Effects of 3-Substituents upon Orientation in the 1,3-Dipolar Cycloaddition Reaction Between 3-Substituted Pyridine *N*-Imides and Ethyl Propiolate: Syntheses of Ethyl 4- and 6-Substituted Pyrazolo[1,5-*a*]-pyridine-3-carboxylates

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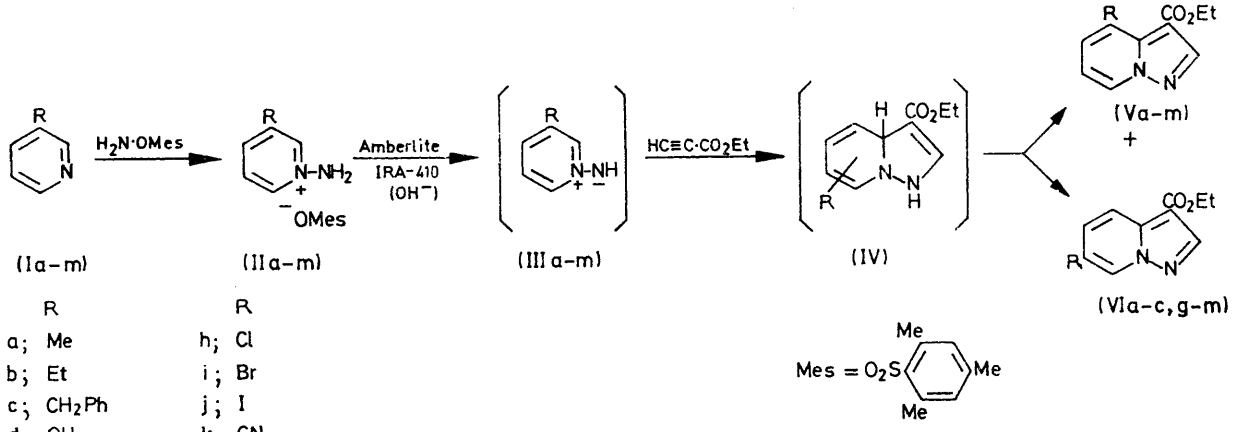
Quantitative data are presented relating to the effects of a series of 3-substituents upon orientation in the formation of ethyl pyrazolo[1.5-*a*]pyridine-3-carboxylates by a 1,3-dipolar cycloaddition reaction between 3-substituted pyridine *N*-imides and ethyl propiolate. The observed regioselectivity is discussed in terms of electronic and steric factors as well as hydrogen-bond formation.

1,3-DIPOLAR cycloaddition reactions between pyridine *N*-imides and activated alkynes and alkenes [*e.g.* (III) ⟶ (V) or (VI)] [1-9] have been used as synthetic routes to pyrazolo[1,5-*a*]pyridine derivatives. If 3-substituted pyridines are used in this reaction, the possibility exists of obtaining either the 4- or the 6-substituted pyrazolo[1,5-*a*]pyridine. Available data [3,6,7]

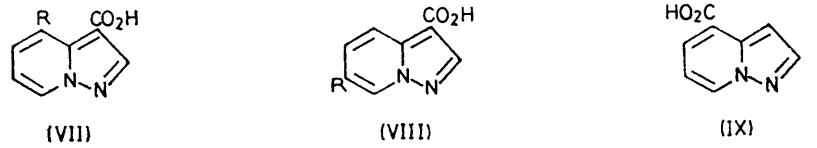
[1] R. Huisgen, R. Grashey, and R. Krischke, *Tetrahedron Letters*, 1962, 387.
[2] T. Okamoto, M. Hirobe, Y. Tamai, and E. Yabe, *Chem. and Pharm. Bull.* (*Japan*), 1966, **14**, 506.
[3] T. Okamoto, M. Hirobe, and E. Yabe, *Chem. and Pharm. Bull.* (*Japan*), 1966, **14**, 523.
[4] V. Boekelheide and N. A. Fedoruk, *J. Org. Chem.*, 1968, **33**, 2062.
[5] T. Sasaki, K. Kanematsu, and Y. Yukimoto, *J. Chem. Soc.* (*C*), 1970, 481.
[6] T. Yamura, A. Yamakami, and M. Ikeda, *J. Pharm. Soc. Japan*, 1971, **91**, 1154.
[7] T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, 1971, **36**, 2978.
[8] T. Sasaki, K. Kanematsu, and A. Kakehi, *Tetrahedron Letters*, 1972, 5245.
[9] Y. Tamura, Y. Miki, and M. Ikeda, *J. Heterocyclic Chem.*, 1973, **10**, 447.

indicate that 3-methylpyridine *N*-imide produces predominantly, or in some cases exclusively, 4-methylpyrazolo[1,5-*a*]pyridines. However, since there are no reports of systematic studies concerning the effects of 3-substituents upon orientation, it has been difficult hitherto to discuss the actual nature of the effects.[10] We now report quantitative data relating to the effects of a series of 3-substituents upon orientation in the cycloaddition reaction between 3-substituted pyridine *N*-imides (III) and ethyl propiolate.



