SYNTHESES OF SOME ω-(1,2,3,6-TETRAHYDRO-1-PYRIDYL)--1-ALKANOLS*

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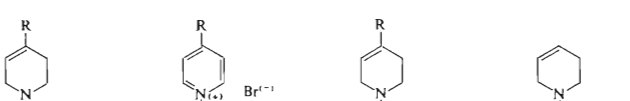
Quaternary salts of pyridine and 4-methylpyridine with ethyl esters of ω-bromoalkanoic acids, *IIa*—*IIe*, were converted into esters *IIIa*—*IIIe* by the action of sodium borohydride. These were further reduced by lithium aluminium hydride to alcohols *Ia*—*Ie*. 4-(1,2,3,6-Tetrahydro-1-pyridyl)--butanol (*Ic*) was also obtained from 1-(3-ethoxycarbonylpropyl)pyridinium bromide (*IIc*) by the action of $LiAlH_4$. The ethyl ester *IIIa* was converted into amide *IV*.

As part of our studies on the syntheses of 1,2,3,6-tetrahydropyridine derivatives, we have dealt with the preparation of ω-(1,2,3,6-tetrahydro-1-pyridyl)-1-alkanols (*Ia*—*Ie*). A rewarding procedure proved to be a two-step reduction of the quaternary salts formed by reaction of pyridine bases with ethyl esters of ω-bromoalkanoic acids, *IIa*—*IIe* (ref.[1]). In the first step the pyridinium ring was reduced with sodium borohydride to the 1,2,3,6-tetrahydropyridine esters *III*; the second step was reduction of the ester group with lithium aluminium hydride, leading to the primary alcohols *Ia*—*Ie*. The yields of the first reduction step were best at a ratio of the quaternary salts to sodium borohydride = 1 : 3, and rose with increasing length of the aliphatic chain.

Having experience with the reduction of alkylpyridinium halides by the action of lithium aluminium hydride[2] we have now attempted a similar reduction of the quaternary salt *IId*. The yield of the desired alcohol *Id* was low. Exposure of ethyl



I *II* *III* *IV*

In formulae *I*—*III*: *a* n = 1, *b* n = 2, *c* n = 3, *d* n = 4, *e* n = 1; *a*—*d* R = H, *e* R = CH_3.

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(1,2,3,4-tetrahydro-1-pyridyl)acetate (*IIIa*) to aqueous ammonia afforded the corresponding amide *IV*.

The esters *IIIa–IIIe* and alcohols *Ia–Ie* were identified by means of their ^{1}H NMR spectra (Tables II and III).

EXPERIMENTAL

The temperature data are not corrected. The ^{1}H NMR spectra of solutions in deuteriochloroform were measured at 35°C, employing an apparatus Varian XL-100-15 (100·1 MHz) and tetramethylsilane as internal standard. The mass spectrum was measured with an apparatus Gas Chromatograph-Mass Spectrometer, Type 9000 LKB, Produkter AB Stockholm. The sample was applied by direct inlet. Gas chromatography was carried out in an apparatus Chrom II (length of column

TABLE I

Alcohols *I* and esters *III*

Compound Yield, %	B.p., °C/kPa	Formula (mol.mass)	Calculated/Found		
			% C	% H	% N
Ia	116/2·1	$C_7H_{13}NO$	66·11	10·30	11·01
51		(127·2)	65·85	10·34	10·96
Ib	124/2·7	$C_8H_{15}NO$	68·04	10·71	9·92
50		(141·2)	68·21	10·65	9·77
Ic	131/2·1	$C_9H_{17}NO$	69·63	11·04	9·02
49		(155·3)	69·79	11·04	9·13
Id	145/2·1	$C_{10}H_{19}NO$	70·96	11·31	8·27
52		(169·3)	70·96	11·21	8·52
Ie	110/1·7	$C_8H_{15}NO$	68·05	10·70	9·92
68		(141·2)	67·76	10·70	10·10
IIIa	128/3·7	$C_9H_{15}NO_2$	63·88	8·93	8·28
35		(169·2)	63·91	9·12	8·12
IIIb	120/3·3	$C_{10}H_{17}NO_2$	65·54	9·35	7·64
18		(183·2)	65·35	9·39	7·61
IIIc	124/2·7	$C_{11}H_{19}NO_2$	66·98	9·71	7·10
45		(197·3)	66·92	9·81	7·16
IIId	141/2·8	$C_{12}H_{21}NO_2$	68·22	10·02	6·63
50		(211·3)	68·19	10·03	6·76
IIIe	128/3·2	$C_{10}H_{17}NO_2$	65·54	9·35	7·64
45		(183·2)	65·49	9·46	7·79

