Synthesis and Reactions of the 1*H*-Imidazo[1,2-*a*]pyrrolo[3,2-*e*]pyridine System

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The reactions of 6-amino-1*H*-pyrrolo[2,3-*b*]pyridines with α-halogenocarbonyl compounds yielded 1*H*-imidazo-[1,2-*a*]pyrrolo[3,2-*e*]pyridines with a variety of alkyl and aryl substitutents. These imidazopyrrolopyridines underwent ready electrophilic substitution at the 3-position; when the 3-position was blocked 8-substitution occurred.

We report here the reaction of 6-amino-1*H*-pyrrolo-[2,3-*b*]pyridines[1] (1) with α-halogenocarbonyl compounds to give 1*H*-imidazo[1,2-*a*]pyrrolo[3,2-*e*]pyridines (2), and a preliminary study of the chemistry of this new system.

The reactions between α-halogenocarbonyl compounds and 6-aminopyrrolopyridines were carried out in a melt (M) or under reflux in aqueous alcohol in the presence of sodium hydrogen carbonate (S). Where both methods M and S were applied the latter gave superior yields. An attempt to prepare 2,3-dimethyl-1*H*-imidazo[1,2-*a*]pyrrolo[3,2-*e*]pyridine (2a) by the reaction of 5-aminoimidazo[1,2-*a*]pyridine (3) with 3-hydroxybutan-2-one yielded no isolable product. Imidazo[1,2-*a*]pyridine (4) and 1*H*-pyrrolo[2,3-*b*]pyridine (5) undergo preferential electrophilic attack at their respective 3-positions.[2,3] It was anticipated therefore that 1*H*-imidazo[1,2-*a*]pyrrolo[2,3-*b*]pyridine (2) would undergo preferential electrophilic attack at the 3- or the 8-position. The unsubstituted ring system was not available for study, since its precursor, 6-amino-1*H*-pyrrolo[1,2-*b*]pyridine could not be synthesised.[1] Treatment of the 2-methylimidazopyrrolopyridine (2b) with Ehrlich's reagent gave a mauve colouration. Similar treatment of the 2,3-dimethyl derivative (2a) gave no colouration. The positive Ehrlich test is, therefore, dependent upon the 3-position being unsubstituted, indicating that the pyrrole ring is more reactive than the imidazole ring in this system. Where both 3- and 8-positions are available for attack, electrophilic mono-substitution occurs exclusively in the 3-position. Where the 3-position is blocked, 8-substitution occurs. Attempts to nitrate (2b) under a variety of conditions gave intractable material.

No *N*-acetyl derivatives of the imidazopyrrolopyridine system were produced, only *C*-substituted compounds, in contrast with the formation of the *N*-acetyl derivative from 1*H*-pyrrolo[2,3-*b*]pyridine and acetic anhydride.[3]

Treatment of the diphenyl derivative (2d) with para-formaldehyde and dimethylamine in butan-1-ol gave 8-(butoxymethyl)-2,3-diphenyl-1*H*-imidazo[1,2-*a*]pyrrolo-[3,2-*e*]pyridine (2n) instead of the expected 8-dimethylaminomethyl compound. Previous applications of the Mannich reaction to reactive heterocycles in butan-1-ol have given normal products.[4] However, treatment of (2a) or (2d) with dimethylamine and formaldehyde in dioxan–acetic acid gave the expected 8-dimethylaminomethyl derivatives (2o and p). These Mannich bases were inert to nucleophilic substitution by cyanide ion. Previous workers[5] reported that 3-dimethylaminomethylimidazo[1,2-*a*]pyridine was similarly inert to nucleophilic substitution, but that its methiodide (3-trimethylammoniomethylimidazo[1,2-*a*]pyridine iodide) reacts with cyanide ion to give the 3-cyanomethyl derivative. Treatment of 8-dimethylaminomethyl-2,3-dimethyl-1*H*-imidazo[1,2-*a*]pyrrolo[3,2-*e*]pyridine (2o) with methyl iodide gave 8-dimethylaminomethyl-2,3,6-trimethyl-1*H*-imidazo[1,2-*a*]pyrrolo[3,2-*e*]pyridinium iodide (6) instead of the expected ammonium derivative (2q). The methiodide (6) was not amenable to nucleophilic substitution by cyanide ion.

EXPERIMENTAL

Full details are available as Supplementary Publication No. SUP 21936 (8 pp.).‡ The methods given below are typical of those used in the preparation of imidazopyrrolopyridines.

Method S.—2,3-*Dimethyl*-1H-*imidazo*[1,2-a]*pyrrolo*[3,2-e]-*pyridine* (2a). This is typical of preparations carried out in solution. A solution of bromoacetaldehyde, prepared by heating its diethyl acetal (3 g, 0.015 mol) and M-hydrochloric acid (1.5 cm³) under reflux for 0.75 h, was added to 6-amino-2,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridine (2 g, 0.012 5 mol) and sodium hydrogen carbonate (1.5 g) in ethanol (10 cm³) and water (10 cm³), and the resulting solution was heated under reflux for 1 h. The mixture was then cooled and the precipitated solid collected and washed with water to give the *imidazopyrrolopyridine* (2a) (2 g, 88%; *cf.* method M 33%), m.p. 320 °C.

