REDUCTION OF 1-ISOQUINOLYL-DIMETHYLMETHANOL AND 1-(1-ISOQUINOLYL)CYCLOHEXANOL*

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Reduction of alcohols *Ia* and *IIa* with zinc and formic acid afforded 1-isopropylisoquinoline (*Ib*) and 1-cyclohexylisoquinoline (*IIb*), respectively, reduction with sodium in 1-butanol led to the 1,2,3,4-tetrahydroisoquinoline derivatives *III*, *IV* and *Va* and electrolytical reduction gave 1-isopropyl-1,2,3,4-tetrahydroisoquinoline (*Vd*) and the 1-cyclohexyl derivative *Ve*, respectively.

Within the framework of synthetic investigations aimed at the preparation of 1,2,3,4-tetrahydroisoquinoline alcohols as potential drugs we studied the reduction of 1-isoquinolyl-dimethylmethanol (*Ia*) and 1-(1-isoquinolyl)cyclohexanol (*IIa*) which are easily accessible from 2-benzoyl-1-cyano-1,2-dihydroisoquinoline[1] and acetone or cyclohexanone[2].

Reduction of *Ia* and *IIa* with zinc and formic acid gave small amount of product which after chromatography afforded 1-isopropylisoquinoline (*Ib*) and 1-cyclohexylisoquinoline (*IIb*), respectively. The alcohols thus behave analogously to the pyridine alcohols which afford corresponding alkylpyridines[3].

Reduction of *Ia* and *IIa* with sodium in boiling 1-butanol led to 1,2,3,4-tetrahydroisoquinoline derivatives, *i.e.* dimethyl-(1,2,3,4-tetrahydro-1-isoquinolyl)methanol (*III*) and 1-(1,2,3,4-tetrahydro-1-isoquinolyl)cyclohexanol (*IV*). The reduction of the alcohol *Ia* afforded, in addition to *III*, also 1,2,3,4-tetrahydroisoquinoline (*Va*) which was obtained in the form of its 2-(4-toluenesulfonyl) derivative *Vb*. The compound *Va* arises most probably by reduction of isoquinoline, formed by cleavage of the alcohol *Ia* with sodium butoxide. Electrolytic reduction of *Ia* on lead electrodes in dilute sulfuric acid gave only one product which was shown to be 1-isopropyl-1,2,3,4-tetrahydroisoquinoline (*Vd*). Analogously we obtained 1-cyclohexyl-1,2,3,4-tetrahydroisoquinoline (*Ve*) from the compound *IIa*.

The literature offers a comparison with analogous reductions of dimethyl-2-pyridylmethanol and dimethyl-2-quinolylmethanol. Reduction of the first alcohol with sodium in ethanol afforded a mixture of dimethyl-2-piperidylmethanol and 2-iso-

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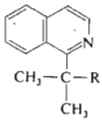

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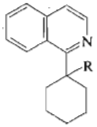
Ib, R = H



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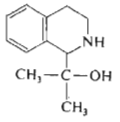
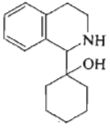
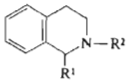
IIb, R = H



III



IV



Va, R^1, R^2 = H
Vb, R^1 = H, R^2 = $SO_2C_7H_7$
Vc, R^1 = $(CH_3)_2CH$, R^2 = $SO_2C_7H_7$
Vd, R^1 = $(CH_3)_2CH$, R^2 = H
Ve, R^1 = C_6H_{11}, R^2 = H

propylpiperidine[4] whereas electrolytic reduction gave a mixture of 2-isopropylpiperidine and 6-isopropyl-3-piperideine[5]. Dimethyl-2-quinolylmethanol was reduced electrochemically to 2-isopropylquinoline[6]. Our results show that reduction of the alcohols *Ia* and *IIa* with zinc and formic acid removes only the hydroxy group, sodium in butanol reduces only the pyridine part of the molecule whereas the electrolytic reduction affects both the pyridine nucleus and the hydroxyl group.

