo*[4,3-b]*pyridine*-6-*carboxylate* (XII). Diethyl 1,3-dimethylpyrazol-4-ylaminomethylenemalonate (1.5 g) gave the *pyrazolopyridine* (0.71 g, 56%), plates, m.p. 292—294° (from dimethylformamide) (Found: C, 55.95; H, 5.6; N, 18.1. $C_{11}H_{13}N_3O_3$ requires C, 56.15; H, 5.55; N, 17.85%), $\lambda_{max.}$ (EtOH) 227 (log ε 4.41) and 303 nm (4.13), $\nu_{max.}$ 3 300—2 500 (N–H), 1 700 (ester C=O), 1 620 (ring C=O), 1 555, 1 535, 1 280 (C–O), 1 270, and 1 120 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 0.83 (1 H, s, 5-H), 5.27 (2 H, q, CH_2), 5.44 (3 H, s, 1-CH_3), 7.20 (3 H, s, 3-CH_3), and 8.42 (3 H, t, CH_2CH_3), τ [$(CD_3)_2SO$] 1.72 (1 H, s, 5-H).

Ethyl 4,7-*dihydro*-2,3-*dimethyl*-7-*oxo*-2H-*pyrazolo*[4,3-b]*pyridine*-6-*carboxylate* (XV). Diethyl 1,5-dimethylpyrazol-4-ylaminomethylenemalonate (0.1 g) gave the *pyrazolopyridine* (0.055 g, 65%), prisms, m.p. 288—290° (from dimethylformamide) (Found: C, 55.45; H, 5.8; N, 17.8. $C_{11}H_{13}N_3O_3$ requires C, 51.15; H, 5.55; N, 17.85%), $\lambda_{max.}$ (EtOH) 233 (log ε 4.32) and 313 (4.05) nm, $\nu_{max.}$ 3 200—2 500 (N–H), 1 670 (ester C=O), 1 635 (ring C=O), 1 580, 1 560, 1 300, and 1 280 cm^{-1} (C–O), τ ($CF_3{\cdot}CO_2H$) 0.78 (1 H, s, 5 H), 5.25 (2 H, q, CH_2), 5.56 (3 H, s, 2-CH_3), 7.10 (3 H, s, 3-CH_3), and 8.41 (3 H, t, CH_2CH_3), τ [$(CD_3)_2SO$] 1.70 (1 H, s, 5-H).

General Method for the Preparation of 4,7-*Dihydro*-7-*oxo*-1H-*pyrazolo*[4,3-b]*pyridine*-6-*carbonitriles* (III; R′ = CN) *from Ethyl Cyano*(*pyrazol*-4-*ylaminomethylene*)*acetates* (II; R′ = CN).—The cyanoacetate was added to boiling Dowtherm (50 ml g^{-1}). The mixture was heated under reflux for 2 h, and diluted with light petroleum, and the precipitated solid was collected.

4,7-*Dihydro*-7-*oxo*-1H-*pyrazolo*[4,3-b]*pyridine*-6-*carbonitrile* (IIIa; R′ = CN). Sublimation (300 °C and 1 mmHg) followed by trituration with ethanol gave the *cyano-compound* (41%), m.p. >340° (Found: M^+, 160.0389. $C_7H_4N_4O$ requires M, 160.0395), $\lambda_{max.}$ (EtOH) 226 (log ε 4.31), 232 (4.27), and 293 nm (3.98), $\nu_{max.}$ 3 300—2 500 (N–H), 2 200 (C≡N), 1 610br (C=O), 1 570, 1 480, 1 415, 1 375, 1 320, and 925 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 1.17 (1 H, s, 3- or 5-H) and 1.33 (1 H, s, 3- or 5-H).

