ELECTROLYTIC AND ZINC AND FORMIC ACID REDUCTIONS OF DIMETHYL-2-QUINOLYL- AND DIMETHYL-4-QUINOLYLMETHANOL

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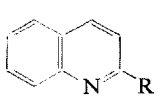
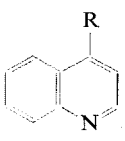
Electrolytic reductions of the mentioned alcohols afford corresponding isopropylquinolines and in the case of the reduction of dimethyl-4-quinolylmethanol also 4-isopropyl-1,2,3,4-tetrahydroquinoline. Reduction with zinc and formic acid gives corresponding 1-formyl-isopropyl--1,2,3,4-tetrahydroquinoline and in the case of dimethyl-4-quinolylmethanol also 1-methyl--4-isopropyl-1,2,3,4-tetrahydroquinoline, 4-isopropyl-1,2,3,4-tetrahydroquinoline, and 4-isopropyl-5,6,7,8-tetrahydroquinoline. The electrolytic as well as sodium borohydride reduction of the quaternary salt of dimethyl-4-quinolylmethanol is also described.

In preceding papers we have described the reductions of dimethylpyridylmethanols both electrolytically[1] and with zinc and formic acid[2]. Electrolytic reduction carried out on lead electrodes in dilute sulfuric acid at constant current affords a mixture of isopropylpiperidines and isopropyl-3-piperideines[1].

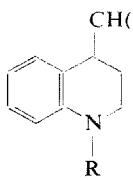
Similar electrolytic reduction of dimethyl-2-quinolylmethanol (*Ia*) gives 2-isopropylquinoline (*Ib*). On electrolytic reduction of dimethyl-4-quinolylmethanol (*IIa*) we obtained, under similar conditions, a mixture of 4-isopropylquinoline (*IIb*) and 4-isopropyl-1,2,3,4-tetrahydroquinoline (*IIIa*). The structure of the base *IIIa* was determined on the basis of analytical and spectral evidence. Further we carried out electrolytic reduction of dimethyl-4-quinolylmethanol methomethyl sulfate, resulting in a mixture of 1-methyl-4-isopropyl-1,2,3,4-tetrahydroquinoline (*IIIb*) and the base *IIIa*. The reduction of tertiary alcohols of the pyridine series with zinc and formic acid was found suitable for the preparation of corresponding alkylpyridines[2]. A similar reduction of alcohol *Ia* gives a mixture in which we proved



Ia, R = $(CH_3)_2C(OH)$
Ib, R = $(CH_3)_2CH$



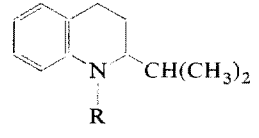
IIa, R = $(CH_3)_2C(OH)$
IIb, R = $(CH_3)_2CH$



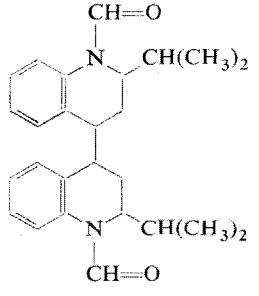
IIIa, R = H
IIIb, R = CH_3
VI, R = CHO

1-formyl-2-isopropyl-1,2,3,4-tetrahydroquinoline (*IVa*) and 1,1′-diformyl-2,2′-diisopropyl-4,4′-bis-1,2,3,4-tetrahydroquinoline (*V*) on the basis of analytical and spectral evidence. Formyl derivative *IVa* was reduced with lithium aluminum hydride to the known[3] 1-methyl-2-isopropyl-1,2,3,4-tetrahydroquinoline (*IVb*).

Reduction of the alcohol *IIa* with zinc and formic acid gives four products which were separated chromatographically and identified as 1-formyl-4-isopropyl-1,2,3,4-tetrahydroquinoline (*VI*), 1-methyl-4-isopropyl-1,2,3,4-tetrahydroquinoline (*IIIb*), 4-isopropyl-1,2,3,4-tetrahydroquinoline (*IIIa*), and 4-isopropyl-5,6,7,8-tetrahydroquinoline (*VII*).