(Ia–m)

R	R
a; Me	h; Cl
b; Et	i; Br
c; CH_2Ph	j; I
d; OH	k; CN
e; NH_2	l; CO_2Et
f; NHAc	m; $CO{\cdot}NEt_2$
g; NMeAc	



A slight modification of the procedure of Boekelheide and Fedoruk [4] was used, in which mixtures of *N*-aminopyridinium mesitylenesulphonates (II) [11] and ethyl propiolate in the presence of anhydrous potassium carbonate in dimethylformamide * were stirred at room temperature for 3 h to give ethyl pyrazolo[1,5-*a*]-pyridine-3-carboxylates [(V) and (VI)] in moderate yields, accompanied by coloured intractable material. The 4- and 6-isomers were separated by preparative t.l.c. on alumina. The product ratio was determined by g.l.c. analysis of the crude reaction mixture obtained after evaporation of the solvent, and the results are summarised in the Table. Structures were readily assigned on the basis of microanalyses [oily compounds were characterised as the crystalline carboxylic acids (VII) and (VIII) †] and i.r., mass, u.v., and n.m.r. spectra. In particular, the n.m.r. spectra of the two isomers show diagnostic differences: those of 4-substituted pyrazolo-[1,5-*a*]pyridines (V) show two broad doublets due to H-5 (τ 1·40—3·58) and H-7 (τ 1·30—2·01) and a doublet of doublets or a triplet due to H-6 (τ 2·90—3·39), whereas those of the 6-substituted isomers (VI) show an AB quartet due to H-4 (τ 1·70—2·03) and H-5 (τ 2·12—2·9) and a broad singlet due to H-7 (τ 0·29—1·73).‡

The results in the Table indicate that (i) unless a large substituent is present at the 3-position, the cycloaddition occurs preferentially at C-2 of the pyridine ring, regardless of the electron-donating or electron-withdrawing character of the substituent; (ii) steric hindrance by a 3-substituent to attack at C-2 becomes important with the larger 3-substituents; and (iii) the 3-hydroxy-, 3-amino-, and 3-acetamido-pyridine *N*-imides produce exclusively 4-substituted pyrazolo[1,5-*a*]pyridines (V).

These data can be rationalised in terms of electronic and steric factors and of hydrogen-bond formation. As already suggested by Huisgen,[12,13] the formation of compounds (V) and (VI) must proceed in two stages: a concerted 1,3-dipolar cycloaddition between (III) and ethyl propiolate leading to the dihydropyridine intermediate (IV), followed by a dehydrogenation to give the final products [(V) and (VI)]. Since most 1,3-dipolar cycloadditions are known to be stereospecific and hence irreversible, it is reasonable to assume that the first step (III) ⟶ (IV) is rate determining and responsible for determining the orientation. In general, 1,3-dipolar

* Replacement of this solvent by methanol or chloroform had little effect on the product distribution.

† Compound (VI) was decarboxylated under hydrolytic conditions to give pyrazolo[1,5-*a*]pyridine-4-carboxylic acid (IX).

‡ Spectroscopic details are available as Supplementary Publication No. SUP 21220 (3 pp.). For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1974, Index Issue.

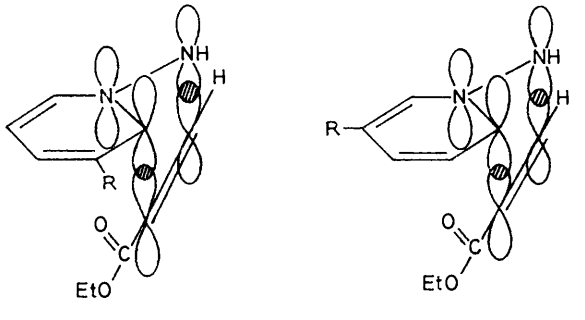
[10] For a detailed discussion of a related problem, see R. A. Abramovitch and T. G. Saha, *Adv. Heterocyclic Chem.*, 1966, **6**, 229.

