280. *Some Dipyridylalkanes.*

By D. E. Ames and J. L. Archibald.

Various dipyridylalkanes and their *N*-oxides were prepared for pharmacological testing. 4-Picoline *N*-oxide can be *C*-alkylated in poor yield in the presence of sodamide and liquid ammonia. Some methoxy- and benzyloxy-picolines can be alkylated similarly.

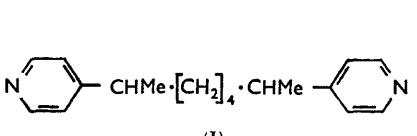
Jampolsky and his collaborators [1] have described the preparation of a series of αω-di-2′-pyridylalkanes and the 4′-pyridyl isomers; some derived quaternary salts show curare-like properties,[2] and Phillips [3] has prepared some diquaternary salts derived from 3-4′-aminobutylpiperidine that had hypotensive action. These observations led us to prepare some substituted dipyridylalkanes and related compounds for pharmacological examination.

Symmetrical αω-dipyridylalkanes were readily obtained by condensing 2-, 3-, or 4-picoline with αω-dihalogenoalkanes in the presence of sodamide and liquid ammonia.[1] 4-Ethylpyridine and 4-methylquinoline were also alkylated with tetramethylene dibromide, to obtain the corresponding diamines (I) and (II). Oxidation of the dipyridylalkanes with peracetic or perbenzoic acid gave the crystalline *NN*′-dioxides. As an alternative synthesis of such dioxides, 4-picoline *N*-oxide was condensed with tetramethylene dibromide in presence of sodamide in liquid ammonia, the *NN*′-dioxide of the diamine (III) being isolated in small yield; as far as we are aware the *C*-alkylation of picoline *N*-oxides has not been reported previously. An attempt to prepare the *N*-mono-oxide from 1,6-di-2′-pyridylhexane failed but the crystalline 1,6-di-4′-pyridylhexane (III) did give a small yield of the mono-oxide.

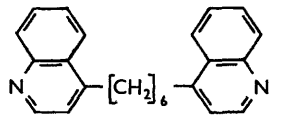
[1] Jampolsky, Baum, Kaiser, Sternbach, and Goldberg, *J. Amer. Chem. Soc.*, 1952, **74**, 5222.
[2] Randall, *Ann. N.Y. Acad. Sci.*, 1951, **54**, 460; *J. Pharmacol. Expt. Therap.*, 1952, **105**, 7; cf. Shapiro *et al.*, *J. Amer. Chem. Soc.*, 1959, **81**, 5140, 5146.
[3] Phillips, *J. Amer. Chem. Soc.*, 1954, **76**, 2211.

The methiodides of 1,6-dipyridylhexane (2′-, 3′-, and 4′-pyridyl groups) were catalytically hydrogenated to the *N*-methylpiperidines, which were converted into the *NN*′-dioxides.

The synthesis of unsymmetrical dipyridylalkanes was next examined. 4-Chlorobutyl acetate could not be condensed with 2-sodiopicoline (even when a large excess of the latter was used), but 4-chlorobutyl tetrahydropyranyl ether did react to give, after acid



(I)



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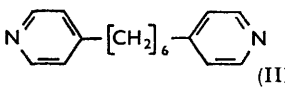

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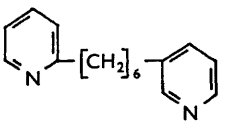


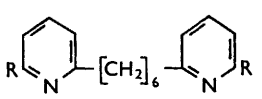
(IV)

hydrolysis, 2-5′-hydroxypentylpyridine. Treatment with hydrobromic acid gave the bromo-amine which, without isolation, was condensed with 3-sodiopicoline, affording 1-2′-pyridyl-6-3′-pyridylhexane (IV). This, and the 2-4′- and 3-4′-isomer, which were prepared similarly but not isolated, were converted into the crystalline *NN*′-dioxides.