Method M.—2,3,7-*Trimethyl*-1H-*imidazo*[1,2-a]*pyrrolo*-[3,2-e]*pyridine* (2c). This is typical of reactions carried out under melt conditions. An intimate mixture of 6-amino-2,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.8 g, 0.005

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‡ For details of Supplementary Publications, see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index Issue.

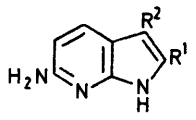
[1] K. C. C. Bancroft, K. Brown, and T. J. Ward, *J.C.S. Perkin I*, 1974, 1852.

[2] J. P. Paolini and R. K. Robins, *J. Org. Chem.*, 1965, **30**, 4085.

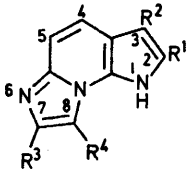
[3] R. E. Willette, *Adv. Heterocyclic Chem.*, 1968, **9**, 27.

[4] M. M. Robison and B. L. Robison, *J. Amer. Chem. Soc.*, 1955, **77**, 457.

[5] L. Almirante, A. Gamba, W. Murmann, A. Mugmaini, P. Rugarli, and N. De Toma, *J. Medicin. Chem.*, 1969 **12**, 122.



(1)



(2)

(1)

a; $R^1 = R^2 = Me$ — S, 88% M, 33% → (2) a; $R^1 = R^2 = Me, R^3 = R^4 = H$

b; $R^1 = Me, R^2 = H$ — S, 52% → (2) b; $R^1 = Me, R^2 = R^3 = R^4 = H$

c; $R^1 = R^2 = Ph$ — M, 25% → (2) c; $R^1 = R^2 = R^3 = Me, R^4 = H$

c; $R^1 = R^2 = Ph$ — S, 76% M, 50% → (2) d; $R^1 = R^2 = Ph, R^3 = R^4 = H$

c; $R^1 = R^2 = Ph$ — M, 18% → (2) e; $R^1 = R^2 = Ph, R^3 = Me, R^4 = H$

d; $R^1 = R^2 = Et$ — S, 10% → (2) f; $R^1 = R^2 = Et, R^3 = R^4 = H$

e; $R^1 = R^2 = C_6H_4 \cdot OMe\text{-}p$ — S, 55% → (2) g; $R^1 = R^2 = C_6H_4 \cdot OMe\text{-}p, R^3 = H$

(2)

Br_2 - $CHCl_3$ (20%) → j; $R^1 = R^2 = Me, R^3 = H, R^4 = Br$

Br_2 - $CHCl_3$ (48%) → h; $R^1 = Me, R^2 = Br, R^3 = R^4 = H$

Br_2 - $CHCl_3$ (60%) → k; $R^1 = R^2 = Ph, R^3 = H, R^4 = Br$

Ac_2O (57%) → l; $R^1 = R^2 = Me, R^3 = H, R^4 = Ac$

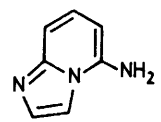
Ac_2O (35%) → i; $R^1 = Me, R^2 = Ac, R^3 = R^4 = H$

Ac_2O (50%) → m; $R^1 = R^2 = Ph, R^3 = H, R^4 = Ac$

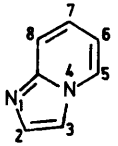
$NHMe_2$, HCl + paraformaldehyde, Bu^nOH (26%) → n; $R^1 = R^2 = Ph, R^3 = H, R^4 = Bu^nO \cdot CH_2$

aq. $NHMe_2$ + aq. HCHO, dioxan, AcOH (69%) → p; $R^1 = R^2 = Ph, R^3 = H, R^4 = Me_2N \cdot CH_2$

aq. $NHMe_2$ + aq. HCHO, dioxan, AcOH (36%) → o; $R^1 = R^2 = Me, R^3 = H, R^4 = Me_2N \cdot CH_2$



(3)



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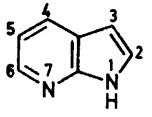

(5)

(6)

o; $R^1 = R^2 = Me, R^3 = H, R^4 = Me_2N \cdot CH_2$ — MeI, dioxan (71%) → (6)

[no (2q) produced; $R^1 = R^2 = Me, R^3 = H, R^4 = Me_3N^+ \cdot CH_2$]

l; $R^1 = R^2 = Me, R^3 = H, R^4 = Ac$ — $NaBH_4$ (100%) → (2r) $R^1 = R^2 = Me, R^3 = H, R^4 = MeCH(OH)$

mol) and 1-chloropropan-2-one (0.5 g, 0.005 4 mol) was stirred at 120 °C for 10 min, then at 180—190 °C for 20 min. The melt was cooled, pulverised, and dissolved in hot ethanol; the solution was basified with sodium hydroxide solution, and poured into water. The precipitate was collected and crystallised from aqueous alcohol to give the *imidazopyrrolopyridine* (2c) (0.25 g, 25%), m.p. >320 °C.

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