THE SYNTHESIS OF SOME ALCOHOLS DERIVED FROM 1,2,3,4-TETRAHYDROISOQUINOLINE AND FROM 1,2,3,4-TETRAHYDROQUINOLINE*

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Dedicated to Professor J. Mostecký on the occasion of his 60 th birthday.

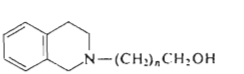
Reduction of ethyl esters of ω-(1,2,3,4-tetrahydro-2-isoquinolyl)alkanoic acids *IVa–e* by means of $LiAlH_4$ was used for the preparation of corresponding primary alcohols *Ia–e*. 6-(1,2,3,4-Tetrahydro-2-isoquinolyl)-1-hexanol (*Ie*) was also obtained on reduction of ester amide *VII*. Reduction of 2-(2-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinoline (*V*) with $LiAlH_4$ gave secondary alcohol *II*; in the quinoline series alcohol *IIIa* was obtained in a similar manner by reduction of ethyl 3-(1,2,3,4-tetrahydro-1-quinolyl)propanoate (*IIIb*).

In connection with the study of hydroborations of unsaturated amines[1,2] we needed the series of (1,2,3,4-tetrahydro-2-isoquinolyl)-1-alkanols *Ia–e*, 1-(1,2,3,4-tetrahydro-2-isoquinolyl)-2-propanol (*II*) and 3-(1,2,3,4-tetrahydro-1-quinolyl)-1-propanol (*IIIa*) for comparison. We obtained these alcohols on reduction of corresponding esters *IVa–e* and *IIIb*, or alcohol *II* on reduction of amide *V* with lithium aluminum hydride. The required esters *IVa*, *IVb* were prepared from isoquinoline by treatment with ethyl bromoacetate or 3-bromopropanoate and reduction of the quaternary salts *VI* by means of sodium borohydride. Ethyl esters *IVc–e* were prepared from 1,2,3,4-tetrahydroisoquinoline on reaction with ethyl ester of corresponding ω-bromoalkanoic acid in the presence of anhydrous potassium carbonate in 2-butanone. 2-(2-Hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinoline (*V*) was formed on reaction of ethyl lactate with 1,2,3,4-tetrahydroisoquinoline. The primary alcohol *Ie* was also formed by treatment of 1,2,3,4-tetrahydroisoquinoline with ethyl 5-chlorocarbonylpentanoate, and subsequent reduction of the ester amide *VII* formed.

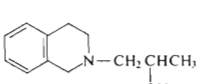
EXPERIMENTAL

The ^1H NMR spectra were measured on a Varian XL-100-15 (100·1 MHz) instrument at 35°C, using tetramethylsilane as internal reference, in deuteriochloroform. The chemical shift values

* Part XII in the series Q u inoline and Isoquinoline Derivatives; Part XI: This Journal *46*, 3285 (1981).



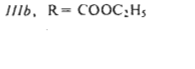
I



II

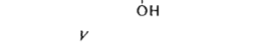
IIIa, R = CH_2OH
IIIb, R = $COOC_2H_5$

IV



V

VIa, $n = 1$
VIb, $n = 2$



VII

For *I*, *IV*: *a*, $n = 1$; *b*, $n = 2$; *c*, $n = 3$; *d*, $n = 4$; *e*, $n = 5$.

are given in ppm and the interaction constants in Hz. The mass spectra were measured on a Gas Chromatograph-Mass Spectrometer Type 9000 LKB, Produkter AB Stockholm. The samples were applied by direct inlet technique. The ionic species were given in m/z units (% of relative intensity). Gas Chromatography was carried out on a Chrom II apparatus (column length 170 cm, diameter 0·6 cm, carrier gas nitrogen, stationary phase a silicone elastomer, 15% E-301 on Chromosorb N-AW-DNCS, detection by FID). For thin-layer chromatography Silufol UV 254 and UV 366 were used (*i.e.* aluminum foil with silica gel, containing a luminescent indicator; starch as binder). Detection was carried out with a Universal UV Lamp Camag (Muttenz-Schweiz) with wave-length ranges 254 and 366 nm, or with iodine vapours. The temperature data are not corrected. Crystalline substances were dried before analysis at 70 Pa for 4 h.