Attention was next turned to the preparation of dipyridylalkanes with substituent groups in the rings. Pyridine *N*-oxide and picoline *N*-oxides are readily nitrated [4] but we were unable to nitrate 1,6-di-2′-pyridylhexane *NN*′-dioxide or its 3′-pyridyl isomer; some side-chain oxidation apparently occurred as only about half of the starting material could be recovered. Similarly 2-heptylpyridine *N*-oxide could not be nitrated (cf. the failure to nitrate 2-heptylquinoline *N*-oxide reported by Ames, Franklin, and Grey [5]).

1,6-Di-2′-pyridylhexane *NN*′-dioxide was not sulphonated under the conditions used for 2-picoline *N*′-oxide.[6] 1,6-Di-2′-pyridylhexane underwent some reaction with potassamide, in a Chichibabin reaction, a very small yield of 1,6-di-(6-acetamido-2-pyridyl)-hexane (V; R = NHAc) being isolated after acetylation.

The alternative approach, involving condensation of substituted picolines with a polymethylene dihalide, was next examined. In a model experiment, the sodio-derivative of 2,6-dibenzyloxy-4-methylpyridine was alkylated in liquid ammonia with hexyl bromide. The product gave 4-heptyl-2,6-dihydroxypyridine on catalytic hydrogenation. Similarly with tetramethylene dibromide the crystalline tetrabenzyloxy-compound (VI; R = CH_2Ph) was obtained, debenzylation giving 1,6-di-(2,6-dihydroxy-4-pyridyl)hexane (VI; R = H).



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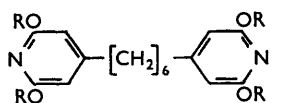

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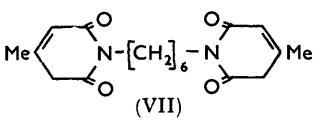

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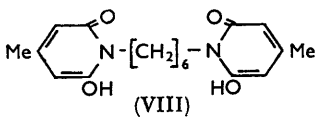

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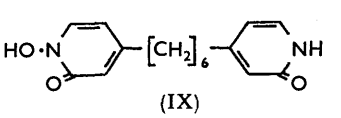

(IX)

2-Benzyloxy-6- and -4-methylpyridine were condensed with tetramethylene dibromide; debenzylation of the crude products gave 1,6-di-(6-hydroxy-2-pyridyl)- and 1,6-di-(2-hydroxy-4-pyridyl)-hexane, respectively. Attempts to alkylate 3-benzyloxy-6- and 2-benzyloxy-5-methylpyridine with tetramethylene dibromide were, however, unsuccessful.

[4] Ochiai, *J. Org. Chem.*, 1953, **18**, 534.
[5] Ames, Franklin, and Grey, *J.*, 1956, 3079.
[6] McElvain and Goese, *J. Amer. Chem. Soc.*, 1943, **65**, 2233.

A monohydroxy-compound, 1-2′-pyridyl-6-(6-hydroxy-2-pyridyl)hexane, was also prepared by condensing the sodio-derivative of 2-benzyloxy-6-methylpyridine with 2-5′-bromopentylpyridine and debenzylating the product. 2-Methoxy-6-methylpyridine was also readily alkylated with tetramethylene dibromide; this result contrasts with the apparent failure of metallation of 2-methoxy-6-methylpyridine, when treated with phenyl-lithium followed by carbon dioxide, reported by Clemo, Fox, and Raper.[7]

Finally some alkylenedipyridones were prepared. Oxidation of hexamethylene dipyridinium dibromide with alkaline potassium ferricyanide gave 1,1′-hexamethylenedi-2-pyridone. β-Methylglutaconic anhydride with hexamethylenediamine gave the imide (VII or its tautomer VIII).

When 1,6-di-(2-methoxy-4-pyridyl)hexane was heated with methyl iodide, the corresponding pyridone, 4,4′-hexamethylenedi-2-pyridone, was formed. In an attempt to prepare the *N*-hydroxypyridone, 2-benzyloxy-4-methylpyridine was alkylated with tetramethylene dibromide and the product oxidised with perbenzoic acid, but, after catalytic debenzylation, only the mono-oxidation product (IX or a tautomer) could be isolated.