4,7-*Dihydro*-1-*methyl*-7-*oxo*-1H-*pyrazolo*[4,3-b]*pyridine*-6-*carbonitrile* (IIIb; R′ = CN). Extraction with boiling water, removal of the solvent, and sublimation of the residue (280 °C and 1 mmHg) gave the *cyano-compound* (24%). Crystallisation from water gave buff plates, m.p. 305—308° [Found: $(M-1)^+$, 173.0461. $C_8H_5N_4O$ requires $(M-1)$, 173.0463], $\nu_{max.}$ 3 500—2 500 (N–H), 2 200 (C≡N), 1 600 (C=O), 1 580, 1 420, 1 350, 1 340, and 670 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 1.44 (1 H, s, 3- or 5-H), 1.64 (1 H, s, 3- or 5-H), and 5.43 (3 H, s, CH_3).

4,7-*Dihydro*-7-*oxo*-1-*phenyl*-1H-*pyrazolo*[4,3-b]*pyridine*-6-*carbonitrile* (IIIc; R′ = CN). Sublimation (300 °C and 1 mmHg) gave the *cyano-compound* (62%). Crystallisation from aqueous dimethylformamide gave prisms, m.p. >330° (Found: M^+, 236.0690. $C_{13}H_8N_4O$ requires M, 236.0698), $\lambda_{max.}$ (EtOH) 227 (log ε 4.46) and 306 nm (4.16), $\nu_{max.}$ 3 300—2 500 (N–H), 2 200 (C≡N), 1 620 (C=O), 1 595, 1 585, 1 560, 1 520, 1 500, 1 410, 1 380, 1 235, 920, and 765 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 1.40 (1 H, s, 3- or 5-H), 1.45 (1 H, s, 3- or 5-H), and 2.37 (5 H, s, Ph).

Diethyl pyrazol-4-ylaminomethylene-malonates and -cyanoacetates

Compd.	M.p. (°C)	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
(IIa; R′ = CO_2Et) [a]	121—122 [f]	70	52.35	6.05	16.8	$C_{11}H_{15}N_3O_4$	52.15	6.0	16.6
(IIb; R′ = CO_2Et) [b]	92—93 [g]	63	54.15	6.4	15.65	$C_{12}H_{17}N_3O_4$	53.9	6.4	15.7
(IIb; R′ = CO_2Et,3-Me) [c]	54—55 [h]	27	55.45	6.95	15.0	$C_{13}H_{19}N_3O_4$	55.45	6.8	14.95
(IIb; R′ = CO_2Et,5-Me) [d]	77—78 [i]	84	55.55	6.7	15.0	$C_{13}H_{19}N_3O_4$	55.45	6.8	14.95
(IIc; R′ = CO_2Et) [e]	102—103 [j]	83	61.75	5.7	12.85	$C_{17}H_{19}N_3O_4$	62.0	5.85	12.75
(IIa; R′ = CN) [a]	183—184 [j]	65	52.2	4.8	26.9	$C_9H_{10}N_4O_2$	52.4	4.9	27.15
(IIb; R′ = CN) [b]	114—115 [f]	57	54.25	5.3	25.35	$C_{10}H_{12}N_4O_2$	54.5	5.5	25.45
(IIc; R′ = CN) [e]	168—169 [k]	84	63.6	4.9	20.15	$C_{15}H_{14}N_4O_2$	63.85	5.0	19.85

Prepared: [a] from 4-nitropyrazole (see ref. 11); [b] from 1-methyl-4-nitropyrazole; [c] from 1,3-dimethyl-4-nitropyrazole (see ref. 12); [d] from 1,5-dimethyl-3-nitropyrazole (see ref. 12); [e] directly from the stable amine (4-amino-1-phenylpyrazole; see ref. 2). Crystallised from: [f] benzene–cyclohexane (charcoal) then carbon tetrachloride; [g] benzene–light petroleum; [h] light petroleum (b.p. 40—60°) [i] light petroleum; [j] ethanol; [k] 2-ethoxyethanol.

