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THE PREPARATION OF NOVEL 4,4'- AND N,N'-LINKED PIPECOLIC ACID DERIVATIVES

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Abstract—Routes used for the preparation of the novel 4,4'- and N,N'-linked pipecolic acids (**1a,b** and **2b,c**) are described and discussed together with the characterisation of the products and intermediates.

As part of an investigation into the stereochemical requirements for chelation a number of novel 4,4'- and N,N'-linked pipecolic acid derivatives (Fig. 1) were required as ligands. We describe herein their preparation and characterisation.

Preparation. The series of reactions used to prepare the linked pipecolic acids is summarised in Schemes 1 and 2. Several of the reactions involved modification of reported methods[1] and a scheme similar to Scheme 1 was recently used by us to prepare a number of *cis* and *trans*-4-substituted pipecolic acids and esters.[2]

Coupling of pyridine nuclei can be achieved by reaction of the potassium salt of 4-picoline with the appropriate dihaloalkane. This method worked well[3] for the reaction with 1,3-dibromopropane but the corresponding reaction with 1,2-dibromoethane gave an unacceptably low yield of 1,4 - di - (4 - pyridyl)butane (2). For this intermediate cathodic coupling[4] of 4-vinylpyridine proved to be the method of choice, a 46% yield of the hydrodimer being obtained.

The steps subsequent to the linking of the pyridine nuclei were straightforward and typical experiments and yields are described in the experimental section and in Table 1. Following hydrolysis of the nitriles the final isolation of the free amino acids was difficult because they are very hygroscopic. Samples were obtained by extraction into benzene or chloroform from aqueous solution at pH 3.2 but it was found to be generally more convenient to handle the compounds as the corresponding ethyl or methyl esters or as the acid hydrochlorides. Titration of the acid hydrochlorides was used to estimate the purity of samples.

Characterisation and stereochemistry. The intermediates given in Schemes 1 and 2 were characterised by the usual combination of spectroscopic methods and the relevant information is summarised in Table 1. Confirmation of the desired substitution pattern comes from consideration of the spectra of the dicyanodipyridyl compounds (**6** and **7**, Table 1). Accurate mass measurements on the molecular ions confirms the molecular formulae. The UV spectra are similar to those of monocyanopyridines.[5] The NMR spectra are essentially simple, as expected for symmetrically substituted dipyridyls. In particular the aromatic proton signals show that the desired 2,2'-substitution has occurred because the signal at lowest field (e.g. for **6**, $\delta = 8.62$ (d, $J = 5$ Hz, 2H)) shows a large *ortho* coupling and must therefore be attributed to the remaining 1 and 1' protons.

Physical properties characteristic of the dimerised pipecolic acid dihydrochlorides are given in Table 2 together with the results of the titrimetric determination of purity. The stereochemistry of these products (*cis–cis*) follows from the conditions used for the final hydrogenation step, i.e. Adams' catalyst in aqueous hydrochloric acid (2N) under hydrogen (1 atm) at 20°. For hydrogenation of 4 - alkylpyridine - 2 - carboxylic acids these conditions gave[2] *cis*-products exclusively. Furthermore the *cis–cis* configuration (all equatorial substitution) is the most stable of the stereoisomeric possibilities.

EXPERIMENTAL

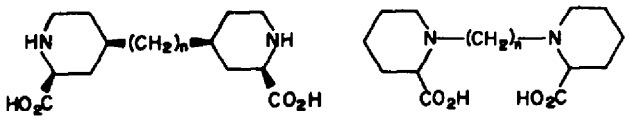
The reaction outlined in Schemes 1 and 2 are typified by the following examples. In each case yields and physical data are given in Table 1.

1,4 - *Di* - (4 - *pyridyl)butane* (2). Tetraethylammonium *p*-toluenesulphonate (40 g, 0.13 mol) was dissolved in N,N'-dimethylformamide (40 ml) and water (2 ml). 4-Vinylpyridine (40 g, 0.38 mol) was added and the mixture electrolysed, under an atmosphere of N_2, at a mercury pool cathode in a conventional undivided cell equipped with a platinum anode and cooled in an ice bath. During 5 hr 0.98 F mol^{-1} were passed at constant current density (0.16 A · cm^{-2}). The product separated from the electrolyte as reaction proceeded and after isolation was crystallised from benzene–petroleum (b.p. 60–80°).