[11] Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita, and M. Ikeda, *Tetrahedron Letters*, 1972, 4133.

[12] R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 633.

[13] R. Huisgen, *J. Org. Chem.*, 1968, **33**, 2291.

cycloadditions have been discussed in terms of a two-phase transition state.[12,13] In the present case, 3-substituted pyridine *N*-imides (III) would be expected to produce two primary adducts (IV) corresponding to two orientations of the 1,3-dipole and ethyl propiolate in the activated complex leading to the transition state (see Figure). Of the two possible orientations,* approach of



FIGURE

the two components as shown in (a) would be more favoured owing to stabilisation by resonance [14] [it being assumed that the transition state resembles the dihydropyridine intermediate (IV)].

Formation of ethyl pyrazolo[1,5-*a*]pyridine-3-carboxylates

	R	(V)	(VI)
a;	Me	68 [a] (25) [b]	32 (16)
b;	Et	70 (23)	30 (11)
c;	CH_2Ph	63 (31)	37 (15)
d;	OH	100 (8) [c]	0
e;	NH_2	100 (8)	0
f;	NHAc	100 (14)	0
g;	NMeAc	73 (20)	27 (13)
h;	Cl	64 (6)	36 (10)
i;	Br	49 (13)	51(16)
j;	I	44 (11)	56 (14)
k;	CN	73 (17)	27 (9)
l;	CO_2Et	65 (31)	35 (11)
m;	$CONEt_2$	36 (17)	64 (46)

[a] Product ratio determined by g.l.c. analyses. [b] Isolated yield (%). [c] Accompanied by a trace of an unidentified product.

The increased proportion of the product (VI) with increase of the bulk of the 3-substituents as seen in the two cases (IIIh) ⟶ (IIIj) and (IIIk) ⟶ (IIIm) may be accounted for by steric factors. Approach of the two components as shown in the Figure (a) would be expected to be hindered as a result of non-bonded interaction between the 3-substituent on the 1,3-dipole and the ethoxycarbonyl group of ethyl propiolate in the transition state.

The exclusive formation of (Vd—f) from (IIId—f), may be ascribed to the formation of a hydrogen bond between the hydrogen atom on the 3-substituent and the carbonyl group of the dipolarophile, whereby the transition state shown in the Figure (a) can gain extra stabilisation. This rationalisation is supported by the fact that the reaction of (IIIg) with ethyl propiolate gave a mixture of (V) and (VI) in the ratio 73 : 27. Apparently the hydrogen bond cannot be formed in this example, so that this ratio can be considered to reflect the general tendency for preferential attack at C-2 and the steric effect of the substituent.

* The possibility of the formation of ethyl pyrazolo[1,5-*a*]-pyridine-2-carboxylates is not taken into consideration here.[4]

† Experimental details are given in the Supplementary Publication (No. SUP 21220).

EXPERIMENTAL

N.m.r. spectra were determined with a Hitachi R-20A spectrometer (tetramethylsilane as internal standard). I.r. spectra were recorded with a Hitachi EPI-G2 spectrophotometer, and u.v. spectra with a Hitachi 124 spectrophotometer. G.l.c. was performed on a Hitachi K53 gas chromatograph [nitrogen as carrier gas; 3·3 ft × ⅛ in column packed with butanediol succinate polyester (BSP) as a 15% coating on Celite 545 at 220°].

N-Aminopyridinium Mesitylenesulphonates (II).—The *N*-aminopyridinium mesitylenesulphonates (IIa—m) were prepared by the procedure described in ref. 11.†

General Procedure for 1,3-*Dipolar Cycloaddition Reactions.*—Potassium carbonate (3·75 mmol) and ethyl propiolate (5 mmol) were added to a stirred solution of the *N*-aminopyridinium mesitylenesulphonate (II) (2·5 mmol) in dimethylformamide (5 ml) at 0°. The mixture was stirred vigorously for 3 h at room temperature and the solvent was evaporated off *in vacuo*. The residue was dissolved in chloroform and insoluble material was filtered off. The filtrate was concentrated *in vacuo* and the residue was separated by p.l.c. [alumina PF_{254}; chloroform–benzene (1 : 10) or ether–light petroleum (b.p. 30—60°) (1 : 10)] to give the products (V) and (VI). Yields and product distribution are summarised in the Table. The oily compounds (Vc and m) and (VIm) were characterised by conversion into the crystalline carboxylic acids. Compound (Vl) gave pyrazolo[1,5-*a*]pyridine-4-carboxylic acid (IX) under hydrolytic conditions.