Experimental

Dipyridylalkanes.—General procedure. The alkylpyridine (1·0 mole) was added gradually to a stirred, freshly prepared suspension of sodamide (1·0 mole) in liquid ammonia (*ca.* 500 c.c.). After the mixture had been stirred for 1 hr. (3 hr. for 3-picolines), the dibromoalkane (0·33 mole) was added gradually and the mixture then allowed to evaporate. Ethanol (50 c.c.) and water (400 c.c.) were added successively, and the *product* was isolated with ether and distilled (see Table 1).

Dipyridylalkane Dimethiodides.—1,6-Di-2′-pyridylhexane (10·9 g.), ethanol (150 c.c.), and methyl iodide (30 c.c.) were refluxed for 5 hr. The *dimethiodide*, which separated on cooling, formed needles (19·8 g.), m. p. 218—219°, from water (Found: C, 41·4; H, 5·0; N, 5·2; I, 48·5. $C_{18}H_{26}N_2I_2$ requires C, 41·2; H, 5·0; N, 5·3; I, 48·4%). 1,6-*Di*-3′-*pyridylhexane dimethiodide*, prepared similarly, formed needles, m. p. 243—245°, from ethanol (Found: C, 41·9; H, 5·0; N, 5·2; I, 46·9%). 1,6-*Di*-4′-*pyridylhexane dimethiodide* was prepared by refluxing the diamine (10·0 g.) with methyl iodide (25 c.c.) and 2-methoxyethanol (25 c.c.) for 6 hr; it formed orange needles, m. p. 173—175°, from ethanol (Found: C, 41·2; H, 5·4; N, 4·8; I, 48·2%).

Dipiperidylalkanes.—The dimethiodide (15 g.) and triethylamine (10 g.) in ethanol (200 c.c.) were hydrogenated with Raney nickel W7 catalyst [8] until absorption ceased. After evaporation of the filtered solution and addition of sodium hydroxide solution, the diamine was isolated with ethyl acetate and distilled. 1,6-*Di*-(1-*methyl*-2-*piperidyl*)*hexane* had b. p. 146—148°/0·1 mm., n_D^{22} 1·4875 (Found: C, 77·3; H, 12·7; N, 10·4. $C_{18}H_{26}N_2$ requires C, 77·1; H, 12·9; N, 10·0%). 1,6-*Di*-(1-*methyl*-3-*piperidyl*)*hexane* had b. p. 132—134°/0·2 mm., n_D^{20} 1·4755 (Found: C, 77·0; H, 12·5; N, 10·7%). 1,6-*Di*-(1-*methyl*-4-*piperidyl*)*hexane* gave crystals of a hydrate from aqueous methanol; after drying over phosphorus pentoxide it had m. p. 45—46° (Found: C, 76·9; H, 13·0; N, 10·0%).

Table 1.

Dipyridylalkanes.

			Found (%)				Required (%)		
Amine	B. p./mm.	M. p.	C	H	N	Formula	C	H	N
1,6-Di-3′-pyridylhexane	165—166°/1·5	—[b]	80·0	8·4	11·5	$C_{16}H_{20}N_2$	80·0	8·4	11·7
1,6-Di-4′-pyridylhexane ...	176—178°/1·0	33—34°	79·8	8·3	11·7	,,	,,	,,	,,
1,7-Di-4′-pyridylheptane...	170—175°/0·1	28—30	80·1	9·0	10·8	$C_{17}H_{22}N_2$	80·3	8·7	11·0
1,8-Di-4′-pyridyloctane ...	185—190°/0·5	36—37	80·1	9·0	10·2	$C_{18}H_{24}N_2$	80·6	9·0	10·4
2,7-Di-4′-pyridyloctane ...	167—170°/0·1	—[c]	80·9	9·6	10·2	,,	,,	,,	,,
1,6-Di-4′-quinolylhexane[d]	—	97—98	84·4	7·2	8·4	$C_{24}H_{24}N_2$	84·6	7·1	8·2

[a] *Picrate*, needles, m. p. 202—204°, from 2-methoxyethanol (Found: C, 48·2; H, 4·0; N, 16·2. $C_{28}H_{26}N_8O_{14}$ requires C, 48·1; H, 3·8; N, 16·0%). [b] n_D^{20} 1·5421. [c] n_D^{20} 1·5349. [d] Prisms from methanol.

[7] Clemo, Fox, and Raper, *J.*, 1954, 2693.

