Syntheses of Pyridine Alkaloids and Related Compounds. Part II.[1] Syntheses of some 4-Alkyl- and 4-(1-Hydroxyalkyl)-piperidines

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Syntheses are described of some 4-alkylpyridines, 4-alkylpiperidines, and 4-(1-hydroxyalkyl)piperidines (alkyl = Pr^n, Bu^n, n-pentyl, phenethyl, and 3-phenylpropyl).

THE previous paper [1] described a new method for the preparation of coniine and conhydrine in good yield. This method has been extended to the syntheses of related compounds with side chains at the 4-positions of the pyridine and piperidine nuclei. Similar compounds have been found to be of special interest in chemotherapy; the benzoates of *N*-alkyl derivatives of 2-(2- or 3-hydroxypropyl)piperidines have been shown to possess local anaesthetic properties.[2-4]

4-Cyanopyridine [5] on condensation with appropriate alkylmagnesium bromides gave the 4-acylpyridines listed in Table 1. The i.r. carbonyl absorptions of these compounds occurred in the range 1680—1690 cm.$^{-1}$. The u.v. spectra all show two maxima, at 216—221 and 260—272 mμ, attributed to K- and B-bands respectively.

The 2,4-dinitrophenylhydrazone hydrobromides and the corresponding bases are listed in Tables 2 and 3 respectively.

Application of the Wolff–Kishner reduction as simplified by Lock [6] gave good yields of 4-alkylpyridines (Table 4).

Reduction of the alkylpyridines with hydrogen over Adams catalyst in N-hydrochloric acid (uptake 3 mol.) gave the corresponding alkylpiperidines (Table 5). The

TABLE 1

4-Acylpyridines

Acyl group	B.p.	n_D^{20}	Yield (%)	Formula	Calc. (%) C	Calc. (%) H	Calc. (%) N	Found (%) C	Found (%) H	Found (%) N	$\nu_{max.}$ (C=O) (cm.$^{-1}$)	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$
Propionyl	140°/30 [a]	1·5227	60·4	C_8H_9NO	71·1	6·7	10·4	71·2	6·8	10·5	1680	221	6600
												272	3270
n-Butyryl	150/30	1·5163	57·5	$C_9H_{11}NO$	72·45	7·4	9·4	72·6	7·1	9·6	1682	222	6100
												272	2970
n-Valeryl	148/20	1·5102	50·9	$C_{10}H_{13}NO$	73·6	8·0	8·6	73·8	7·8	8·4	1680	221	3400
												270	2970
Phenacetyl	178/10 [b]		35·4	$C_{13}H_{11}NO$	79·2	5·6	7·1	79·2	5·5	6·9	1690	219	6100
												260	3350
3-Phenylpropionyl	218/20	1·5724	39·4	$C_{14}H_{13}NO$	79·6	6·2	6·6	79·6	6·3	6·4	1690	216	7000
												260	2100

[a] Lit., 212—214° (ref. 7). [b] M.p. 53—54°.

[1] Part I, K. B. Prasad and S. C. Shaw, *Chem. Ber.*, 1965, **98**, 2822.

[2] W. H. Hunt and R. J. Fosbinder, *Anaesthesiology*, 1940, **1**, 305.

[3] C. W. Tullock and S. M. McElvain, *J. Amer. Chem. Soc.*, 1939, **61**, 961.

[4] J. F. O. Leary, D. E. Leary, and I. H. Slater, *Proc. Soc. Exp. Biol. Med.*, 1951, **76**, 738.

[5] E. Feeley and E. M. Beavers, *J. Amer. Chem. Soc.*, 1959, **81**, 4004.

[6] G. Lock, *Monatsh.*, 1954, **85**, 802.