1,5 - *Di* - (4 - *pyridyl)pentane* (3). A soln of potassamide was prepared in liquid ammonia (2 l.) in the usual way starting from K metal (20 g, 0.51 mol). 4-methylpyridine (47 g, 0.51 mol) was added followed after 15 min by 1,3-dibromopropane (51 g, 0.25 mol). The mixture was stirred for 1 hr and ammonium chloride (16 g, 0.3 mol) added. The ammonia was allowed to evaporate, water (150 ml) added, and the product extracted into ether soln which was washed (H_2O) and dried (K_2CO_3). The isolated product was finally crystallised from benzene–petroleum (b.p. 40–60°).

1,4 - *Di(4' - pyridyl - 1' - oxide)butane* (4). To (1,4 - Di - pyridyl)butane (53 g, 0.25 mol) was added peracetic acid soln (120 ml of 40% w/v, 0.63 mol) at a rate which kept the temp. below 70°. The temp. was then maintained at 80° for several min. The soln cooled to 0° and basified (6N NaOH) to a pH 10–11. The Na salt which precipitated during 6 hr was filtered off and washed (H_2O, 3 × 100 ml). After concentration the filtrate was subjected to freeze drying and the solid obtained was placed in a Soxhlet thimble and leached with chloroform (1 l.). The chloroform extract was dried (K_2CO_3) and the solvent evaporated under reduced pressure.

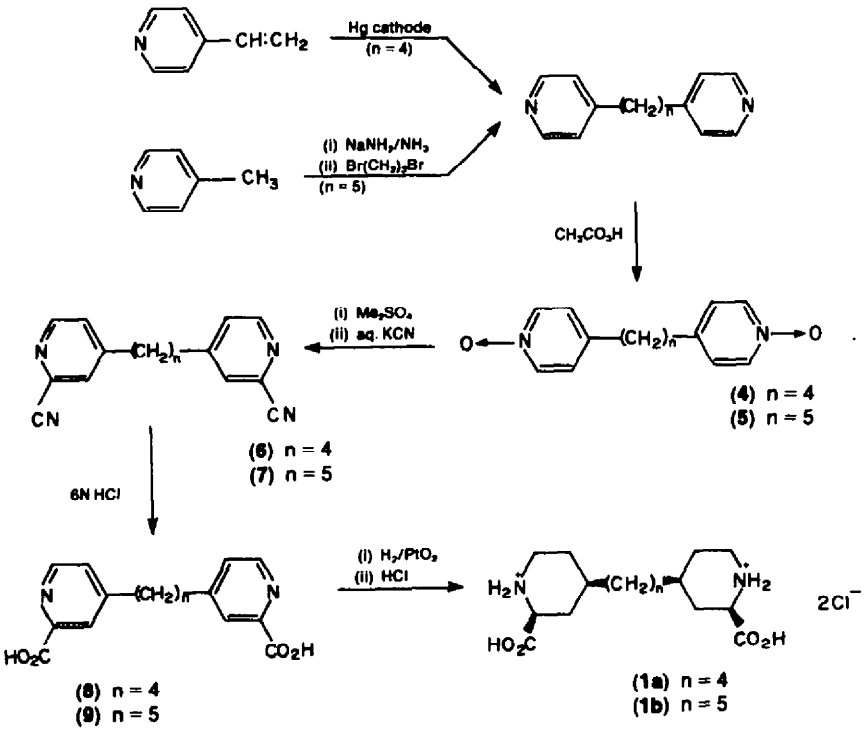
1,4 - *Di(4',2' - cyanopyridyl)butane* (6). Dimethyl sulphate (31.1 g, 0.25 mol) was added to 4 (30 g, 0.12 mol) at 0°. The mixture was slowly warmed and maintained at 80° for 1 hr. The mixture was cooled to −5° and to the crude product NaCN aq.