TABLE II

^{1}H NMR spectra of esters *III*

Proton[a]	*IIIa*	*IIIb*	*IIIc*	*IIId*	*IIIe*
CH_2COO	—	2·34[b]	2·04[c]	2·08[c]	—
$N—CH_2$	3·28	|	|	|	3·28
	s, 2 H	|	|	|	s, 2 H
H-2	2·70	2·84	|	|	2·50–2·78
	t, 2 H, J = 6 Hz		|	|	m, 2 H
H-3	2·04–2·32	2·04–2·32	2·60	2·62	1·92–2·22
	m, 2 H	m, 2 H			m, 2 H
H-6[d]	3·06–3·20	2·92–3·04	2·90–3·04	2·90–3·04	2·90–3·14
$(CH_2)_{n-2}$	—	—	1·72–1·98	1·44–1·80	—
			m, 2 H	m, 4 H	

[a] For *IIIa*–*IIIe* 1·24 (t, 3 H, J = 7 Hz) and 4·12 ± 0·04 (q, 2 H, J = 7 Hz) OCH_2CH_3; for *IIIa*–*IIId* 5·46–5·88 (m, 2 H) CH=CH; for *IIIe* 5·22–5·48 (m, 1 H) CH=C—; 1·64 (s, 3 H) CH_3—C. [b] m, 6 H; [c] m, 8H; [d] always m, 2 H.

TABLE III

^{1}H NMR spectra of ω-(1,2,3,6-tetrahydro-1-pyridyl)-1-alkanols (*I*)

Compound	H-6	H-2, $N—CH_2$	H-3	$(CH_2)_{n-2}$	CH_2O	O—H[a]
Ia	2·96–3·08	2·50–2·70	2·06–2·28	—	3·63[b]	3·34
	m, 2 H	m, 4 H	m, 2 H		t, 2 H	bs, 1 H
Ib	2·96–3·08	2·50–2·76	2·06–2·28	1·58–1·88	3·78[b]	5·00
	m, 2 H	m, 4 H	m, 2 H	m, 2 H	t, 2 H	bs, 1 H
Ic	2·96–3·08	2·38–2·68	2·08–2·32	1·56–1·88	3·48–3·72	5·02
	m, 2 H	m, 4 H	m, 2 H	m, 4 H	m, 2 H	bs, 1 H
Id	2·82–3·08	2·04–2·62		1·56–1·88	3·58[b]	2·82–3·08
	m, 3 H[c]	m, 6 H		m, 4 H	t, 2 H	
Ie[d]	2·80–3·06	2·50–2·72	1·98–2·24	—	3·64[b]	3·16
	m, 2 H	m, 4 H	m, 2 H		t, 2 H	bs, 1 H

[a] Shifted with increasing temperature; [b] J = 6 Hz; [c] together with OH, separated signals at elevated temperature; [d] for *Ie* 1·66 (s, 3 H) $CH_3—C_{(4)}$; 5·22–5·48 (m, 1 H), CH=C; for compounds *Ia*–*Id* 5·48–5·90 (m, 2 H) CH=CH.

170 cm, I.D. 0·6 cm, nitrogen as carrier, the stationary phase silicone elastomer 15% E-301 on Chromosorb N-AW-DMCS, or 15% Carbowax 20M on Chromaton N-AW-HMDS, detection by FID). Thin-layer chromatography ran on Silufol plates UV 254 (wide pore silica gel Silpearl with a luminiscent indicator for UV light 254 nm on an aluminium foil, with starch as binder); the spots were detected using a Universal UV Lamp Camag (Muttenz, Schweiz) and iodine vapour in the system benzene–ethanol 9 : 1.