EXPERIMENTAL

Column chromatography was carried out on Silpearl UV 254, thin-layer chromatography on Silufol UV 254 and 366 sheets (aluminium foil with silica gel, containing a luminiscence indicator; binder starch). Spots were detected with a Universal UV-Lampe Camag (Muthenz, Switzerland) at 254 or 366 nm or with iodine vapour. The IR spectra were taken in chloroform on a Perkin–Elmer 325 spectrophotometer, ^{1}H-NMR spectra on a Varian XL-100-15 instrument (100·1 MHz) at 37°C or on a Tesla BS 477 instrument (60 MHz) at 27°C, internal standard tetramethylsilane. The temperature data are uncorrected.

Reduction of Dimethyl-1-isoquinolylmethanol (*Ia*) with Zinc and Formic Acid

A mixture of the alcohol *Ia* (2·0 g; 0·011 mol), zinc powder (13·2 g) and 98% formic acid (20 ml) was refluxed for 11 h, made alkaline and the product was taken up in ether. The usual work-up procedure afforded 1·52 g of product, boiling at 128—133°C/4 kPa. Since the fraction was not homogeneous (thin-layer chromatography), it was chromatographed on silica gel L 100/160 μ (200 g). Elution with ethyl acetate afforded 0·72 g (39·4%) of *Ib*, b.p. 135°C/4 kPa, picrate, m.p. 216—217°C (ref.[7,8] reports m.p. 215—217°C).

The reduction of 1-(1-isoquinolyl)cyclohexanol (*IIa*) was carried out analogously: 3·0 g (0·013 mol) of *IIa* gave 0·21 g of the product *IIb*, boiling at 107°C/10·7 Pa. ^{1}H-NMR spectrum

($CDCl_3$, δ): 1·0—2·35 (m, 10 H) cyclohexane CH_2; 7·2—8·5 (m, 6 H) aromatic protons; 3·60 (m, 1 H) cyclohexane CH. The spectrum agrees with that[9] of *IIb*.

Reduction of Dimethyl-1-isoquinolylmethanol (*Ia*) with Sodium in 1-Butanol

The alcohol *Ia* (5·61 g; 0·03 mol) was reduced with sodium (8·3 g) in boiling 1-butanol (100 ml). After dissolution of the sodium the mixture was heated and steam-distilled. The distillate was acidified with hydrochloric acid, the aqueous layer separated, made alkaline and extracted with chloroform. The usual isolation afforded 2·5 g of an oil which deposited crystals of the product *III*, m.p. 77—81°C (ethanol). For $C_{12}H_{17}NO$ (191·3) calculated: 75·35% C, 8·96% H, 7·32% N; found: 75·20% C, 8·94% H, 7·22% N. IR spectrum ($CHCl_3$): 3370 cm^{-1} ν(OH).

Mother liquors (1·7 g) from crystallization of *III* were mixed with 10% NaOH (34 ml) and *p*-toluenesulfonyl chloride (3·4 g) was added. After brief heating on a water bath the mixture was acidified with hydrochloric acid and the separated product *Vb* (1·2 g) was crystallized from ethanol, m.p. 144—145·5°C (reported[10] m.p. 142°C). For $C_{16}H_{17}NO_2S$ (287·4) calculated: 66·97% C, 5·96% H, 4·87% N, 11·15% S; found: 66·61% C, 6·02% H, 5·17% N, 11·10% S. ^{1}H-NMR spectrum ($CDCl_3$, δ): 1·94 (s, 3 H) CH_3—C_6H_4; 2·28—2·60 (m, 2 H) CH_2 (position 3); 2·9 (t, 2 H, J = 4 Hz) CH_2 (position 4); 3·78 (s, 2 H) CH_2 (position 1); 6·34—7·46 (m, 8 H) aromatic protons.