Attempted Cyclisation of Ethyl Cyano(*pyrazol*-4-*ylaminomethylene*)*acetate* (IIa; R′ = CN) *with Polyphosphoric Acid.*—The cyanoacetate (0.5 g) and polyphosphoric acid (10 g) were heated on a steam-bath for 1 h. The mixture was cooled and basified with 20% sodium hydroxide solution to give *ethyl pyrazol*-4-*ylaminomethylenemalonamate* (IIa; R′ = CO·NH_2) (0.34 g, 63%). Crystallisation from ethyl acetate gave pale yellow prisms, m.p. 153—154° (Found: C, 48.45; H, 5.6; N, 24.8. $C_9H_{12}N_4O_3$ requires C, 48.2; H, 5.4; N, 25.0%), $\nu_{max.}$ 3 500—2 500 (N–H), 1 640br (C=O), 1 560, 1 470 br, 1 370, 1 320, 1 280, and 1 260 cm^{-1}. When the reaction was carried out at 180 °C for 2 h an intractable brown solid was obtained.

Attempted Cyclisation of Ethyl Cyano-(1-*phenylpyrazol*-4-*ylaminomethylene*)*acetate* (IIc; R′ = CN) *with Polyphosphoric Acid.*—Treatment on a steam-bath under the above conditions gave *ethyl* 1-*phenylpyrazol*-4-*ylaminomethylenemalonamate* (IIc; R′ = CO·NH_2) (94%). Crystallisation from ethyl acetate gave pale yellow needles, m.p. 163—164° (Found: C, 59.9; H, 5.35; N, 18.4. $C_{15}H_{16}N_4O_3$ requires C, 60.0; H, 54.4; N, 18.65%), $\nu_{max.}$ 3 500—3 400 (N–H), 1 670 (ester C=O), 1 650 (amide C=O), 1 550, 1 470, 1 300, 1 255, and 760 cm^{-1}.

The malonamate (IIc; R′ = CO·NH_2) was unchanged when heated in polyphosphoric acid for 1 h at 140—150 °C. Treatment at 180 °C for 2 h gave an intractable oil.

Attempted Preparation of 5,7-*Dimethyl*-1-*phenyl*-1H-

[11] E. Buchner and M. Fritsche, *Annalen*, 1893, **273**, 252.
[12] K. von Auwers and K. Bahr, *J. prakt. Chem.*, 1927, **116**, 65.

pyrazolo[4,3-b]*pyridine*.— 4-(1-Phenylpyrazol-4-ylamino)-pent-3-en-2-one [13] (0.2 g) and polyphosphoric acid (5 g) were heated at 160—180 °C for 90 min. The mixture was cooled, basified with 20% sodium hydroxide solution, and extracted with ether (3 × 20 ml). The dried ($MgSO_4$) extract was evaporated to yield a yellow oil (0.1 g). T.l.c. showed the oil to be a mixture of starting material and 4-amino-1-phenylpyrazole.

2-*Nitro*-3-(1-*phenylpyrazol*-4-*ylamino*)*propenal* (V).—A stirred solution of 4-amino-1-phenylpyrazole (0.5 g) in ethanol (5 ml) and 5% hydrochloric acid (5 ml) was treated with a solution of nitrosodiomalonaldehyde monohydrate (0.5 g) in water (5 ml). The mixture was stirred for 1 h and the precipitated solid was collected to give the *propenal* (0.6 g, 74%). Crystallisation from acetic acid gave yellow needles, m.p. 231—232° (decomp.) (Found: C, 55.75; H, 4.0; N, 22.0. $C_{12}H_{10}N_4O_3$ requires C, 55.6; H, 3.9; N, 21.85%), $\nu_{max.}$ 3 200 (N–H), 1 650 (C=O), 1 620, 1 510, and 1 340 (NO_2), and 1 315 cm^{-1}.