TABLE 2

2,4-Dinitrophenylhydrazone hydrobromides of 4-acylpyridines

Acyl group	M.p. (decomp.)	Formula	Calc. (%) C	H	Br	N	Found (%) C	H	Br	N
Propionyl	256° [a]	$C_{14}H_{14}BrN_5O_4$	42·4	3·6	20·2	17·7	42·2	4·1	20·4	17·7
n-Butyryl	252 [b]	$C_{15}H_{16}BrN_5O_4$	43·9	3·9	19·5	17·1	43·8	4·2	19·3	17·2
n-Valeryl	250 [b]	$C_{16}H_{18}BrN_5O_4$	45·3	4·3	18·8	16·5	45·4	4·5	18·7	16·7
Phenacetyl	255 [b]	$C_{19}H_{16}BrN_5O_4$	49·8	3·5	17·4	15·3	49·6	3·6	17·6	15·35
3-Phenylpropionyl	262 [b]	$C_{20}H_{18}BrN_5O_4$	50·85	3·8	16·95	14·8	50·8	3·9	16·8	14·7

[a] Yellow cubes from methanol. [b] Yellow cubes from benzene and light petroleum.

TABLE 3

2,4-Dinitrophenylhydrazones of 4-acylpyridines

Acyl group	M.p. (from methanol)	Formula	Calc. (%) C	H	N	Found (%) C	H	N
Propionyl	208°	$C_{14}H_{13}N_5O_4$	53·3	4·15	22·2	53·3	4·2	22·1
n-Butyryl	160	$C_{15}H_{15}N_5O_4$	54·7	4·6	21·3	54·5	4·6	21·1
n-Valeryl	169	$C_{16}H_{17}N_5O_4$	56·0	5·0	20·4	55·95	5·1	20·2
Phenacetyl	156	$C_{19}H_{15}N_5O_4$	60·5	4·0	18·6	60·3	4·2	18·4
3-Phenylpropionyl	238	$C_{20}H_{17}N_5O_4$	61·4	4·4	17·9	61·5	4·4	17·7

TABLE 4

4-Alkylpyridines

Alkyl group	B.p.	n_D^{20}	Yield (%)	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	Picrates M.p.
n-Propyl	116°/40 mm. [a]	1·4977	76·7	214	1600	131° [f]
				257	2230	
n-Butyl	100/20 [b]	1·4945	73·0	213	2140	111 [g]
				256	2360	
n-Pentyl	102/10 [c]	1·4902	74·7	212	2540	96 [h]
				256	1770	
Phenethyl	160/25 [d]	1·5786	47·4	214	1245	168
				252	4120	
3-Phenylpropyl	152/20 [e]	1·5681	52	221	3200	146
				257	3250	
				290sh		

[a] Lit., 184—186° (E. Koenigs and W. Jaeschke, *Ber.*, 1921, **54**, 1351), 189°/776 mm. (J. F. Arens and J. P. Wibaut, *Rec. Trav. chim.*, 1942, **61**, 59), 80°/20 mm., n_D^{20} 1·4966 (J. P. Wibaut and J. W. Hey, *Rec. Trav. chim.*, 1953, **72**, 513), 172—172·5°/748 mm., n_D^{20} 1·4465 (W. Wawzonek, M. F. Nelson, and P. J. Thelen, *J. Amer. Chem. Soc.*, 1952, **74**, 2894; [b] lit., 98°/20 mm., n_D^{20}/1·4937 (Wibaut and Hey in ref. *a*), 193—194°/745 mm., n_D^{20} 1·4472 (Wawzonek *et al.* in ref. *a*); [c] lit., 114°/20 mm., n_D^{20} 1·4908 (Wibaut and Hey in ref. *a*); [d] m.p. 68—69° [lit., 70—71° (F. W. Bergstron, T. R. Norton, and R. A. Seibert, *J. Org. Chem.*, 1945, **10**, 452]; [e] lit., 150—152°/6 mm. (Bergstron *et al.* in ref. *d*); [f] yellow needles from methanol [lit., 131—131·6° (Arens and Wibaut in ref. *a*), 135° (Koenigs and Jaeschke in ref. *a*)]; [g] lit., 112° (M. Miocque, *Bull. Soc. chim. France*, 1960, 322); [h] lit., 104° (Wibaut and Hey in ref. *a*).

TABLE 5

4-Alkylpiperidines

Alkyl group	B.p.	n_D^{20}	Yield (%)	Formula	Calc. (%) C	H	N	Found (%) C	H	N
n-Propyl [a]	62°/2 mm.	1·4882	60	$C_8H_{17}N$	75·5	13·4	11·0	75·4	13·5	11·2
n-Butyl [a]	90/2	1·4718	63	$C_9H_{19}N$	76·5	13·55	9·9	76·4	13·7	10·1
n-Pentyl	92/2	1·4747	71	$C_{10}H_{21}N$	77·3	13·6	9·0	77·2	13·5	9·3
Phenethyl	180 */20 [b]	1·5139	54	$C_{13}H_{19}N$	82·5	10·1	7·4	82·35	10·2	7·5
3-Phenylpropyl	155 */2	1·5415	77	$C_{14}H_{21}N$	82·7	10·4	6·9	82·6	10·3	7·0

* Bath temp.