(1a) n = 4
(1b) n = 5

(2a) n = 2
(2b) n = 3

Fig. 1. 4,4'- and N,N'-Linked pipecolic acids.



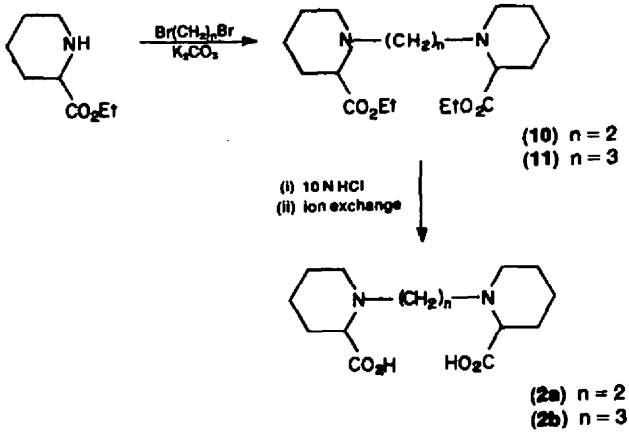
(4) n = 4
(5) n = 5

(6) n = 4
(7) n = 5

(8) n = 4
(9) n = 5

(1a) n = 4
(1b) n = 5

Scheme 1. 4,4'-Linked pipecolic acids.



(10) n = 2
(11) n = 3

(2a) n = 2
(2b) n = 3

Scheme 2. N,N'-Linked pipecolic acids.

Table 1. Characterisation of intermediates (see Schemes 1 and 2)

Compound No.	Yield (%)[a]	m.p./b.p. (°C)	NMR	MS	IR (cm^{-1})	UV ($\lambda_{max(nm),EtOH}$)
2	46	118–19[b]			1601	256 ($\epsilon = 4.0 \times 10^3$)
3	47	55–57[c]			1602	256 ($\epsilon = 4.3 \times 10^3$)
4	54	283–84	[d]8.68 (d, J = 7 Hz, 4H), 7.86 (d, J = 7 Hz, 4H), 3.3–2.7 (m, 4H), 2.2–1.6 (m, 4H).	No molecular ion observed	ν_{NO}, 1260	267 ($\epsilon = 3.3 \times 10^4$)
5	70	231–33	[d]8.12 (d, J = 6.5 Hz, 4H), 7.08 (d, J = 6.5 Hz, 4H), 2.8–2.4 (m, 4H), 1.9–1.1 (m, 6H).	No molecular ion observed	ν_{NO}, 1260	267 ($\epsilon = 3.1 \times 10^4$)
6	—	131–33	[d]8.62 (d, J = 5.0 Hz, 2H), 7.62–7.47 (q, 2H), 7.35 (d, J = 5.0 Hz, 2H), 3.0–2.4 (m, 4H), 2.1–1.4 (m, 6H).	M^+, m/e = 262.1218 ($C_{16}H_{14}N_4$ requires 262.1210)	ν_{CN}, 2225	265 ($\epsilon = 6.4 \times 10^3$)
7	—	102–4	[d]8.58 (d, J = 5.0 Hz, 2H), 7.62–7.47 (q, 2H), 7.36 (d, J = 5.0 Hz, 2H), 2.9–2.4 (m, 4H), 2.1–1.0 (m, 6H).	M^+, m/e = 276.1369 ($C_{17}H_{16}N_4$ requires 276.1375)	ν_{CN}, 2230	265 ($\epsilon = 6.0 \times 10^3$)
8	78	225–27	[f]9.22 (d, J = 6.0 Hz, 2H), 8.85 (s, 2H), 8.58 (d, J = 6.0 Hz, 2H), 3.1–2.6 (m, 4H), 1.9–1.4 (m, 4H).	M^+, m/e = 300.1101 ($C_{16}H_{16}N_2O_4$ requires 300.1110)	ν_{CO}, 1715	264 ($\epsilon = 7.2 \times 10^3$)
9	83	234–36	[f]8.94 (d, J = 6.0 Hz, 2H), 8.52 (d, J = 1.5 Hz, 2H), 8.22 (d, J = 6.0 Hz, 2H, 3.4–2.7 (m, 4H), 2.2–1.1 (m, 6H).	M^+, m/e = 314.1267 ($C_{17}H_{18}N_2O_4$ requires 314.1267)	ν_{CO}, 1718	264 ($\epsilon = 6.6 \times 10^3$)
10	50	165–8/0.6 mm	[g]4.12 (q, J = 7.0 Hz, 4H), 3.40–1.30 (broad m, 18H), 2.51 (s, 4H), 1,27 (t, J = 7.0 Hz, 6H).	M^+, m/e = 340.237 ($C_{18}H_{32}N_2O_4$ requires 340.236)	ν_{CO}, 1733	—
11	74	171–3/2 mm	[g]4.11 (q, J = 7.0 Hz, 4H), 3.35–1.30 (broad m, 24H), 1.26 (t, J = 7 Hz, 6H).	M^+, m/e = 354.2513 ($C_{19}H_{34}N_2O_4$ requires 354.2519)	ν_{CO}, 1733	—