Attempted Preparation of 6-*Nitro*-1-*phenyl*-1H-*pyrazolo*-[4,3-b]*pyridine*.—(*a*) 2-Nitro-3-(1-phenylpyrazol-4-ylamino)-propenal (0.1 g), 4-amino-1-phenylpyrazole hydrochloride (0.075 g), and acetic acid (2 ml) were heated under reflux for 18 h. The mixture was cooled and basified with 10% sodium carbonate solution to give starting material (0.06 g).

(*b*) 2-Nitro-3-(1-phenylpyrazol-4-ylamino)propenal (0.1 g) and 20% hydrochloric acid (2 ml) were heated under reflux for 1 h. The mixture was cooled, basified, and extracted with ether (3 × 20 ml). The dried ($MgSO_4$) extract was evaporated to yield 4-amino-1-phenylpyrazole (0.03 g, 49%).

4-*Cinnamamido*-1-*phenylpyrazole* (VI).—Cinnamic acid (0.74 g) and thionyl chloride (5 ml) were heated under reflux for 30 min and the excess of thionyl chloride was removed by evaporation. The residual cinnamoyl chloride was added to 4-amino-1-phenylpyrazole (0.8 g), sodium carbonate (0.8 g), and benzene (20 ml). The mixture was heated under reflux for 1 h and filtered hot, and the solid was extracted with boiling benzene. Evaporation of the combined extracts and trituration of the residue with light petroleum gave the *cinnamamide* (0.67 g, 46%). Crystallisation from ethanol gave prisms, m.p. 190—191° (Found: C, 74.95; H, 5.3; N, 14.4. $C_{18}H_{15}N_3O$ requires C, 74.7; H, 5.4; N, 14.5%), $\nu_{max.}$ 3 200 (N–H), 1 660 (C=O), 1 630, 1 600, 1 540, 1 510, 1 415, 1 405, 1 200, 975, and 755 cm^{-1}.

Attempted Preparation of 1,4,6,7-*tetrahydro*-1,7-*diphenyl*-1H-*pyrazolo*[4,3-b]*pyridin*-5-*one*.—4-Cinnamamido-1-phenylpyrazole (0.2 g) and polyphosphoric acid (5 g) were heated at 140 °C for 1 h. The mixture was cooled and basified with 20% sodium hydroxide solution to give starting material (0.15 g).

Ethyl 3-(*Pyrazol*-4-*ylamino*)*crotonate* (VII; H *for* Ph).—4-Nitropyrazole (1.13 g), 10% palladium–charcoal (0.14 g), and methanol (40 ml) were shaken with hydrogen at 5 atm for 3 h. Filtration and evaporation yielded the crude 4-aminopyrazole, which was treated with ethyl acetoacetate (1.43 g) and concentrated hydrochloric acid (0.2 ml). The mixture was heated on a steam-bath for 5 min to yield an oily solid. Trituration with aqueous ethanol gave the *crotonate* (1.31 g, 67%). Crystallisation from benzene–cyclohexane gave needles, m.p. 119—120° (Found: C, 55.55; H, 6.8; N, 21.4. $C_9H_{13}N_3O_2$ requires C, 55.35; H, 6.75; N, 21.5%), $\nu_{max.}$ 3 400—2 500 (N–H), 1 650 (C=O), 1 620, 1 260 (C–O), and 1 160 cm^{-1}.

1,4-*Dihydro*-5-*methylpyrazolo*[4,3-b]*pyridin*-7-*one* (VIII).—Ethyl 3-(pyrazol-4-ylamino)crotonate (1.5 g) was added to boiling Dowtherm (75 ml). The mixture was heated under reflux for 15 min, then cooled, and on dilution with light petroleum gave the *pyrazolopyridine* (0.78 g, 68%). Crystallisation from aqueous ethanol gave prisms, m.p. >330° (Found: M^+, 149.0591. $C_7H_7N_3O$ requires M, 149.0589), $\nu_{max.}$ 3 500—2 500 (N–H), 1 605 (C=O), 1 555, 1 520, 1 415, 1 265, and 945 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 1.43 (1 H, s, 3-H), 2.78 (1 H, s, 6-H), and 7.10 (3 H, s, CH_3).