2-Ethoxycarbonylmethylisoquinolinium Bromide (*VIa*)

A mixture of 10 g (0·078 mol) of isoquinoline, 45 ml of benzene and 16·7 g (0·10 mol) of ethyl bromoacetate was allowed to stand for 10 days. The separated crystals were filtered off under

suction, m.p. 199–201°C (ethanol), yield 21·8 g (95%). For $C_{13}H_{14}BrNO_2$ (296·2) calculated: 52·73% C, 4·76% H, 26·98% Br, 4·73% N; found: 52·90% C, 4·99% H, 26·64% Br, 4·74% N.

Ethyl 6-Oxo-6-(1,2,3,4-tetrahydro-2-isoquinolyl)hexanoate (*VII*)

Ethyl chloroformylpentanoate[3] (4·3 g; 0·023 mol) was added to a solution of 6·0 g (0·046 mol) of 1,2,3,4-tetrahydroisoquinoline in 20 ml of benzene and the mixture was allowed to stand for 4 days. The separated hydrochloride of 1,2,3,4-tetrahydroisoquinoline (m.p. 195–196°C, in agreement with literature[4]) was filtered off under suction. The benzene solution was washed with Na_2CO_3 solution and water and distilled, b.p. 170–171°C/2·7 Pa (0·02 Torr); yield 3·3 g (51%). For $C_{17}H_{23}NO_3$ (289·4) calculated: 70·56% C, 8·01% H, 4·84% N; found: 70·31% C, 8·04% H, 4·94% N. ^{1}H NMR spectrum, ppm: 1·23 (3 H, t, J = 7 Hz) CH_3; 1·52–1·89 (m, 4 H) $COCH_2$·.CH_2CH_2; 2·18–2·52 (m, 4 H) $NCOCH_2$ and CH_2COO; 2·72–2·97 (m, 2 H) H on $C_{(4)}$ of tetrahydroisoquinoline; 3·58–3·88 (m, 2 H) H on $C_{(3)}$ of tetrahydroisoquinoline 4·08 (q, 2 H, J = = 7 Hz) OCH_2; 4·64 (d, 2 H, J = 11 Hz) H on $C_{(1)}$ of tetrahydroisoquinoline; 7·00–7·28 (m, 4 H) arom. H.

2-(2-Hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinoline (*V*)

A mixture of 10·7 g (0·08 mol) of 1,2,3,4-tetrahydroisoquinoline and 10·4 g (0·088 mol) of ethyl (±)-lactate was allowed to stand at room temperature for 18 days and then distilled: main fraction, b.p. 135°C/2·0 Pa (0·015 Torr), m.p. 99·5–101°C (ethanol), yield 4·7 g (29%). For $C_{12}H_{15}NO_2$ (205·3) calculated: 70·22% C, 7·37% H, 6·82% N; found: 70·25% C, 7·63% H, 6·94% N. ^{1}H NMR spectrum, ppm: 1·36 (d, 3 H, J = 7 Hz) CH_3; 2·88 (t, 2 H, J = 6 Hz) H on $C_{(4)}$ of tetrahydroisoquinoline; 3·62 (t, 2 H, J = 6 Hz) H on $C_{(3)}$ of tetrahydroisoquinoline; 3·94 (d, 1 H, J = 7·5 Hz) OH; 4·54 (m, 1 H) CHO; 4·74 (s, 2 H) H on $C_{(1)}$ of tetrahydroisoquinoline; 6·96–7·40 (m, 4 H) aromatic protons.