[8] Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 698.

Pyridine was quaternised with 1,6-dibromohexane and the salt, m. p. 239—240°, was hydrogenated similarly. 1,6-Dipiperidinohexane had b. p. 130—134°/1·5 mm. von Braun [9] gave b. p. 198°/16 mm.

Dipiperidinoalkane NN′-*Dioxides*.—1,6-Dipiperidinohexane (6·2 g.) in chloroform (20 c.c.) was cooled below 0° while 5M-peracetic acid (11 c.c.) in chloroform was added gradually. The solution was kept at room temperature overnight and shaken with a slurry of potassium carbonate (30 g.) in water (20 c.c.), the separated aqueous layer being washed repeatedly with chloroform. Evaporation of the dried (K_2CO_3) solution and recrystallisation from benzene–chloroform gave 1,6-*dipiperidinohexane* NN′-*dioxide* (3·0 g.) as a very deliquescent solid, m. p. 152—154° (Found: C, 65·3; H, 10·7; N, 9·6. $C_{16}H_{32}N_2O_2,\frac{1}{2}H_2O$ requires C, 65·5; H, 11·3; N, 9·6%). The following compounds were prepared similarly: 1,6-*di*-(1-*methyl*-2-*piperidyl*)-*hexane* NN′-*dioxide*, very deliquescent, m. p. 157—159°, from chloroform–light petroleum (b. p. 40—60°) (Found: C, 67·6; H, 11·2; N, 8·8. $C_{18}H_{36}N_2O_2,\frac{1}{2}H_2O$ requires C, 67·3; H, 11·6; N, 8·7%); 1,6-*di*-(1-*methyl*-3-*piperidyl*)*hexane* NN′-*dioxide*, m. p. 171—176° (Found: C, 65·4; H, 11·0; N, 8·7. $C_{18}H_{36}N_2O_2,H_2O$ requires C, 65·4; H, 11·6; N, 8·5%); and 1,6-*di*-(1-*methyl*-4-*piperidyl*)*hexane* NN′-*dioxide*, needles, m. p. 250° (decomp.), from chloroform (Found: C, 68·8; H, 11·5; N, 8·9. $C_{18}H_{36}N_2O_2$ requires C, 69·2; H, 11·6; N, 9·0%).

2-4′-*Chlorobutoxytetrahydropyran*.—Dihydropyran (27·9 g.) was added to 4-chlorobutanol (30·9 g.) containing 2 drops of concentrated hydrochloric acid. After the initial exothermic reaction had been moderated by cooling, the mixture was left for 3 hr. Addition of sodium hydroxide (2 g.) and distillation then gave the *ether* (50·5 g.), b. p. 118—120°/15 mm., n_D^{21} 1·4601 (Found: C, 56·0; H, 9·0; Cl, 17·9. $C_9H_{17}ClO_2$ requires C, 56·1; H, 8·9; Cl, 18·4%).

2-5′-*Hydroxypentylpyridine*.—2-Sodiopicoline (from sodium, 9 g., in liquid ammonia, *ca.* 250 c.c.) was alkylated with the chloro-ether (47·8 g.) as in previous cases. When the ammonia had evaporated, ethanol (20 c.c.) and then 2N-hydrochloric acid (100 c.c.) were added and the mixture was stirred for 1 hr. After basification with potassium carbonate (50 g.) in water (100 c.c.), the product was isolated with chloroform and distilled. 2-5′-*Hydroxypentylpyridine* (30·6 g.) had b. p. 127—130°/0·1 mm., n_D^{22} 1·5010 (Found: C, 72·7; H, 9·0; N, 9·0. $C_{10}H_{15}NO$ requires C, 72·7; H, 9·2; N, 8·5%). 4-5′-*Hydroxypentylpyridine*, prepared similarly, had b. p. 136—140°/0·2 mm., n_D^{20} 1·5120, f. p. 21—23° (Found: C, 72·6; H, 9·1; N, 8·1%).