Ethyl 4-methylpyrazolo[1,5-a]*pyridine-3-carboxylate* (Va) had m.p. 60—61° [from light petroleum (b.p. 30—60°)] (Found: C, 64·7; H, 6·0; N, 13·9. $C_{11}H_{12}N_2O_2$ requires C, 64·7; H, 5·9; N, 13·7%); $\nu_{max.}$ (KCl) 1705 cm^{-1}; $\lambda_{max.}$ (EtOH) 218·5sh, 222·5, 242, 249·5sh, and 299·5 nm (log ε 4·52, 4·59, 3·84, 3·77, and 4·10); the *6-methyl isomer* (VIa) had m.p. 82—83° [from light petroleum (b.p. 30—60°)] (Found: C, 64·7; H, 5·9; N, 13·3%); $\nu_{max.}$ (KCl) 1675 cm^{-1}; $\lambda_{max.}$ (EtOH) 219sh, 221·5, 225·5, 242, 248sh, and 305 nm (log ε 4·46, 4·49, 4·56, 4·00, 4·00, and 3·97); the *4-ethyl derivative* (Vb) had m.p. 30—30·5° (from ethanol–water) (Found: C, 66·3; H, 6·6; N, 12·7. $C_{12}H_{14}N_2O_2$ requires C, 66·0; H, 6·5; N, 12·8%); $\nu_{max.}$ (KCl) 1700 cm^{-1}; $\lambda_{max.}$ (EtOH) 218sh, 222, 242, 250sh, and 300 nm (log ε 4·39, 4·48, 3·71, 3·65, and 3·98); the *6-ethyl isomer* (VIb) had m.p. 53·5—55° (from ethanol–water) (Found: C, 65·9; H, 6·6; N, 12·8%); $\nu_{max.}$ (KCl) 1690 cm^{-1}; $\lambda_{max.}$ (EtOH) 221·5, 225·5, 243, 248sh, and 304 nm (log ε 4·47, 4·55, 3·98, 3·96, and 3·96); the *4-benzyl derivative* (Vc) was an oil, $\nu_{max.}$ ($CHCl_3$) 1705 cm^{-1}; $\lambda_{max.}$ (EtOH) 219, 224, 242, 251·5sh, and 302·5 nm (log ε 4·49, 4·50, 3·87, 3·78, and 3·99); the *6-benzyl isomer* (VIc) had m.p. 93—94° [from light petroleum (b.p. 60—80°)] (Found: C, 72·8; H, 5·8; N, 9·9. $C_{17}H_{16}N_2O_2$ requires C, 72·8; H, 5·75; N, 10·0%); $\nu_{max.}$

[14] H. L. Bradlow and C. A. Vanderwerf, *J. Org. Chem.*, 1951, **16**, 73.