General Method for the Preparation of Ethyl 7-*Chloropyrazolo*[4,3-b]*pyridine*-6-*carboxylates*.—The oxo-compound and phosphoryl chloride (10 ml g^{-1}) were heated under reflux for 4 h. The solvent was evaporated off under reduced pressure and the residue was basified with 10% sodium carbonate solution.

Ethyl 7-*chloro*-1-*methyl*-1H-*pyrazolo*[4,3-b]*pyridine*-6-*carboxylate* (XIX; Cl *for* OEt). Ethyl 4,7-dihydro-1-methyl-7-oxo-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylate (0.5 g) gave the *chloro-compound* (0.45 g, 83%), m.p. 75° (from light petroleum) (Found: C, 50.05; H, 4.45; Cl, 15.05; N, 17.45. $C_{10}H_{10}ClN_3O_2$ requires C, 50.1; H, 4.2; Cl, 14.8; N, 17.55%), $\nu_{max.}$ 1 730 (C=O), 1 270, 1 235, 1 165, 1 025, and 830 cm^{-1}, τ 1.16 (1 H, s, 5-H), 1.80 (1 H, s, 3-H), 5.50 (2 H, q, CH_2), 5.56 (3 H, s, 1-CH_3), and 8.55 (3H, t, CH_2CH_3).

Ethyl 7-*chloro*-1,3-*dimethyl*-1H-*pyrazolo*[4,3-b]*pyridine*-6-*carboxylate* (XX; Cl *for* OEt). Ethyl 4,7-dihydro-1,3-dimethyl-7-oxo-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylate (3 g) gave the *chloro-compound* (3.03 g, 94%), m.p. 95—96° from light petroleum (b.p. 80—100°) (Found: C, 51.95; H, 4.9; Cl, 13.8; N, 16.35. $C_{11}H_{12}ClN_3O_2$ requires C, 52.05; H, 4.75; Cl, 14.0; N, 16.55%), $\nu_{max.}$ 1 730 (C=O), 1 490, 1 330, 1 220, 1 085, 795, 790, and 665 cm^{-1}, τ 1.21 (1 H, s, 5-H), 5.52 (2 H, q, CH_2), 5.63 (3 H, s, 1-CH_3), 7.35 (3 H, s, 3-CH_3), and 8.53 (3 H, t, CH_2CH_3).

Ethyl 7-*chloro*-2,3-*dimethyl*-2H-*pyrazolo*[4,3-b]*pyridine*-6-*carboxylate* (XXI; Cl *for* OEt). Ethyl 4,7-dihydro-2,3-dimethyl-7-oxo-2*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylate (1.25 g) gave the *chloro-compound* (1.13 g, 83%), m.p. 88—89° [from light petroleum (b.p. 80—100°)] (Found: C, 52.15; H, 4.9; Cl, 14.2; N, 16.4. $C_{11}H_{12}ClN_3O_2$ requires C, 52.05; H, 4.75; Cl, 14.0; N, 16.55%), $\nu_{max.}$ 1 710 (C=O), 1 375, 1 230, 1 180, and 1 030 cm^{-1}, τ 1.18 (1 H, s, 5-H), 5.56 (2 H, q, CH_2), 5.81 (3 H, s, 2-CH_3), 7.29 (3 H, s, 3-CH_3), 8.55 (3 H, q, CH_2CH_3).

General Method for the Preparation of Ethyl 7-*Ethoxypyrazolo*[4,3-b]*pyridine*-6-*carboxylates*.—The chloro-compound (1 g) was added to a solution of sodium (1.2 equiv.) in super-dry ethanol (10 ml) and the mixture was left at room temperature for 18 h. The solvent was removed and water (20 ml) added to the residue. The mixture was extracted with chloroform (3 × 20 ml); the extract was dried ($MgSO_4$) and evaporated.