Ethyl 3-(1,2,3,4-tetrahydro-1-quinolyl)propanoate (*IIIb*)

Hydrogen chloride gas was introduced into a boiling solution of 15 g (0·08 mol) of 3-(1,2,3,4-tetrahydro-1-quinolyl) propanoic acid hydrochloride[5] in 150 ml of ethanol for 5 h. Ethanol was distilled off and the residue dissolved in a small amount of water, alkalized with a saturated K_2CO_3 solution, the product was extracted with ether, dried over $MgSO_4$, ether was distilled off and the residue distilled; b.p. of the main fraction was 135–139°C/7 Pa (0·05 Torr), yield 7·3 g (39%). For $C_{14}H_{19}NO_2$ (233·3) calculated: 72·07% C, 8·21% H, 6·00% N; found: 72·24% C, 8·36% H, 6·18% N. ^{1}H NMR spectrum, ppm: 1·26 (t, 3 H, J = 6 Hz) CH_3; 1·94 (q, 2 H, J = 6 Hz) H on $C_{(3)}$ of tetrahydroquinoline; 2·50–2·80 (m, 4 H) H on $C_{(4)}$ of tetrahydroquinoline and CH_2CO; 3·28 (t, 2 H, J = 6 Hz) H on $C_{(2)}$ of tetrahydroquinoline; 3·46–3·70 (m, 2 H) N—CH_2—C—CO; 4·13 (q, 2 H, J = 6 Hz) OCH_2; 6·50–6·64 (m, 2 H) and 6·91–7·16 (m, 2 H) arom. H.

Ethyl (1,2,3,4-tetrahydro-2-isoquinolyl)acetate (*IVa*)

$NaBH_4$ (7·82 g; 0·207 mol) was added to a solution of 20·4 g (0·06 mol) of *VIa* in 150 ml of ethanol and the mixture was stirred for 2·5 h. After concentration in a vacuum the residue was dissolved in water, the solution was alkalized with Na_2CO_3 and the product extracted with ether. Working up afforded 8·4 g (56%) of *IVa*, b.p. 125–126°C/12 Pa (0·09 Torr). Literature[6] gives b.p. 91 to 94°C/0·01 Torr. For $C_{13}H_{17}NO_2$ (219·3) calculated: 71·21% C, 7·81% H, 6·39% N; found: 71·28% C, 7·78% H, 6·51% N. ^{1}H NMR spectrum, ppm: 1·29 (t, 3 H, J = 7 Hz) CH_3; 2·85 to

3·07 (m, 4 H) 2 H on $C_{(3)}$ and 2 H on $C_{(4)}$ of tetrahydroisoquinoline; 3·39 (s, 2 H) N—CH_2CO; 3·78 (s, 2 H) H on $C_{(1)}$ tetrahydroisoquinoline; 4·19 (q, 2 H, J = 7 Hz) OCH_2; 6·88—7·26 (m, 4 H) aromatic protons.

Ethyl 3-(1,2,3,4-tetrahydro-2-isoquinolyl)propanoate (*IVb*)

A solution of 12·9 g (0·1 mol) of isoquinoline in 50 ml ethanol and 20·0 g (0·11 mol) of ethyl bromopropanoate (prepared from 3-bromopropanonitrile in analogy to ref.[7]) in 50 ml of ethanol was refluxed for 80 h. After evaporation of ethanol a syrupy salt was obtained (26·1 g) which was dissolved in 50 ml of ethanol and reduced with 6·4 g (0·17 mol) of $NaBH_4$ in 150 ml of ethanol at 90°C, for 2 h. After evaporation of the mixture the product was extracted with chloroform. Distillation gave a main product with b.p. 139—144°C/13 Pa (0·1 Torr); yield 5·8 g (29·5%). For $C_{14}H_{19}NO_2$ (233·3) calculated: 72·07% C, 8·21% H, 6·00% N; found: 72·06% C, 8·29% H, 6·08% N.