1-2′-*Pyridyl*-6-3′-*pyridylhexane*.—The alcohol (10 g.) was refluxed for 5 hr. with 48% hydrobromic acid (100 c.c.), and the solution was evaporated to dryness *in vacuo*. After addition of potassium carbonate (30 g.) in water (20 c.c.), the mixture was extracted with ether, and the extracts were dried (K_2CO_3). The ethereal solution was immediately added to 3-sodiopicoline (0·18 mol.) in liquid ammonia (*ca.* 400 c.c.); the mixture was stirred under reflux for 2 hr. and left to evaporate. Addition of sodium carbonate solution, isolation with ethyl acetate, and fractional distillation gave the diamine (6·5 g.), b. p. 153—157°/0·2 mm., n_D^{20} 1·5402 (Found: C, 79·7; H, 8·6; N, 11·4. $C_{16}H_{20}N_2$ requires C, 80·0; H, 8·3; N, 11·7%).

Dipyridylalkane NN′-*Dioxides*.—The diamine (in chloroform) was treated with perbenzoic or peracetic acid (2·5 mol.) in chloroform, the mixture being cooled below 10° during the addition. After being kept at room temperature overnight, the mixture was washed with concentrated potassium carbonate solution, dried (K_2CO_3), and evaporated *in vacuo*, the residue being crystallised (see Table 2).

Alkylation of 4-*Picoline* N-*Oxide*.—4-Picoline *N*-oxide (12 g.) was added in one portion to sodamide (from sodium, 2·5 g.) in liquid ammonia (350 c.c.). The solution, which rapidly became reddish-violet, was refluxed for 2 hr.; tetramethylene dibromide (10·8 g.) was added gradually and the mixture was allowed to evaporate. After addition of potassium carbonate (50 g.) in water (100 c.c.), the mixture was extracted repeatedly with chloroform. Evaporation of the dried (K_2CO_3) solution gave a gum which was extracted with boiling benzene–light petroleum (b. p. 60—80°) (6 × 100 c.c.). The combined extracts were evaporated to small bulk and the resulting solid recrystallised from benzene (charcoal), to give 1,6-di-4′-pyridylhexane *NN*′-dioxide, m. p. and mixed m. p. 237—240°.

1,6-*Di*-4′-*pyridylhexane* N-*Mono-oxide*.—The diamine (5·0 g.) in chloroform (15 c.c.) was treated at <0° gradually with 6M-peracetic acid in chloroform (3·6 c.c.). After 5 hr. at room temperature, the solution was washed with potassium carbonate solution (5 g.) in water (10 c.c.), dried (K_2CO_3), and evaporated; fractional crystallisation from benzene–light petroleum (b. p.

[9] von Braun, *Ber.*, 1910, **43**, 2862.

60—80°) gave the *mono*-N-*oxide* (1·1 g.), needles, m. p. 93—94° (Found: C, 74·8; H, 7·8; N, 11·3. $C_{16}H_{20}N_2O$ requires C, 75·0; H, 7·9; N, 10·9%).

1,6-*Di*-(6-*acetamido*-2-*pyridyl*)*hexane*.—Potassamide was prepared from potassium (4·0 g.) in liquid ammonia, and the ammonia was allowed to evaporate. Dimethylaniline (12 g.) and 1,6-di-2′-pyridylhexane (12 g.) were added and the mixture was heated at 170° for 5 hr. Methanol and N-sodium hydroxide were added to the cooled mass, which was then extracted repeatedly with chloroform. The tarry residue obtained by evaporation was refluxed for 1 hr.

TABLE 2.

Dipyridylalkane *NN*′-dioxides.