The quaternary salts *IIa*—*IIc* were prepared by a described procedure[1]; the salts *IId*—*IIe* were obtained analogously. These strongly hygroscopic compounds were collected on a filter under nitrogen, washed with benzene, dried *in vacuo* at room temperature, and used without having been analysed.

Ethyl (1,2,3,6-tetrahydro-1-pyridyl)acetate (*IIIa*)

To a solution of N-(ethoxycarbonylmethyl)pyridinium bromide[1] (49·2 g, 0·02 mol) in ethanol (440 ml) were added small portions of $NaBH_4$ (a total of 22·7 g, 0·60 mol) under stirring and cooling. The stirring was continued for 1·5 h at room temperature. The ethanol was then removed *in vacuo*, the residue was dissolved in water (100 ml), saturated with Na_2CO_3, extracted into four 30 ml portions of ether and dried with $MgSO_4$. The ether was distilled off and the residue was twice distilled *in vacuo*; yield 11·9 g (35%) of *IIIa*, b.p. 128°C/3·8 kPa (28 Torr).

2-(1,2,3,6-Tetrahydro-1-pyridyl)ethanol (*Ia*)

To a suspension of $LiAlH_4$ (1·37 g, 0·036 mol) in ether (120 ml) was added dropwise the ester *IIIa* (3·0 g, 0·018 mol) in ether (20 ml). The mixture was boiled for 3 h under a reflux condenser, cooled down and decomposed with 4% NaOH (6 ml). After stirring for 15 min the precipitate of the hydroxides was collected on a filter and washed with ether (100 ml). The combined filtrates were dried with K_2CO_3. The ether was distilled off, the residue was distilled *in vacuo* and redistilled; yield 1·15 g (51%) of a liquid, b.p. 116°C/2·1 kPa (16 Torr), a single compound by GLC and TLC. The esters *IIIb*—*IIIe* and the alcohols *Ib*—*Ie* were obtained by procedures analogous to those used for the preparation of *IIIa* and *Ia*, respectively.

4-(1,2,3,6-Tetrahydro-1-pyridyl)butanol (*Ic*)

To a stirred suspension of $LiAlH_4$ (1·52 g, 0·04 mol) in ether (130 ml) was added dropwise *IIc* (5·48 g, 0 02 mol) in dichloromethane (30 ml). The mixture was boiled under a reflux condenser for 6 h, cooled down and decomposed (ref.[3]). After stirring for 15 min the precipitate was collected on a filter and washed with ether (100 ml). The combined filtrates were dried with K_2CO_3. The ether and dichloromethane were distilled off, the product was distilled *in vacuo* and redistilled; yield 0·50 g (16%) of a liquid, b.p. 126°C/1·9 kPa (14 Torr). TLC, GLC and the NMR spectra identified it as the alcohol *Ic*.

(1,2,3,6-Tetrahydro-1-pyridyl)acetamide (*IV*)

A mixture of *IIIa* (1·0 g, 0·006 mol) and 26% aqueous ammonia (10 ml) was stirred for 8 h. The separated flakes were collected on a filter and crystallized from a mixture cyclohexane–ethanol 20 : 1; yield 0·55 g (66%), m.p. 124—125°C. For $C_7H_{12}N_2O$ (140·2) calculated: 59·98% C, 8·63% H, 19·98% N; found: 59·83% C, 8·58% H, 19·98% N. ^{1}H NMR spectrum: 2·04—2·30 (m, 2 H) for $C_{(3)}$; 2·64 (t, $J = 6$ Hz, 2H) H for $C_{(2)}$; 2·86—3·18 (m, 2 H) H for $C_{(6)}$ and NCH_2CONH_2; 5·50—5·88 (m, 2 H) CH=CH; 6·44 and 7·10 (2 × bs, 2 H) $CONH_2$. Mass

spectrum: (m/z, % rel. intensity): 141 (M^+, 5%); 97 ($M^+ - CONH_2$, 100%); 83 ($M^+ - CH_2CONH_2$, 60%).

The elemental analyses were performed at the Analytical Department of the Institute (head Dr L. Helešic), the NMR spectra were measured under the direction of Dr P. Trška, the mass spectrum was measured by Dr J. Novák.

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