[a] W. Wawzonek, M. F. Nelson, and P. J. Thelen, *J. Amer. Chem. Soc.*, 1952, **74**, 2894. [b] Lit., 200—210°/80 mm. (K. Friedlander *Ber.*, 1905, **38**, 2837).

TABLE 6

N-Benzoyl derivatives of 4-alkylpiperidines

Alkyl group	B.p.*	M.p.	Formula	Calc. (%) C	H	N	Found (%) C	H	N
n-Propyl	180°/20mm.	109° †	$C_{15}H_{21}NO$	77·9	9·1	6·05	77·8	9·2	6·2
n-Butyl	185/20	101 †	$C_{16}H_{23}NO$	78·3	9·4	5·7	78·2	9·5	5·6
n-Pentyl	193/20	94 †	$C_{17}H_{25}NO$	78·7	9·7	5·4	78·5	9·8	5·3
Phenethyl	180/20	126 †	$C_{20}H_{23}NO$	81·9	7·9	4·8	81·7	7·9	4·6
3-Phenylpropyl	200/20	145 †	$C_{21}H_{25}NO$	82·0	8·2	4·55	81·9	8·3	4·7

* Bath temp. † Light yellow liquid, white solid on cooling.

TABLE 7
4-(1-Hydroxyalkyl)piperidines

Alkyl group	B.p.	M.p.	n_D^{20}	Yield (%)	Formula	Calc. (%) C	Calc. (%) H	Calc. (%) N	Found (%) C	Found (%) H	Found (%) N	$\lambda_{max.}$ (mμ)	$\epsilon_{max.}$	$\nu_{max.}$ (O–H; cm.$^{-1}$)
n-Propyl	54°/2 mm.	111°	1·4609	66·2	$C_8H_{17}NO$	67·1	12·0	9·8	67·15	12·0	9·6	225	323	3270
												268	143	
n-Butyl	185/20 *	119	1·4654	60·5	$C_9H_{19}NO$	68·7	12·2	8·9	68·6	12·1	9·0	222	211	3270
												261	112	
n-Pentyl	114/2 *	124	1·4675	59·0	$C_{10}H_{21}NO$	70·1	12·35	8·2	70·3	12·2	8·3	225	450	3270
												226	242	
Phenethyl	180/20 *	124	1·5367	62·7	$C_{13}H_{19}NO$	76·05	9·3	6·8	76·1	9·4	6·7	220	1290	3290
												261	615	
3-Phenylpropyl	190/20 *	131	1·5539	68·3	$C_{14}H_{21}NO$	76·7	9·65	6·3	76·5	9·5	6·2	219	2420	3290
												257	1500	

* Bath temp.

TABLE 8
NO-Dibenzyl derivatives of 4-(1-hydroxyalkyl)piperidines

Alkyl group	B.p.	M.p.	Formula	Calc. (%) C	Calc. (%) H	Calc. (%) N	Found (%) C	Found (%) H	Found (%) N
n-Propyl	110°/5 mm.	122°	$C_{22}H_{25}NO_3$	75·2	7·2	4·0	75·2	7·2	4·0
n-Butyl	170/2	95	$C_{23}H_{27}NO_3$	75·6	7·4	3·8	75·7	7·3	3·9
n-Pentyl	220/20	85	$C_{24}H_{29}NO_3$	75·95	7·75	3·7	75·8	7·9	3·8
Phenethyl	130/4 *	115	$C_{27}H_{27}NO_3,H_2O$	75·15	6·8	3·25	75·2	6·75	3·3
3-Phenylpropyl	200/2 *	144	$C_{28}H_{29}NO_3$	78·7	6·8	3·3	78·6	6·9	3·3

* Bath temp.

corresponding *N*-benzoyl derivatives (Table 6) were also prepared.