		Found (%)				Required (%)		
Dioxide of	M. p.	C	H	N	Formula	C	H	N
1,6-Di-2′-pyridylhexane [a]	140—141°	70·4	7·2	10·2	$C_{16}H_{20}N_2O_2$	70·6	7·4	10·3
1,6-Di-3′-pyridylhexane [b]	186—188	70·8	7·2	10·2	,,	,,	,,	,,
1,2-Di-4′-pyridylethane [c]	236—238 *	66·4	5·6	12·8	$C_{12}H_{12}N_2O_2$	66·7	5·6	13·0
1,5-Di-4′-pyridylpentane [a]	218—220 *	69·4	7·0	10·5	$C_{15}H_{18}N_2O_2$	69·7	7·0	10·9
1,6-Di-4′-pyridylhexane [b]	241—244	70·0	7·4	10·3	,,	,,	,,	,,
1,7-Di-4′-pyridylheptane [d]	152—154	71·0	8·0	9·6	$C_{17}H_{22}N_2O_2$	71·3	7·7	9·8
1,8-Di-4′-pyridyloctane [d]	155—157	72·4	8·3	9·4	$C_{18}H_{24}N_2O_2$	72·0	8·1	9·3
2,7-Di-4′-pyridyloctane [d]	130—132	71·6	8·1	9·6	,,	,,	,,	,,
1-2′-Pyridyl-6-3′-pyridylhexane [d]	108—110	70·0	7·3	10·2	,,	,,	,,	,,
1-2′-Pyridyl-6-4′-pyridylhexane [b]	135—137	68·6	7·7	9·7	$C_{16}H_{20}N_2O_2,\frac{1}{2}H_2O$	68·3	7·5	10·0
1-3′-Pyridyl-6-4′-pyridylhexane [b]	142—144	70·1	7·6	10·1	,,	,,	,,	,,
1,6-Di-4′-quinolylhexane [c]	184—186	76·9	6·5	7·8	$C_{24}H_{24}N_2O_2$	77·4	6·5	7·5

[a] From chloroform–light petroleum (b. p. 60—80°). [b] From benzene. [c] From ethyl methyl ketone–methanol. [d] From ethyl methyl ketone. * Decomp.

with acetic acid (5 c.c.) and acetic anhydride (5 c.c.). After evaporation, the residue was dissolved in benzene containing a little acetic acid; the solution was allowed to evaporate slowly and eventually deposited a sticky solid. This was extracted repeatedly with boiling hexane and, on concentration of the solution, a very small amount of the *diamide* separated as prisms, m. p. 174—176° (Found: C, 67·9; H, 7·3; N, 15·6. $C_{20}H_{26}N_4O_2$ requires C, 67·8; H, 7·4; N, 15·8%).

4-*Heptyl*-2,6-*dihydroxypyridine*.—2,6-Dibenzyloxy-4-methylpyridine [10] (8·0 g.) in ether (30 c.c.) was added to sodamide (from sodium, 0·61 g.) in liquid ammonia (*ca.* 50 c.c.). After the mixture had been stirred under reflux for 2 hr., hexyl bromide (4·4 g.) was added and stirring was continued for 2 hr. Isolated in the manner already described, 2,6-*dibenzyloxy*-4-*heptylpyridine* (7·9 g.) had b. p. 202—220°/0·1 mm. (Found: C, 79·9; H, 8·0; N, 3·6. $C_{26}H_{31}NO_2$ requires C, 80·2; H, 7·6; N, 3·6%).

This compound (7·9 g.) in ethanol (200 c.c.) and ethyl methyl ketone (50 c.c.) was hydrogenated over 5% palladised calcium carbonate until absorption ceased. Concentration of the filtered solution gave 4-*heptyl*-2,6-*dihydroxypyridine* (3·8 g.), plates, m. p. 190—191° (from ethanol) (Found: C, 68·9; H, 8·8; N, 7·3. $C_{12}H_{19}NO_2$ requires C, 68·9; H, 9·2; N, 6·7%).

1,6-*Di*-(2,6-*dibenzyloxy*-4-*pyridyl*)*hexane*.—Alkylation of 2,6-dibenzyloxy-4-methylpyridine (10 g.) with tetramethylene dibromide (7·1 g.) in the same way gave the *tetrabenzyloxy-compound* (6·4 g.), needles, m. p. 90—91·5° (from ethanol) (Found: C, 79·1; H, 6·6; N, 4·5. $C_{44}H_{44}N_2O_4$ requires C, 79·5; H, 6·7; N, 4·2%).

1,6-*Di*-(2,6-*dihydroxy*-4-*pyridyl*)*hexane*.—Obtained similarly by catalytic debenzylation, the *tetrahydroxy-compound*, m. p. 262—265°, crystallised from acetic acid as a light brown powder (Found: C, 63·1; H, 6·3; N, 8·8. $C_{16}H_{20}N_2O_4$ requires C, 63·1; H, 6·6; N, 9·2%).