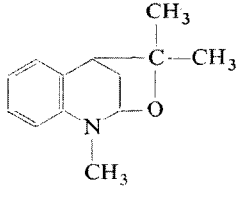


IVa, R = CHO
IVb, R = CH_3

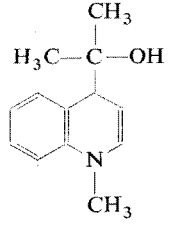


V

VII



VIII



IX

Eventually we carried out the reduction of dimethyl-4-quinolylmethanol methiodide with sodium borohydride, obtaining a product to which we assigned on the basis of analytical and spectral data the structure of 1,4,4-trimethyl-1,2,4,5-tetrahydro-2,5-methano-3,1-benzoxazepine (*VIII*). Its formation may be explained by the primary formation of 1,4-dihydro derivative *IX*.

EXPERIMENTAL

Gas chromatography was carried out on a Chrom II apparatus (column length 170 cm, diameter 0·6 cm, 20% Tridox on Celite, nitrogen as carrier gas). The ^{1}H-NMR spectra were measured on a Varian XL-100-15 (100·1 Mc) instrument in deuteriochloroform and tetrachloromethane

with tetramethylsilane as internal standard. The IR spectra were measured on a Perkin-Elmer Model 325 in chloroform and tetrachloromethane, and the UV spectra on an Optica Milano CS 4 NI spectrophotometer, in ethanol. The mass spectra were measured on a Gas Chromatograph-Mass Spectrometer LKB 9000 Produkter AB Stockholm.

Electrolytic Reduction of 2-Quinolyldimethylmethanol (*Ia*)

A solution of 5·7 g (0·03 mol) of compound *Ia* (ref.[4]) in 100 ml of 20% sulfuric acid was submitted to electrolytic reduction on lead cathode (2·5 hours, 10 Ah, 200%). The catholyte was filtered, alkalized with 40% sodium hydroxide and the products were extracted with chloroform. After drying the extract with $MgSO_4$ chloroform was distilled off to give 4·3 g (75%) of a mixture with b.p. 76—90°C/0·7 Torr. Thin-layer chromatography (Silufol, ethyl acetate–cyclohexane 1 : 2) enabled the identification of two components, with R_F 0·44 and 0·61. The first was the starting alcohol *Ia*. Comparison with a standard indicated that the second was 2-isopropylquinoline (*Ib*). Gas chromatography showed that the mixture contained 75% of the original alcohol and 25% of the 2-isopropylquinoline.

2-Isopropylquinoline (*Ib*)

A mixture of 11·4 g (0·06 mol) of compound *Ia*, 110 ml of 56% hydriodic acid, and 3·5 g of red phosphorus was stirred and heated on a water bath for 15 hours. Zinc powder (20 g) was then added and the mixture stirred at room temperature for 1·5 hours. The filtrate was alkalized with 10% sodium hydroxide and extracted with chloroform, and the extract dried over $MgSO_4$. Distillation gave 8·5 g (75%) of a mixture, b.p. 68°C/0·7 Torr, containing 86% of 2-isopropylquinoline (*Ib*) and 14% of 2-quinolyldimethylmethanol (*Ia*) (gas chromatography). Fractional distillation gave 2-isopropylquinoline[5], b.p. 82°C/0·7 Torr.