Ethyl 4-(1,2,3,4-tetrahydro-2-isoquinolyl)butanoate (*IVc*)

Anhydrous K_2CO_3 (4·5 g; 0·033 ml), several crystals of KI and a solution of 5·8 g (0·03 mol) of ethyl 4-bromobutanoate[8] in 5 ml of 2-butanone were added to a solution of 4 g (0·03 mol) of 1,2,3,4-tetrahydroisoquinoline in 15 ml of 2-butanone and the mixture was refluxed under stirring for 5 h. The solid material was filtered off under suction and boiled with 2-butanone. The combined butanone filtrates were dried over $MgSO_4$ and distilled, b.p. 102—120°C/2·7 Pa (0·02 Torr); yield 4·7 g (63%). For $C_{15}H_{21}NO_2$ (247·35) calculated: 72·84% C, 8·56% H, 5·66% N; found: 72·75% C, 8·82% H, 5·59% N. ^{1}H NMR spectrum, ppm: 1·26 (t, 3 H, J = 7 Hz) CH_3; 1·93 (q, 2 H, J = 7 Hz) $NCH_2CH_2CH_2COOC_2H_5$; 2·26—3·00 (m, 8 H) 2 H on $C_{(3)}$, 2 H on $C_{(4)}$ of tetrahydroisoquinoline, NCH_2 and $CH_2COOC_2H_5$; 3·64 (s, 2 H) H on $C_{(1)}$ of tetrahydroisoquinoline; 4·11 (q, 2 H, J = 7 Hz) OCH_2; 6·90—7·26 (m, 4 H) aromatic protons.

Ethyl 5-(1,2,3,4-tetrahydro-2-isoquinolyl)pentanoate (*IVd*)

The preparation was carried out analogously as in the case of *IVc*; b.p. 119—120°C/2·7 Pa (0·02 Torr), yield 72·6%. For $C_{16}H_{23}NO_2$ (261·4) calculated: 73·53% C, 8·87% H, 5·36% N; found: 73·38% C, 8·87% H, 5·32% N. ^{1}H NMR spectrum, ppm: 1·22 (t, 3 H, J = 7 Hz) CH_3, 1·47—1·85 (m, 4 H) $NCH_2CH_2CH_2CH_2COOC_2H_5$; 2·21—2·95 (m, 8 H) H on $C_{(3)}$ and $C_{(4)}$ tetrahydroisoquinoline, NCH_2 and $CH_2COOC_2H_5$; 3·56 (s, 2 H) H on $C_{(1)}$ of tetrahydroisoquinoline; 4·07 (q, 2 H, J = 7 Hz) OCH_2; 6·91—7·27 (m, 4 H) aromatic protons.

Ethyl 6-(1,2,3,4-tetrahydro-2-isoquinolyl)hexanoate (*IVe*)

The preparation was carried out analogously as in the case of *IVc*; b.p. 137—138°C/5·5 Pa (0·04 Torr), yield 65·3%. For $C_{17}H_{25}NO_2$ (275·4) calculated: 74·14% C, 9·15% H, 5·09% N; found: 74·01% C, 9·14% H, 4·93% N. ^{1}H NMR spectrum, ppm: 1·19 (t, 3 H, J = 7 Hz) CH_3; 1·38—1·93 (m, 6 H) $NCH_2CH_2CH_2CH_2CH_2COOC_2H_5$; 2·15—2·95 (m, 8 H) H on $C_{(3)}$ and $C_{(4)}$ of tetrahydroisoquinoline, NCH_2 and $CH_2COOC_2H_5$; 3·53 (s, 2 H) H on $C_{(1)}$ of tetrahydroisoquinoline; 4·04 (q, 2 H) OCH_2; 6·87—7·21 (m, 4 H) arom. protons.