(KCl) 1695 cm^{-1}; $\lambda_{max.}$ (EtOH) 223sh, 226, 241·5, 249sh, and 305 nm (log ε 4·50, 4·51, 4·17, 4·11, and 4·02); the *4-hydroxy-derivative* (Vd) had m.p. 98—98·5° [from light petroleum (b.p. 30—60°)] (Found: C, 58·5; H, 4·7; N, 13·3. $C_{10}H_{10}N_2O_3$ requires C, 58·25; H, 4·9; N, 13·6%); $\nu_{max.}$ (KCl) 1625 cm^{-1}; $\lambda_{max.}$ (EtOH) 225, 277sh, 288, 315, and 328 nm (log ε 4·27, 3·70, 3·89, 4·25, and 4·27); the *4-amino-derivative* (Ve) had m.p. 71—73° [from light petroleum (b.p. 30—60°)] (Found: C, 58·2; H, 5·5; N, 20·0. $C_{10}H_{11}N_3O_2$ requires C, 58·5; H, 5·4; N, 20·5%); $\nu_{max.}$ (KCl) 1685 and 1620 cm^{-1}; $\lambda_{max.}$ (EtOH) 223sh, 298, and 335 nm (log ε 3·96, 3·95, and 4·17); the *4-acetamido-derivative* (Vf) had m.p. 135—136° [from light petroleum (b.p. 60—80°)] (Found: C, 58·3; H, 5·4; N, 16·7. $C_{12}H_{13}N_3O_3$ requires C, 58·3; H, 5·3; N, 17·0%); $\nu_{max.}$ (KCl) 1695, 1650, and 1630 cm^{-1}; $\lambda_{max.}$ (EtOH) 216, 232sh, 255·5, 264sh, 304sh, 317, and 331 nm (log ε 4·41, 4·21, 3·81, 3·77, 4·15, 4·22, and 4·15); the *4-(N-methylacetamido)-derivative* (Vg) had m.p. 141—142° [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 59·9; H, 5·9; N, 15·9. $C_{13}H_{15}N_3O_3$ requires C, 59·8; H, 5·8; N, 16·1%); $\nu_{max.}$ (KCl) 1710 and 1660 cm^{-1}; $\lambda_{max.}$ (EtOH) 219sh, 223, 238, 246sh, 292·5sh, and 306 nm (log ε 4·38, 4·43, 3·93, 3·85, 3·81, and 3·82); the *6-(N-methylacetamido)-isomer* (VIg) had m.p. 172—173·5° [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 59·8; H, 5·8; N, 15·9%); $\nu_{max.}$ (KCl) 1700 and 1660 cm^{-1}; $\lambda_{max.}$ (EtOH) 220, 225sh, 242sh, 247, and 301 nm (log ε 4·29, 4·28, 4·23, 4·24, and 3·87); the *4-chloro-derivative* (Vh) had m.p. 60—60·5° [from light petroleum (b.p. 60—80°)] (Found: C, 53·2; H, 4·0; N, 12·6. $C_{10}H_9ClN_2O_2$ requires C, 53·5; H, 4·0; N, 12·5%); $\nu_{max.}$ (KCl) 1720 cm^{-1}; $\lambda_{max.}$ (EtOH) 219·5sh, 224, 239·5, 297sh, 306, and 318·5 nm (log ε 4·39, 4·46, 3·86, 3·89, 3·89, and 3·85); the *6-chloro-isomer* (VIh) had m.p. 110—111° [from light petroleum (b.p. 60—80°)] (Found: C, 53·5; H, 4·1; N, 12·2%); $\nu_{max.}$ (KCl) 1685 cm^{-1}; $\lambda_{max.}$ (EtOH) 225·5, 229, 241·5, 247sh, and 309 nm (log ε 4·45, 4·54, 4·26, 4·23, and 3·88); the *4-bromo-derivative* (Vi) had m.p. 68—69° [from light petroleum (b.p. 60—80°)] (Found: C, 44·9; H, 3·4; N, 10·4. $C_{10}H_9BrN_2O_2$ requires C, 4·46; H, 3·4; N, 10·4%); $\nu_{max.}$ (KCl) 1725 cm^{-1}; $\lambda_{max.}$ (EtOH) 219·5sh, 224, 241·5sh, 296·5sh, 309, and 321sh nm (log ε 44·6. 4·47, 3·90, 3·91, 3·93, and 3·87); the *6-bromo-isomer* (VIi) had m.p. 119—120° [from light petroleum (b.p. 60—80°)] (Found: C, 44·8; H, 3·45; N, 10·15%); $\nu_{max.}$ (KCl) 1680 cm^{-1}; $\lambda_{max.}$ (EtOH) 227sh, 231, 242, 248·5sh, and 309 nm (log ε 4·42, 4·47, 4·31, 4·28, and 3·86); the *4-iodo-derivative* (Vj) had m.p. 80—81° [from light petroleum (b.p. 60—80°)] (Found: C, 38·1; H, 3·0; N, 8·8. $C_{10}H_9IN_2O_2$ requires C, 38·0; H, 2·9; N, 8·9%); $\nu_{max.}$ (KCl) 1715 cm^{-1}; $\lambda_{max.}$ (EtOH) 219sh, 221·5, 243sh, 307, and 315sh nm (log ε 4·37, 4·40, 3·92, 3·84, and 3·76); the *6-iodo-isomer* (VIj) had m.p. 120—121° [from light petroleum (b.p. 60—80°)] (Found: C, 38·0; H, 3·0; N, 8·7%); $\nu_{max.}$ (KCl) 1680 cm^{-1}; $\lambda_{max.}$ (EtOH) 217·5sh, 221, 247sh, 251, 310·5, and 322sh nm (log ε 4·22, 4·22, 4·45, 4·47, 3·89, and 3·83); the *4-cyano-derivative* (Vk) had m.p. 174—175° [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 61·3; H, 4·3; N, 19·5. $C_{11}H_9N_3O_2$ requires C, 61·4; H, 4·2; N, 19·5%); $\nu_{max.}$ (KCl) 2210 and 1720 cm^{-1}; $\lambda_{max.}$ (EtOH) 226·5sh, 231·5, 244·5, 249sh, 278sh, 288, 297, and 331 nm (log ε 4·23, 4·32, 4·30, 4·29, 3·49, 3·61, 3·65, and 3·62); the *6-cyano-isomer* (VIk) had m.p. 140—140·5° [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 61·1; H, 4·1; N, 20·0%); $\nu_{max.}$ (KCl) 2230 and 1695 cm^{-1}; $\lambda_{max.}$ (EtOH) 216, 234sh, 240·5, 246·5, 299, and 308sh nm (log ε 4·21, 4·50, 4·59, 4·46, 4·06, and 4·02); diethyl pyrazolo[1,5-*a*]pyridine-3,4-dicarboxylate (Vl) was an oil, $\nu_{max.}$ ($CHCl_3$) 1725 and 1710 cm^{-1}; $\lambda_{max.}$ (EtOH) 224·5, 243, 294, and 318·5sh nm (log ε 4·23, 4·03, 3·76, and 3·63); the *3,6-dicarboxylate* (VIl) had m.p. 88—89° [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 59·75; H, 5·4; N, 10·6. $C_{13}H_{14}N_2O_4$ requires C, 59·5; H, 5·4; N, 10·7%); $\nu_{max.}$ (KCl) 1725, 1695, and 1630 cm^{-1}; $\lambda_{max.}$ (EtOH) 218, 237sh, 242, 248sh, and 301 nm (log ε 4·31, 4·56, 4·59, 4·49, and 4·24); ethyl 4-diethylcarbamoylpyrazolo[1,5-*a*]pyridine-3-carboxylate (Vm) was an oil, $\nu_{max.}$ ($CHCl_3$) 1715, 1670, and 1630 cm^{-1}; $\lambda_{max.}$ (EtOH) 222·5, 239, 248sh, 292sh, and 306 nm (log ε 4·38, 3·98, 3·91, 3·76, and 3·77); the 6-diethylcarbamoyl isomer (VIm) was an oil, $\nu_{max.}$ ($CHCl_3$) 1700 and 1620 cm^{-1}; $\lambda_{max.}$ (EtOH) 222·5, 242·5, 248sh, and 297 nm (log ε 4·32, 4·24, 4·23, and 3·98).