Ethyl 7-*ethoxy*-1-*methyl*-1H-*pyrazolo*[4,3-b]*pyridine*-6-*carboxylate* (XIX). Ethyl 7-chloro-1-methyl-1*H*-pyrazolo-[4,3,-*b*]pyridine-6-carboxylate gave a pale yellow oil which crystallised from light petroleum (b.p. 40—60°) to give the *ethoxy-compound* (0.79 g, 76%), m.p. 41—42° (Found: C, 57.85; H, 6.05; N, 16.7. $C_{12}H_{15}N_3O_3$ requires C, 57.8; H, 6.05; N, 16.85%), $\lambda_{max.}$ (EtOH) 229 (log ε 4.51), 277 (3.71), and 306 nm (3.63), $\nu_{max.}$ 1 725 (C=O), 1 365, 1 340, 1 230, 1 135, and 1 110 cm^{-1}, τ 1.21 (1 H, s, 5-H), 1.87 (1 H, s, 3-H), 5.3—5.8 (4 H, m, 2 × CH_2), 5.70 (3 H, s, 1-CH_3), and 8.3—8.7 (6 H, m, 2 × CH_2CH_3), τ [$(CD_3)_2SO$] 1.35 (1 H, s, 5-H).

[13] S. V. Tabak, I. I. Grandberg, and A. N. Kost, *Zhur. obshchei Khim.*, 1964, **34**, 2756.

Ethyl 7-ethoxy-1,3-dimethyl-1H-pyrazolo[4,3-b]*pyridine-6-carboxylate* (XX). Ethyl 7-chloro-1,3-dimethyl-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylate gave the *ethoxy-compound* (0.9 g, 87%), which was crystallised from light petroleum (b.p. 40—60°); m.p. 38—40° (Found: C, 59.2; H, 6.7; N, 15.85. $C_{13}H_{17}N_3O_3$ requires C, 59.3; H, 6.5; N, 15.95%), $\lambda_{max.}$ (EtOH) 234 (log ε 4.54), 276 (3.70), and 316 nm (3.68) $\nu_{max.}$ 1 725 (C=O), 1 370, 1 330, 1 230, 1 205, and 1 030 cm^{-1}, τ 1.23 (1 H, s, 5-H), 5.3—5.9 (4 H, m, 2 × CH_2), 5.76 (3 H, s, 1-CH_3), 7.37 (3 H, s, 3-CH_3), and 8.3—8.7 (6 H, m, 2 × CH_2CH_3), τ [$(CD_3)_2SO$] 1.38 (1 H, s, 5-H).

Ethyl 7-ethoxy-2,3-dimethyl-2H-pyrazolo[4,3-b]*pyridine-6-carboxylate* (XXI). Ethyl 7-chloro-2,3-dimethyl-2*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylate gave the *ethoxy-compound* (0.8 g, 77%). Crystallisation from light petroleum gave material with m.p. 75—77° (Found: C, 59.4; H, 6.4; N, 16.2 $C_{13}H_{17}N_3O_3$ requires C, 59.3; H, 6.5; N, 15.95%), $\lambda_{max.}$ 237 (log ε 4.61), 283 (3.66), and 318 nm (3.83), $\nu_{max.}$ 1 690 (C=O), 1 375, 1 330, 1 180, and 1 040 cm^{-1}, τ 1.26 (1 H, s, 5-H), 4.92 (2 H, q, 3-O·CH_2·CH_3), 5.52 (2 H, q, CO_2·CH_2·CH_3), 5.91 (3 H, s, 2-CH_3), 7.35 (3 H, s, 3-CH_3), and 8.3—8.8 (6 H, m, 2 × CH_2CH_3), τ [$(CD_3)_2SO$] 1.47 (1 H, s, 5-H).