Reduction of Alcohol *Ia* with Zinc and Formic Acid

A mixture of 11 g (0·058 mol) of compound *Ia* and 100 ml of 98% formic acid was refluxed at 170°C bath temperature for 2 hours. Zinc (75 g; 1·15 mol) was then added and the mixture refluxed for 2·5 hours. Finally 30 ml of formic acid were added and the refluxing continued for 13 hours. After cooling the mixture was alkalized with 40% sodium hydroxide and the alkaline suspension extracted with ether and the extract dried over magnesium sulfate. After evaporation of ether 1,1′-diformyl-2,2′-diisopropyl-4,4′-bis-1,2,3,4-tetrahydroquinoline (*V*) (0·16 g) separated, m.p. 256°C (ethanol). Mass spectrum: $M^+ = 404$. For $C_{26}H_{32}N_2O_2$ (404·6) calculated: 77·19% C, 7·97% H, 6·93% N; found: 76·97% C, 8·17% H, 6·81% N. ^{1}H-NMR spectrum (δ-values): 0·74—0·82 (d, d, 12 H, 7 Hz) $(C\underline{H}_3)_2CH$; 1·70—1·76 (m, 4 H) CH_2(3); 1·94—2·32 (m, 2 H) $C\underline{H}(CH_3)_2$; 2·84—2·98 (m, 2 H) CH (4); 4·42—4·69 (m, 2 H) CH (2); 7·16—7·30 (m, 8 H) aromatic; 8·59 (s, 2 H) C$\underline{H}$=O. IR spectrum (cm^{-1}): 1 660 (s) ν(NCHO).

Distillation of the liquid residue gave 5 g (43%) of 1-formyl-2-isopropyl-1,2,3,4-tetrahydroquinoline (*IVa*), b.p. 98°C/1 Torr. Mass spectrum: $M^+ = 203$. For $C_{13}H_{17}NO$ (203·3) calculated: 76·81% C, 8·43% H, 6·89% N; found: 76·60% C, 8·71% H, 6·88% N. ^{1}H-NMR spectrum (δ-values): 0·87—0·94 (d, d, 6 H, 4 Hz) $(C\underline{H}_3)_2CH$; 1·67—2·09 (m, 3 H) CH_2 (3) and $C\underline{H}(CH_3)_2$; 2·67—2·89 (m, 2 H) CH_2 (4); 4·33—4·56 (m, 1 H) CH (2), 7·00—7·23 (m, 4 H) aromatic; 8·65 (s, 1 H) C$\underline{H}$=O. IR spectrum (cm^{-1}): 1 660 (s), ν(NCHO).

1-Methyl-2-isopropyl-1,2,3,4-tetrahydroquinoline (*IVb*)

A solution of 2·5 g (0·012 mol) of compound *IVa* in 10 ml of diethyl ether was added to a suspension of 1·4 g (0·037 mol) of lithium aluminum hydride in 15 ml of diethyl ether dropwise under stirring and the mixture was refluxed for 14 hours. After decomposition according to ref.[6] the filtrate was dried over potassium carbonate. Distillation gave 1·3 g (98%) of product, b.p. 80°C/0·7 Torr. Literature[3] gives b.p. 265—266°C. ^{1}H-NMR spectrum (δ-values): 0·81, 0·89 (d, d, 6 H, 7 Hz) $CH(C\underline{H}_3)_2$; 1·54—2·08 (m, 3 H) $C\underline{H}(CH_3)_2$ and CH_2 (3), 2·54—3·00 (m, 3 H) $C\underline{H}$ (2) and CH_2 (4); 2·95 (s, 3 H) $NC\underline{H}_3$; 6·42—7·10 (m, 4 H) aromatic. IR spectrum (cm^{-1}): 2800 $\nu(CH_3)$ in NCH_3.