[a]From preceding step; [b]Lit. 120° (Ref. 4); [c]Lit. 58° (Ref. 3); [d](CF_3CO_2D), at 60 MHz; [e]$\delta(CDCl_3)$; [f]$\delta(D_2O)$ using hydrochloride; [g]$\delta(CCl_4)$.

Table 2. Characterisation of 4,4'- and N,N'-linked pipecolic acids[a]

Compound No.	m.p. (°C)	IR (cm^{-1})	Purity by titration (%)[b]
1a	275–78	1743, 1640, 1540	96
1b	240–45	1743, 1600, 1560	96
2a	239–42	1730	98
2b	267–68	1730, 1520	95

[a]As dihydrochlorides; [b]Using the potentiometric method described in Ref. 2. Judged accurate to ±1%.

(21 g, 0.43 mol, in 150 ml H_2O) was added. The soln was maintained at −10° for 48 hr after which the crude product separated as a thick oil. The oil was extracted into $CHCl_3$ (4 × 50 ml) which was washed (H_2O, 3 × 25 ml), dried (K_2CO_3) and evaporated. The residual red-brown liquid was chromatographed (Alumina, Merck Grade I, eluant 30% $CHCl_3$–petroleum (b.p. 60–80°)) to give a low (4%) yield of the desired product.

1,4 - *Di(4' - picolinic acid)butane* (8). Compound 6, (5.2 g, 0.02 mol), was heated under reflux with HCl aq. (100 ml, 6N) for 5 hr. The volume was reduced to 10 ml by evaporation at reduced pressure, water (50 ml) was added, and the volume again reduced to 10 ml. The pH was adjusted to 3.2 using 6N NaOH. The soln was freeze dried and the resulting solid leached with $CHCl_3$ in a Soxhlet apparatus. The acid crystallised from the $CHCl_3$ extract.

cis–cis - 1,4 - *Di(4' - piperidine - 2' - carboxylic acid)butane dihydrochloride* 1a. Adam's catalyst (0.03 g) was suspended in 2N HCl (30 ml) and prehydrogenated at an atm. pres. of H_2 in a conventional all-glass apparatus. The acid 8 (3 g, 0.01 mol) was added and the rate of uptake of H_2 recorded. When the theoretical uptake was achieved the soln was filtered and evaporated to dryness.

1,3 - *Di(2' - ethoxycarbonylpiperidino)propane* (11). Ethyl pipecolate (8.8 g, 0.05 mol) was added to a stirred soln of 1,3-dibromopropane (5.1 g, 0.025 mol) in dry benzene (40 ml) in the presence of anhyd K_2CO_3 (3.5 g, 0.025 mol). The mixture was heated under reflux for 15 hr. NaBr was filtered off and benzene removed from the filtrate. The residual product was distilled under reduced pressure.

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