1,6-*Di*-(6-*hydroxy*-2-*pyridyl*)*hexane*.—2-Benzyloxy-6-methylpyridine [11] (30·0 g.) was added to potassamide (from potassium, 6 g.) in liquid ammonia (*ca.* 300 c.c.) and treated with tetramethylene dibromide (10·5 g.) in the usual manner. Catalytic debenzylation of the crude product gave the *dihydroxy-compound* (8·6 g.), needles, m. p. 241—244° (from butanol) (Found: C, 70·6; H, 7·5; N, 10·3. $C_{16}H_{20}N_2O_2$ requires C, 70·6; H, 7·4; N, 10·3%). A similar experiment with sodamide gave only 1 g. of product.

Alkylation of 2-benzyloxy-4-methylpyridine [12] (25 g.) in the presence of potassamide,

[10] Ames and Grey, *J.*, 1955, 631.
[11] Adams and Miyano, *J. Amer. Chem. Soc.*, 1954, **76**, 3170.
[12] Lott and Shaw, *J. Amer. Chem. Soc.*, 1949, **71**, 70.

followed by debenzylation, similarly gave 1,6-*di*-(2-*hydroxy*-4-*pyridyl*)*hexane* (1·6 g.), needles, m. p. 284—285° (from acetic acid) (Found: C, 70·8; H, 7·4; N, 10·2%).

3-*Benzyloxy*-6-*methylpyridine*.—3-Hydroxy-6-methylpyridine [13] (5·0 g.) in ethanol (10 c.c.) and benzyl bromide (8·6 g.) were added successively to sodium ethoxide solution (from ethanol, 30 c.c., and sodium, 1·3 g.). After the mixture had been refluxed for 2 hr., water (50 c.c.) was added. Isolated with ether, the *base* (5·1 g.) had b. p. 100—102°/0·05 mm., m. p. 27—29° (Found: C, 78·6; H, 6·7; N, 6·9. $C_{13}H_{13}NO$ requires C, 78·4; H, 6·6; N, 7·0%).

2-*Benzyloxy*-5-*methylpyridine*.—Potassium hydroxide (15 g.) in benzyl alcohol (48 g.) and xylene (40 c.c.) was refluxed while water was removed azeotropically. 2-Bromo-5-methylpyridine [14] (30 g.) was added gradually and the mixture was heated at 200° for 3 hr. Addition of water and isolation with ether gave the *base* (23·1 g.), b. p. 118—124°/0·1 mm., m. p. 30—31° (Found: C, 78·7; H, 6·6; N, 6·5%).

1-2′-*Pyridyl*-6-(6-*benzyloxy*-2-*pyridyl*)*hexane*.—2-5′-Hydroxypentylpyridine (16 g.) was converted into the bromo-compound in the manner described and condensed with 2-benzyloxy-6-methylpyridine in the presence of sodamide. Catalytic hydrogenation of the crude product furnished 1-2′-*pyridyl*-6-(6-*hydroxy*-2-*pyridyl*)*hexane* (3·2 g.), needles, m. p. 95—97° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 74·4; H, 8·1; N, 10·3. $C_{16}H_{20}N_2O$ requires C, 75·0; H, 7·9; N, 10·9%).

1,6-*Di*-(6-*methoxy*-2-*pyridyl*)*hexane*.—2-Methoxy-6-methylpyridine [7] (10·0 g.) was condensed with tetramethylene dibromide in the presence of potassamide according to the general procedure. The *base* (6·0 g.) had b. p. 142—148°/0·1 mm., n_D^{25} (1·5316 (Found: C, 71·6; H, 7·8; N, 9·5. $C_{18}H_{24}N_2O_2$ requires C, 71·9; H, 8·1; N, 9·3%).

1,6-*Di*-(2-*methoxy*-4-*pyridyl*)*hexane*.—2-Methoxy-4-methylpyridine [15] (31 g.) was condensed with tetramethylene dibromide in the presence of sodamide in the usual manner. The *base* (17 g.) formed prisms, m. p. 60—61°, from light petroleum (b. p. 60—80°) (Found: C, 71·7; H, 8·1; N, 9·1. $C_{18}H_{24}N_2O_2$ requires C, 71·9; H, 8·1; N, 9·3%).