General Method for the Preparation of Ethyl 4-Ethyl-4,7-dihydro-7-oxopyrazolo[4,3-b]*pyridine-6-carboxylates.*— The pyrazolopyridone (1 g) was added to a solution of sodium (1.1 equiv.) in super-dry ethanol (20 ml). Ethyl iodide (2.8 g) in ethanol (10 ml) was added and the mixture was heated at 68 °C for 5 h, then set aside at room temperature for 18 h. The solvent was removed and the residue treated with N-sodium hydroxide (20 ml). The solution was extracted with chloroform (3 × 20 ml); the extract was dried ($MgSO_4$) and evaporated to give the *N*-ethyl compound. Acidification of the aqueous phase gave starting material (30—40%).

Ethyl 4-ethyl-4,7-dihydro-1-methyl-7-oxo-1H-pyrazolo[4,3-b]*pyridine-6-carboxylate* (XI). Ethyl 4,7-dihydro-1-methyl-7-oxo-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylate gave the *N*-ethyl compound (0.68 g, 60%), m.p. 97—99° (from cyclohexane–toluene). A, satisfactory analysis was not obtained (Found: C, 59.45; H, 6.35; N, 16.0. Calc. for $C_{12}H_{15}N_3O_3$:C, 57.8; H, 6.05; N, 16.85%), $\lambda_{max.}$ 228 (log ε 4.26) and 304 nm (4.13), $\nu_{max.}$ 1 720 (ester C=O), 1 620 (ring C=O), 1 315, 1 220, and 1 105 cm^{-1}, τ 1.73 (1 H, s, 5-H), 2.40 (1 H, s, 3-H), 5.3—6.1 (4 H, m, 2 × CH_2), 5.62 (3 H, s, 1-CH_3), and 8.2—8.7 (6 H, m, 2 × CH_2CH_3), τ [$(CD_3)_2SO$] 1.58 (1 H, s, 5-H).

Ethyl 4-ethyl-4,7-dihydro-1,3-dimethyl-7-oxo-1H-pyrazolo[4,3-b]*pyridine-6-carboxylate* (XIII). Ethyl 4,7-dihydro-1,3-dimethyl-7-oxo-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylate gave the N-*ethyl compound* (0.35 g, 31%), m.p. 162—163° (from carbon tetrachloride) (Found: C, 59.05; H, 6.45; N, 16.1. $C_{13}H_{17}N_3O_3$ requires C, 59.3; H, 6.5; N, 15.95%), $\lambda_{max.}$ 227 (log ε 4.38) and 308 nm (4.2), $\nu_{max.}$ 1 715 (ester C=O), 1 620 (ring C=O), 1 580, 1 300, 1 120, and 800 cm^{-1}, τ 1.85 (1 H, s, 5-H), 5.45—6.1 (4 H, m, 2 × CH_2), 5.74 (3 H, s, 1-CH_3), 7.46 (3 H, s, 3-CH_3), and 8.4—8.8 (6 H, m, 2 × CH_2-CH_3), τ [$(CD_3)_2SO$] 1.63 (1 H, s, 5-H).

Ethyl 4-ethyl-4,7-dihydro-2,3-dimethyl-7-oxo-2H-pyrazolo[4,3-b]*pyridine-6-carboxylate* (XVI). Ethyl 4,7-dihydro-2,3-dimethyl-7-oxo-2*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylate gave the N-*ethyl compound* (0.41 g, 37%), m.p. 184—185° (from ethanol–benzene) (Found: C, 59.1; H, 6.55; N, 16.0. $C_{13}H_{17}N_3O_3$ requires C, 59.3; H, 6.5; N, 15.95%), $\lambda_{max.}$ 233 (log ε 4.37) and 318 nm (4.20), $\nu_{max.}$ 1 665 (ester C=O), 1 635 (ring C=O), 1 595, 1 580, 1 320, 1 235, and 1 190 cm^{-1}, τ 1.90 (1 H, s, 5-H), 5.3—6.1 (4 H, m, 2 × CH_2), 6.02 (3 H, s, 2-CH_3), 7.39 (3 H, s, 3-CH_3), and 8.3—8.7 (6 H, m, 2 × CH_2CH_3), τ [$(C_3D)_2SO$] 1.65 (1H, s, 5-H).