2-(1,2,3,4-Tetrahydro-2-isoquinolyl)ethanol (*Ia*)

Compound *VIa* (5·0 g; 0·023 mol) in 20 ml of diethyl ether was added dropwise to a stirred suspension of 2·3 g (0·046 mol) of 75% $LiAlH_4$ in 80 ml of diethyl ether and the mixture was refluxed

for 3 h. After decomposition with 10 ml of 4% NaOH the separated hydroxides were filtered off under suction and washed with diethyl ether. From the ethereal fractions 2·2 g (54·5%) of *Ia* were obtained, with b.p. 95–96°C/1·3 Pa (0·01 Torr). Literature[6] gives b.p. 102–107°C/0·02 Torr. ^{1}H NMR spectrum, ppm: 2·58–2·99 (m, 6 H) H on $C_{(3)}$ and $C_{(4)}$ of tetrahydroisoquinoline and NCH_2; 3·00–3·12 (s, 1 H) OH (at 60°C it is shifted to 2·86–2·97); 3·58–3·79 (m, 4 H) CH_2OH and H on $C_{(1)}$; 6·88–7·24 (m,4H) aromatic protons.

3-(1,2,3,4-Tetrahydro-2-isoquinolyl)-1-propanol (*Ib*)

The preparation was carried out analogously as in the case of *Ia*; b.p. 110°C/2 Pa (0·015 Torr), yield 30%. Lit.[9] gives b.p. 197°C/13 Torr. ^{1}H NMR spectrum, ppm; 1·58–1·90 (q, 2 H) CH_2.CH_2CH_2OH; 2·50–2·94 (m, 6 H) H on $C_{(3)}$ and $C_{(4)}$ of tetrahydroisoquinoline, NCH_2; 3·54 (s, 2 H) H on $C_{(1)}$ of tetrahydroisoquinoline; 3·48–3·78 (m, 2 H) CH_2O; 4·74 (s, 1 H) OH (shifting during heating); 6·69–7·12 (m, 4 H) aromatic H.

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

The preparation was carried out analogously as in the case of *Ia*; b.p. 115–117°C/2·7 Pa (0·02 Torr), yield 54·2%. For $C_{13}H_{19}NO$ (205·3) calculated: 76·06% C, 9·33% H, 6·82% N; found: 75·83% C, 9·43% H, 6·90% N. ^{1}H NMR spectrum, ppm: 1·44–1·96 (m, 4 H) $NCH_2CH_2CH_2$.CH_2OH; 2·24–3·04 (m, 6 H) H on $C_{(3)}$ and $C_{(4)}$ of tetrahydroisoquinoline, NCH_2; 3·43 to 3·62 (m, 2 H) CH_2O; 3·64 (s, 2 H) H on $C_{(1)}$ of tetrahydroisoquinoline; 4·94–5·71 (s, 1 H) OH (at 60°C it is shifted to 4·45–5·18); 6·86–7·28 (m, 4 H) aromatic protons. Mass spectrum: 205 (M^+, 5%), 146 ($M^+ - CH_2CH_2CH_2OH$, 100%).

5-(1,2,3,4-Tetrahydro-2-isoquinolyl)-1-pentanol (*Id*)

The preparation was carried out as in the case of *Ia*; b.p. 134–137°C/2·7 Pa (0·02 Torr), m.p. 46–49°C, yield 42%. For $C_{14}H_{21}NO$ (219·3) calculated: 76·67% C, 9·65% H, 6·39% N; found: 76·71% C, 9·84% H, 6·39% N. ^{1}H NMR spectrum, ppm: 1·25–1·80 (m, 6 H) $NCH_2CH_2CH_2$.CH_2CH_2OH; 2·41–3·17 (m, 7 H) H on $C_{(3)}$ and $C_{(4)}$ of tetrahydroisoquinoline, NCH_2 and OH; 3·45–3·57 (m, 2 H) CH_2O; 3·60 (s, 2 H) H on $C_{(1)}$ of tetrahydroisoquinoline; 6·91–7·30 (m, 4 H) aromatic protons.