4-Quinolyldimethylmethanol (*IIa*)

Ethyl cinchoninate[7] (50·7 g; 0·252 mol) in 210 ml of diethyl ether was added dropwise under stirring to an ethereal solution of methylmagnesium iodide prepared from 15·2 g (0·63 mol) of magnesium and 89·5 g (0·63 mol) of methyl iodide. The mixture was refluxed for 2 hours. After decomposition by pouring it onto ice 65 ml of 98% acetic acid were added under stirring and the mixture was alkalized with 40% sodium hydroxide. The ethereal layer was separated and the aqueous layer extracted with chloroform. Both organic layers were washed with saturated sodium hydrogen sulfite solution, sodium hydrogen carbonate solution and eventually with water. After drying both extracts over $MgSO_4$ and evaporation of the solvent, solid materials precipitated which were identical in both cases. Yield 31·6 g (67%), m.p. 150—151°C (benzene). For $C_{12}H_{13}NO$ (187·3) calculated: 76·98% C, 7·00% H, 7·48% N; found: 77·11% H, 7·21% H, 7·58% N. ^{1}H-NMR spectrum (δ-values): 1·83 (s, 6 H) $(C\underline{H}_3)_2C(OH)-$; 3·72 (s, 1 H) $O\underline{H}$; 7·31 to 8·95 (m, 6 H) aromatic. IR spectrum (cm^{-1}): 3600, 3250 ν(OH), 1150 δ(OH).

4-Quinolyldimethylmethanol Methiodide

A mixture of 3·7 g (0·020 mol) of 4-quinolyldimethylmethanol, 3·24 g (0·022 mol) of methyl iodide, and 50 ml of methanol was refluxed for 14 hours. Distillation off of the volatile components gave 3·5 g (54%) of product, m.p. 202—203°C (acetone–methanol). For $C_{13}H_{16}INO$ (312·3) calculated: 47·43% C, 4·90% H, 38·55% I, 4·26% N; found: 47·70% C, 5·00% H, 38·26% I, 3·97% N.

Electrolytic Reduction of 4-Quinolyldimethylmethanol (*IIa*)

A solution of 4 g (0·021 mol) of alcohol *IIa* in 200 ml of 20% sulfuric acid was reduced in an electrolyser with lead electrodes (5 hours, 17·5 Ah, 500%). The catholyte was filtered under suction, alkalized with 40% sodium hydroxide and extracted with chloroform. After drying over magnesium sulfate the extract was worked up and distilled to give 3·5 g of crude product. Thin-layer chromatography on Silufol (benzene–methanol 9 : 1) helped to identify two main components with R_F 0·5 and 0·77. The third, smaller spot was found to be identical with the starting *IIa*. Column chromatography on alumina (activity II/III according to Brockmann) gave: 4-isopropyl-1,2,3,4-tetrahydroquinoline (*IIIa*), R_F 0·5, b.p. 82°C/0·8 Torr. Mass spectrum: M^+ = = 175. For $C_{12}H_{17}N$ (175·3) calculated: 82·23% C, 9·77% H, 7·99% N; found: 82·54% C, 9·79% H, 8·26% N. ^{1}H-NMR spectrum (δ-values): 0·86, 0·97 (d, d, 6 H, 6 Hz) $CH(C\underline{H}_3)_2$; 1·70—2·20 (m, 3 H) $C\underline{H}(CH_3)_2$ and CH_2 (3); 2·40—2·64 (m, 1 H) CH (4); 3·12—3·38 (m, 2 H) CH_2 (2); 3·64 (s, 1 H) NH; 6·36—7·02 (m, 4 H) aromatic. IR spectrum (cm^{-1}): 3440 ν(NH), 2920, 2850 $\nu(CH_2)$, 1380 $\delta(CH_3)$. 4-Isopropylquinoline (*IIb*), R_F 0·77, b.p. 96°C/0·5 Torr. For $C_{12}H_{13}N$ (171·3) calculated: 84·17% C, 7·65% H, 8·18% N; found: 84·02% C, 7·95% H, 8·16% N.

^{1}H-NMR spectrum (δ-values): 1·35 (d, 6 H, 6 Hz) $CH(C\underline{H}_3)_2$; 3·68 (q, 1 H, 7 Hz) $C\underline{H}(CH_3)_2$; 7·24 (d, 1 H, 3 Hz) CH (3); 7·38–8·17 (m, 4 H) aromatic, 8·79 (d, 1 H, 4 Hz) CH (2).