General Method for the Preparation of 4-Ethyl-4,7-dihydro-7-oxopyrazolo[4,3-b]*pyridine-6-carboxylic Acids.*—The ester (1 g), N-sodium hydroxide (15 ml), and ethanol (10 ml) were kept at room temperature for 3 days. The ethanol was removed *in vacuo* and the remaining aqueous solution acidified with acetic acid.

4-Ethyl-4,7-dihydro-1-methyl-7-oxo-1H-pyrazolo[4,3-b]*pyridine-6-carboxylic acid.* Ethyl 4-ethyl-4,7-dihydro-1-methyl-7-oxo-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylate gave the *acid* (0.71 g, 80%), m.p. 188—189° (from ethanol) (Found: C, 54.0; H, 5.1; N, 19.0. $C_{10}H_{11}N_3O_3$ requires C, 54.3; H, 5.0; N, 19.0%), $\nu_{max.}$ 2 800—2 100w (O–H), 1 705 (C=O), 1 615 (ring C=O), 1 410, 1 310, 1 260, 970, 805, and 730 cm^{-1}, τ (CF_3·CO_2H) 0.79 (1 H, s, 5-H), 1.38 (1 H, s, 3-H), 5.19 (2 H, q, CH_2), 5.42 (3 H, s, 1-CH_3), and 8.21 (3 H, t, 4-CH_2CH_3).

4-Ethyl-4,7-dihydro-1,3-dimethyl-7-oxo-1H-pyrazolo[4,3-b]*pyridine-6-carboxylic acid.* Ethyl 4-ethyl-4,7-dihydro-1,3-dimethyl-7-oxo-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylate gave the *acid* (0.87 g, 97%), m.p. 199—201° (from ethanol) (Found: C, 56.0; H, 5.65; N, 18.05. $C_{11}H_{13}N_3O_3$ requires C, 56.15; H, 5.55; N, 17.85%), $\nu_{max.}$ 2 800—2 200w (O–H), 1 725 (C=O), 1 610 (ring C=O), 1 510, 1 315, 805, and 740 cm^{-1}, τ (CF_3·CO_2H) 0.91 (1 H, s, 5-H), 5.11 (2 H, q, CH_2), 5.48 (3 H, s, 1-CH_3), 7.06 (3 H, s, 3-CH_3), and 8.20 (3 H, t, 4-CH_2CH_3).

4-Ethyl-4,7-dihydro-2,3-dimethyl-7-oxo-2H-pyrazolo[4,3-b]*pyridine-6-carboxylic acid.* Ethyl 4-ethyl-4,7-dihydro-2,3-dimethyl-7-oxo-2*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylate gave the *acid* (0.81 g, 91%), m.p. 286—287° (from 2-ethoxyethanol) (Found: C, 56.05; H, 5.6; N, 17.7. $C_{11}H_{13}N_3O_3$ requires C, 56.15; H, 5.55; N, 17.85%), $\nu_{max.}$ 2 800—2 110w (O–H), 1 710 (C=O), 1 605br (ring C=O), 1 275, and 810 cm^{-1}, τ (CF_3·CO_2H) 0.86 (1 H, s, 5-H), 5.09 (2 H, q, CH_2), 5.16 (3 H, s, 2-CH_3), 6.97 (3 H, s, 3-CH_3), and 8.17 (3 H, t, 4-CH_2CH_3).

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