Reduction of 1-(1-isoquinolyl)cyclohexanol (*IIa*) (4·54 g; 0·02 mol) with sodium in 1-butanol was carried out in an analogous manner as described in the preceding experiment. Chloroform extraction of the solution, remaining after steam-distillation, afforded 2 g of an oil, b.p. 110 to 125°C/6·4 Pa, which on cooling deposited 1·5 g (32·5%) of the product *IV*, m.p. 87—89°C (cyclohexane). For $C_{15}H_{21}NO$ (231·3) calculated: 77·88% C, 9·15% H, 6·05% N; found: 78·04% C, 9·35% H, 5·93% N. ^{1}H-NMR spectrum ($CDCl_3$, δ): 0·86—1·9 (m, 10 H) $(CH_2)_5$; 2·4—3·44 (m, 6 H) 2 CH_2 (position 3, 4), OH, NH; 3·84 (s, 1 H) CH (position 1); 6·94—7·28 (m, 4 H) aromatic protons.

Electrolytic Reduction of 1-Isoquinolyl-dimethylmethanol (*Ia*)

A solution of the alcohol *Ia* (6·53 g; 0·035 mol) in 20% sulfuric acid (150 ml) was reduced on lead electrodes with constant current 3·5 A (total 11·25 Ah, *i.e.* 200% of the amount of electricity required for the reduction to *Vd*). The catholyte was made alkaline and the mixture was extracted with ether and chloroform. The extracts afforded a mixture which on distillation gave 2·05 g (33·5%) of *Vd*, b.p. 103—104°C/1·1 kPa. For $C_{12}H_{17}N$ (175·3) calculated: 82·23% C, 9·78% H, 7·99% N; found: 82·42% C, 9·89% H, 7·93% N. ^{1}H-NMR spectrum ($CDCl_3$, δ): 0·7 and 1·07 (d, 3 H, J = 8 Hz) 2 CH_3; 2·08—2·56 (m, 1 H) $(CH_3)_2CH$; 2·56—3·40 (m, 4 H) CH_2 (position 3,4); 3·8—3·97 (d, 1 H, J = 3 Hz) CH (position 1); 6·94—7·32 (m, 4 H) aromatic protons. *p*-Toluenesulfonyl derivative, m.p. 112—114°C (ethanol). (For product obtained by Pictet-Spengler reaction, reported[11] m.p. 76°C.) For $C_{19}H_{23}NO_2S$ (329·5) calculated: 69·27% C, 7·04% H, 4·25% N, 9·73% S; found: 69·23% C, 7·07% H, 4·56% N, 9·57% S. ^{1}H-NMR spectrum ($CDCl_3$, δ): 0·95 and 1·10 (d, 3 H, J = 7 Hz) 2 CH_3; 1·92—2·14 (m, 1 H) $(CH_3)_2CH$; 2·27 (s, 3 H) CH_3—C_6H_4; 2·62 (t, 2 H, J = 7 Hz) CH_2 (position 3); 3·64 (t, 3 H, J = 7 Hz) CH_2 (position 4); 4·54 (d, 1 H, J = 7 Hz) CH (position 1); 6·66—7·58 (m, 8 H) aromatic protons.

Electrolytic reduction of 1-(1-isoquinolyl)cyclohexanol (*IIa*) (6·45 g; 0·03 mol) was carried out analogously as described for *Ia*, affording 4·8 g of a yellow oil, b.p. 115—125°C/20 Pa. This was subjected to chromatography (Silpearl UV 254; chloroform–ethanol) and gave 3·05 g of *IIa* and 1 g of *IIb*, b.p. 117—120°C/13·3 Pa. For $C_{15}H_{21}N$ (215·3) calculated: 83·67% C, 9·83% H, 6·50% N; found: 83·43% C, 9·73% H, 6·47% N. ^{1}H-NMR spectrum ($CDCl_3$, δ): 1·0—1·98 (m,

11 H) $(CH_2)_5$, NH; 2·6—3·34 (m, 4 H) 2 CH_2 (positions 3 and 4); 3·65—4·0 (m, 1 H) CH (position 1); 6·98—7·4 (m, 4 H) aromatic protons.

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