1,1′-*Hexamethylenedi*-2-*pyridone*.—Hexamethylene dipyridinium dibromide (25 g.) in water (100 c.c.) was added to a stirred solution of potassium ferricyanide (150 g.) and potassium hydroxide (50 g.) in water (600 c.c.). The mixture was left at room temperature for 4 days and then extracted with chloroform, the combined extracts being washed with water (50 c.c.), dried (Na_2SO_4), and evaporated. The *dipyridone* (7·2 g.) formed prisms, m. p. 94—95°, from ethyl acetate (Found: C, 70·5; H, 7·7; N, 9·7. $C_{16}H_{20}N_2O_2$ requires C, 70·6; H, 7·4; N, 10·3%).

1,1′-*Hexamethylenedi*-(6-*hydroxy*-4-*methyl*-2-*pyridone*) (VIII).—β-Methylglutaconic anhydride [16] (4 g.) and hexamethylene diamine (1·9 g.) in xylene (50 c.c.) were refluxed, water being removed azeotropically. Most of the xylene was removed by distillation (bath finally at 200°) and the cooled residue was triturated with 2-methoxyethanol–ethyl methyl ketone (75 c.c.; 2 : 1). Evaporation of the filtered solution gave grey material, m. p. 165—170°, unchanged by recrystallisation from 2-methoxyethanol. Distillation at 0·05 mm. (bath 200°) gave an almost colourless *product*, m. p. 180—182° (Found: C, 65·2; H, 7·5; N, 8·5. $C_{18}H_{24}N_2O_4$ requires C, 65·0; H, 7·3; N, 8·4%).

4,4′-*Hexamethylenedi*-(1-*methyl*-2-*pyridone*).—1,6-Di-(2-methoxy-4-pyridyl)hexane (3·9 g.) in 2-methoxyethanol (25 c.c.) and methyl iodide (25 c.c.) was refluxed (bath, 130°) for 12 hr. After removal of solvents by distillation (bath, 200°), the residue was heated at 200° for 1 hr. The mass solidified on cooling, and recrystallisation from ethyl methyl ketone gave the *dipyridone*, prisms, m. p. 141—142° (Found: C, 71·9; H, 8·0; N, 9·4. $C_{18}H_{24}N_2O_2$ requires C, 72·0; H, 8·1; N, 9·3%).

4-[6-(1,2-*Dihydro*-2-*oxo*-4-*pyridyl*)*hexyl*]-1-*hydroxy*-2-*pyridone* (IX).—2-Benzyloxy-4-methylpyridine (25 g.) was alkylated with tetramethylene dibromide as described above. Starting materials were removed by distillation at 0·5 mm. (bath, 200°) and the residue was dissolved in chloroform (150 c.c.). The filtered (charcoal) solution was added gradually to a 0·45M-solution (320 c.c.) of perbenzoic acid in chloroform at 5°. The solution was left at room temperature overnight, washed thrice with potassium carbonate solution, and evaporated. The residual gum was hydrogenated in ethanol (100 c.c.) and ethyl methyl ketone (50 c.c.) with 5% palladised strontium carbonate (9 g.) until absorption ceased. A mixture of catalyst and precipitate,

[13] Marion and Cockburn, *J. Amer. Chem. Soc.*, 1949, **71**, 3402.
[14] Boyer and Reinisch, *J. Amer. Chem. Soc.*, 1960, **82**, 2218.
[15] Wiberg, Shryne, and Kintner, *J. Amer. Chem. Soc.*, 1957, **79**, 3160.
[16] Rogerson and Thorpe, *J.*, 1905, **87**, 1687.

collected by filtration, was extracted with boiling ethanol (5 × 100 c.c.), and the combined filtrates were evaporated *in vacuo*. Recrystallisation from 2-methoxyethanol and then from water gave the *product* as cream prisms, m. p. 205—207° (Found: C, 66·4; H, 7·2; N, 9·5. $C_{16}H_{20}N_2O_3$ requires C, 66·6; H, 7·0; N, 9·7%).

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