Hydrogenation of the 4-acylpyridines in N-hydrochloric acid in the presence of freshly reduced Adams catalysts (uptake *ca.* 4 mol.) caused reduction of both the carbonyl group and the pyridine nucleus (*cf.* ref. 1). The products lacked i.r. carbonyl absorption and showed a broad band between 3270 and 3290 cm.$^{-1}$ (NH and OH stretch). The u.v. spectra show two maxima of much lower intensity (219—225 and 257—268 mμ).

EXPERIMENTAL

Unless otherwise stated, light petroleum refers to the fraction b.p. 60—80°, u.v. spectra were measured with a Unicam SP 800 instrument for solutions in ethanol, and i.r. spectra were measured with a Unicam SP 200 instrument for solutions in chloroform. Microanalytical samples were analysed in West Germany at the Ruhr Max Planck Institute. Analytical samples were dried at room temperature in a vacuum desiccator.

4-Acylpyridines.—*4-Propionylpyridine.* 4-Cyanopyridine (26 g., 0·25 mole) in dry ether (75 ml.) was slowly added to a cooled and stirred solution of ethylmagnesium bromide in dry ether (100 ml.) [from magnesium (6·6 g.; 0·28 g. atom), ethyl bromide (30 g.; 0·28 atom)]. The mixture was refluxed for 4 hr., then cooled (ice-bath) and decomposed by dropwise addition of cold water (50 ml.) followed by 5N-hydrochloric acid (100 ml.). The aqueous layer was separated and the ethereal solution was extracted with 2N-hydrochloric acid (2 × 50 ml.). The combined aqueous extracts were heated (1 hr.) on a water-bath, cooled, basified (K_2CO_3), and extracted with chloroform. Distillation of the dried (Na_2SO_4) extract gave 4-propionylpyridine [7,8] Other 4-acylpyridines (Table 1) were prepared by similar methods. The corresponding 2,4-dinitrophenylhydrazone hydrobromides are listed in Table 2. Basification (Na_2CO_3) of these salts followed by extraction with chloroform gave the free 2,4-dinitrophenylhydrazones (Table 3).

4-Alkylpyridines.— *4-(n-Propyl)pyridine.* 4-Propionylpyridine (8 g.) and hydrazine hydrate (99·9%; 16 g.) were refluxed for 2 hr. The mixture was cooled, mixed with powdered potassium hydroxide (32 g.), and heated (120—150°) until evolution of nitrogen ceased (2 hr.). It was cooled, diluted with water, and extracted with ether. Distillation of the dried (Na_2SO_4) extract gave the 4-(n-propyl)pyridine as an oily liquid. Other 4-alkyl pyridines (Table 4) were prepared by similar methods. The corresponding picrates (crystallised from ethanol) are listed in Table 4.

4-Alkylpiperidines.—*4-(n-Propyl)piperidine.* 4-(n-Propyl)pyridine (2 g.) and Adams catalyst (150 mg.) in N-hydrochloric acid (50 ml.) were hydrogenated (uptake 1250 c.c., *ca.* 3 mol.) at 22°/745 mm. for 77 hr. The catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was basified with 10% sodium hydroxide solution and extracted with chloroform. Distillation of the dried (Na_2SO_4) extract gave 4-(n-propyl)-piperidine. Other 4-alkylpyridine (Table 5) were prepared by similar methods. The corresponding *N*-benzoyl derivatives are listed in Table 6.

4-(1-Hydroxyalkyl)piperidines.— *4-(1-Hydroxy-n-propyl)-piperidine.* 4-Propionylpyridine (3 g.) and Adams catalyst (150 mg.) in N-hydrochloric acid (50 ml.) were hydrogenated for 79 hr. (uptake 2230 c.c. at 22°/752 mm.). The catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was basified with 10% sodium hydroxide and extracted with ether. Distillation of the dried (Na_2SO_4) extract gave 4-(1-hydroxy-n-propyl)-piperidine. Other 4-(1-hydroxyalkyl)piperidines (Table 7) were prepared by similar methods. The *NO*-dibenzoyl derivatives are listed in Table 8.

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[7] A. Pinner, *Ber.*, 1901, **34**, 4234.
[8] Chin-Chiun Chu and P. C. Teague, *J. Org. Chem.*, 1958, 1578.