Pyrazolo[1,5-a]*pyridine-3-carboxylic Acids* [(VII) *and* (VIII)].—Solutions of ethyl pyrazolo[1,5-*a*]pyridine-3-carboxylates (0·5 mmol) in methanol (2 ml) containing 3 drops of 10% sodium hydroxide solution were refluxed for 2—3 h. The solvent was evaporated off *in vacuo* and the residue was diluted with water (3 ml) and washed with ether (3 ml). The aqueous layer was acidified with 10% hydrochloric acid. The white precipitate was collected and recrystallised from benzene. The following pyrazolo[1,5-*a*]-pyridine-3-carboxylic acids were prepared from the corresponding oily esters by this procedure; *4-benzyl* (VIIc) (67%), m.p. 186—187° (Found: C, 71·1; H, 4·8; N, 10·9. $C_{15}H_{12}N_2O_2$ requires C, 71·4; H, 4·8; N, 11·1%); *4-diethylcarbamoyl* (VIIm) (33%), m.p. 193—194° (Found: C, 60·0; H, 5·9; N, 16·2. $C_{13}H_{15}N_3O_3$ requires C, 59·8; H, 5·8; N, 16·1%); *6-diethylcarbamoyl* (VIIIm) (30%), m.p. 192—193° (Found: C, 59·8; H, 5·8; N, 15·6%).

Pyrazolo[1,5-a]*pyridine-4-carboxylic Acid* (IX).—This *acid* (IX) was obtained in 61% yield from the oily ester (Vl) (131 mg) by the procedure just described; m.p. 277—278° (from benzene) (Found: C, 58·7; H, 3·95; N, 16·65%; M^+, 148, $C_8H_6NO_2$ requires C, 59·3; H, 3·7; N, 17·3%; *M*, 148); $\nu_{max.}$ (KCl) 2650—2400 and 1700 cm^{-1}. The n.m.r. spectrum was not determined owing to low solubility to various solvents. The structural assignment rests on the basis of spectral data, the consideration of its origin, and the fact that its m.p. differs from that of the known isomeric 3-carboxylic acid (lit.,[4] 223—224°).

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