Picrate, m.p. 172°C (acetone–methanol). Literature[8] gives m.p. 172–173°C.

Reduction of Alcohol *IIa* with Zinc and Formic Acid

A mixture of 3·5 g (0·019 mol) of alcohol *IIa* and 30 ml of 98% formic acid was refluxed at 160°C for two hours. Zinc powder (25 g, 0·384 mol) was then added and refluxing was continued for another 2·5 hours. Finally formic acid was added (20 ml) and the mixture refluxed for an additional 10 hours. After cooling the liquid was decanted, zinc boiled with water, and the liquid materials combined and alkalized with 40% NaOH. After extraction with ether the extract was dried over $MgSO_4$, ether was distilled off and the residue chromatographed on thin layer (Silufol, benzene–chloroform 1 : 1) for identification. Four components were identified with R_F values 0·73, 0·62, 0·44 and 0·20. The reaction mixture (2·5 g) was separated by column chromatography on silica gel. For elution benzene was used first, followed by its mixtures with increasing amounts of chloroform. The following products were isolated: 1-Methyl-4-isopropyl-1,2,3,4-tetrahydroquinoline (*IIIb*), R_F 0·73, b.p. 89°C/1·5 Torr, mass spectrum $M^+ = 189$. For $C_{13}H_{19}N$ (189·3) calculated: 82·48% C, 10·12% H, 7·40% N; found: 82·61% C, 10·17% H, 7·62% N. ^{1}H-NMR spectrum (δ-values): 0·87, 0·93 (d, d, 6 H, 3 Hz) $CH(C\underline{H}_3)_2$; 1·70–2·10 (m, 3 H) $C\underline{H}(CH_3)_2$ and CH_2 (3); 2·24–2·52 (m, 1 H) CH (4); 2·84 (s, 3 H) $NC\underline{H}_3$; 2·94–3·42 (m, 2 H) $C\underline{H}_2$ (2); 6·30–7·00 (m, 4 H) aromatic. IR spectrum (cm^{-1}): 2960, 2870 $\nu(CH_3)$, 2930, 2840 $\nu(CH_2)$, 2800 $\nu(CH_3)$ in NCH_3, 1600, 1500 ν(C=C) aromatic nucleus, 1380 $\delta(CH_3)$. 1-Formyl-4-isopropyl-1,2,3,4-tetrahydroquinoline (*VI*), R_F 0·44, m.p. 130°C/10 Torr. For $C_{13}H_{17}NO$ (203·3) calculated: 76·81% C, 8·42% H, 6·89% N; found: 76·56% C, 8·70% H, 7·00% N. Mass spectrum: $M^+ = 203$. ^{1}H-NMR spectrum (δ-values): 0·88, 0·95 (s, s, 6 H) $CH(C\underline{H}_3)_2$; 1·70 to 2·30 (m, 3 H) $C\underline{H}(CH_3)_2$ and CH_2 (3); 2·42–2·66 (m, 1 H) CH (4); 3·20–4·12 (m, 2 H) CH_2 (2) AB system: $H_1 = 4·02$, $H_2 = 3·60$. 7·06–7·20 (m, 4 H) aromatic; 8·75 (s, 1 H) CH=O. IR spectrum (cm^{-1}): 1675 ν(NCHO), 1600, 1580, 1500 ν(C=C) on aromatic nucleus. 4-Isopropyl-5,6,7,8-tetrahydroquinoline (*VII*), R_F 0·20, b.p. 122°C/10 Torr. Mass spectrum: $M^+ = 175$. ^{1}H-NMR spectrum (δ-values): 1·17–1·23 (s, s, 6 H) $CH(C\underline{H}_3)_2$; 1·60–1·97 (m, 4 H) $C\underline{H}_2C\underline{H}_2$ (6 and 7); 2·40–3·20 (m, 5 H) $C\underline{H}(CH_3)_2$ and $C\underline{H}_2CH_2$ (5 and 8); 6·84 (d, 1 H, 6 Hz) CH (3); 8·15 (d, 1 H, 5 Hz) CH (2). IR spectrum (cm^{-1}): 2960, 2870 $\nu(CH_3)$, 2930, 2830 $\nu(CH_2)$, 1580, 1560 ν(C=N) in heterocycle, 1380 $\delta(CH_3)$. The component (R_F 0·62) was identified as 4-isopropyl-1,2,3,4-tetrahydroquinoline (*IIIa*, see p. 761).