6-(1,2,3,4-Tetrahydro-2-isoquinolyl)-1-hexanol (*Ie*)

a) The preparation was carried out analogously as in the case of *Ia*; b.p. 147–149°C/1·3 Pa (0·01 Torr), yield 53%.

b) Compound *VII* (3·3 g; 0·011 mol) in 20 ml of diethyl ether was added dropwise to a stirred suspension of 1·15 g of $LiAlH_4$ in 60 ml of diethyl ether and the mixture was refluxed under stirring for 3 h. Working up of the mixture gave 0·5 g (19%) of *Ie*, b.p. identical as under *a*). For $C_{15}H_{23}NO$ (223·4) calculated: 77·21% C, 9·93% H, 6·00% N; found: 77·42% C, 10·03% H, 6·09% N. ^{1}H NMR spectrum, ppm: 1·10–1·91 (m, 8 H) $NCH_2CH_2CH_2CH_2CH_2CH_2OH$; 2·25 (s, 1 H) OH (at 60°C it is shifted to 1·88); 2·38–3·07 (m, 6 H) H on $C_{(3)}$ and $C_{(4)}$, NCH_2; 3·45 to 3·81 (m, 4 H) H on $C_{(1)}$ of tetrahydroisoquinoline, CH_2O, 6·91–7·24 (m, 4 H) aromatic H.

1-(1,2,3,4-Tetrahydro-2-isoquinolyl)-2-propanol (*II*)

A solution of 0·8 g (0·004 mol) of *V* in 10 ml of tetrahydrofuran was added dropwise to a stirred suspension of 0·2 g (0·004 mol) of 70% $LiAlH_4$ in 15 ml of tetrahydrofuran and the mixture was

refluxed under stirring for 3 h. Working up of the mixture gave 0·3 g (40%) of *II*, b.p. 142°C/2·0 kPa (15 Torr). For $C_{12}H_{17}NO$ (191·3) calculated: 75·35% C, 8·96% H, 7·32% N; found: 75·08% C, 9·16% H, 7·27% N. ^{1}H NMR spectrum, ppm: 1·18 (d, 2 H, J = 7 Hz) CH_3; 2·20—2·54 (m, 2 H) H on $C_{(4)}$ of tetrahydroisoquinoline; 2·57—3·12 (m, 4 H) H on $C_{(3)}$ of tetrahydroisoquinoline, NCH_2; 3·32 (s, 1 H) OH; 3·54 (d, 1 H, J = 13 Hz) and 3·78 (d, 1 H, J = 13 Hz) H on $C_{(1)}$ of tetrahydroisoquinoline; 3·76—4·10 (m, 1 H) CHOH; 6·86—7·12 (m, 4 H) aromatic protons.

3-(1,2,3,4-Tetrahydro-1-quinolyl)-1-propanol (*IIIa*)

This was prepared by reduction of *IIIb*, analogously as *Ia*; b.p. 115°C/1·3 Pa (0·01 Torr), yield 76%. Literature[10] gives b.p. 227—229°C/18 Torr. ^{1}H NMR spectrum, ppm: 1·63—2·01 (m, 5 H) H on $C_{(3)}$ of tetrahydroquinoline, $CH_2CH_2CH_2OH$; 2·57—2·77 (t, 2 H) H on $C_{(4)}$ of tetrahydroquinoline; 3·08—3·37 (m, 4 H) and 3·54—3·67 (m, 2 H) $CH_2CH_2CH_2OH$, H on $C_{(2)}$ of tetrahydroquinoline; 6·30—6·54 and 6·66—7·07 (2 m, 4 H) aromatic protons.

The elemental analyses were carried out in the analytical department (head Dr L. Helešic) and the NMR *spectra measured under the direction of Dr P. Trška.*

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