Electrolytic Reduction of 4-Quinolyldimethylmethanol Methomethyl Sulfate

A mixture of 3 g (0·016 mol) of 4-quinolyldimethylmethanol, 2·1 g (0·017 mol) of dimethyl sulfate, and 50 ml of methanol was refluxed for 14 hours on a water bath. After distillation off of the volatile components and cooling 4·9 g (97·8%) of crystalline product were obtained, which became fluid in air.

A solution of 5·3 g (0·017 mol) of the quaternary salt in 200 ml of 20% sulfuric acid was reduced in an electrolyser with lead electrodes (2 hours, 11·5 Ah, 500%). The catholyte was alkalized with 40% sodium hydroxide solution, extracted with chloroform, and the chloroform layer separated and dried over $MgSO_4$. Distillation of the residue gave 1·2 g of product, b.p. 98°C/1·5 Torr. Using thin layer chromatography on alumina (act. II–III according to Brockmann) in benzene–heptane 1 : 1 the presence of two components of R_F 0·77 and 0·27 was demonstrated. The mixture was separated by column chromatography under the same conditions. Both above mentioned substances were obtained and identified: *IIIb* (R_F 0·77) and *IIIa* (R_F 0·27).

Reduction of 4-Quinolyldimethylmethanol Methiodide with Sodium Borohydride

A solution of 0·5 g of sodium hydroxide in 30 ml of water was added to a solution of 3·5 g (0·011 mol) of the quaternary salt in 30 ml of warm water and sodium borohydride (1 g, 0·024 mol) dissolved in 15 ml of water was then added dropwise to the mixture. The mixture was stirred at room temperature for 30 minutes, at 60°C for 40 minutes, and again at room temperature for one hour. After extraction with chloroform the organic layer was dried over $MgSO_4$ and analysed by thin-layer chromatography on alumina (act. II—III according to Brockmann) in benzene–methanol 10 : 1. Two spots appeared. That with R_F 0·82 prevailed. The second component, R_F 0·31, corresponded to alcohol *IIa*. The mixture was separated by column chromatography on alumina (act. II—III, benzene as eluent.) The product of R_F 0·82 was identified as 1,4,4-trimethyl-1,2,4,5-tetrahydro-2,5-methano-3,1-benzoxazepine (*VIII*), b.p. 76—78°C/0·6 Torr. For $C_{13}H_{17}NO$ (203·3) calculated: 76·81% C, 8·48% H, 6·89% N; found: 76·52% C, 8·47% H, 7·18% N. Mass spectrum: $M^+ = 203$. ^{1}H-NMR spectrum (δ-values): 1·02, 1·26 (s, s, 6 H) $CH(C\underline{H}_3)_2$; 2·04—2·60 (m, 2 H) CH_2 (3), 2·70 (d, 1 H, 4 Hz) CH (4); 2·94 (s, 3 H) $NC\underline{H}_3$; 4·90 (d, 1 H, 5 Hz) CH (2); 6·48—7·16 (m, 4 H) aromatic, CH_2 (3) AB system: H (3′) 2·14, H (3) 2·46, $J_{3,3'}$ 11 Hz, $J_{2,3}$ 5 Hz, $J_{2,3'}$ 0, $J_{4,3}$ 4 Hz, $J_{4,3'}$ 0. UV spectrum (nm, ethanol): 258, 296, IR spectrum (cm^{-1}): 1045 (s), 1082 (s) ν(C—O—C).

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