REDUCTION OF 2-, 3- AND 4-ACETYLQUINOLINES BY TRIETHYLAMMONIUM FORMATE

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The reduction of 2-, 3- and 4-acetylquinolines (*Ia–c*) by triethylammonium formate affects both the pyridine part of the quinoline nucleus and the carbonyl groups, giving rise to products *II–VI*.

A previous paper[1] dealt with the reduction of acids of the quinoline series by triethylammonium formate. As a sequel to this study we now describe reduction of 2-, 3- and 4-acetylquinolines by the same agent. In all experiments 1-formyl-C-ethyl--1,2,3,4-tetrahydroquinolines (*IIa–c*) were isolated. In addition to these products of reduction of the acetyl group and the pyridine part of the molecule we obtained other ones. 2-Acetylquinoline (*Ia*) gave 2-quinolone (*III*), arising probably by a nucleophilic attack of the formate anion on position 2 with the simultaneous elimination of the acetyl group, and 1-(2-quinonyl) ethanol (*Id*). 4-Acetylquinoline (*Ic*) gave the tetrahydro derivative *IIc*, 4-ethylquinoline (*Ie*) and 4-ethyl-1-formyl-1,2-dihydroquinoline (*IVb*). The reaction course was most complex in the reduction of 3-acetylquinoline (*Ib*); in addition to *IIb* we identified the product of the 1,4-addition (*V*) and products *IId-f*, *IVa* and *VI*. *IIf* appeared to be a mixture of two diastereoisomers (^{1}H-NMR analysis). Separate reductions of 3-acetyl-1,4-dihydroquinoline (*V*) and 3-acetyl-1-formyl-1,2,3,4-tetrahydroquinoline (*IId*) gave the same products as the reduction of 3-acetylquinoline (*Ib*). Hence it can be judged that the reduction of *Ib* also proceeds *via* the 1,4-dihydro product *V*. The primary attack on the pyridine part of the quinoline skeleton is probably followed very closely by reduction of the carbonyl group, producing the corresponding quinolylethanol or ethylquinoline. Further stage of the reduction affects the quinoline nucleus at position 2 or 4, leading finally to the 1,2-dihydroquinoline derivatives *IVa–b*, or the 1,2,3,4-tetrahydroquinoline derivatives *IIa–c* and *VI*. Evidence for this is the isolation of 1-(2-quinolyl)ethanol (*Id*) in the reduction of *Ia*, and 4-ethylquinoline (*Ie*) in the reduction of *Ic*. The compound *Ie* was reported[2] to arise from 1-(4-quinolyl)ethanol heated

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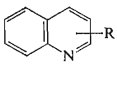
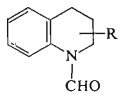
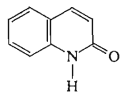


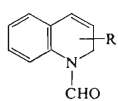
Ia, R = 2-$COCH_3$
Ib, R = 3-$COCH_3$
Ic, R = 4-$COCH_3$
Id, R = 2-$CH(OH)CH_3$
Ie, R = 4-CH_2CH_3



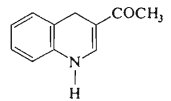
IIa, R = 2-CH_2CH_3
IIb, R = 3-CH_2CH_3
IIc, R = 4-CH_2CH_3
IId, R = 3-$COCH_3$
IIe, R = 3-$CH(OCHO)CH_3$
IIf, R = 3-$CH(OH)CH_3$



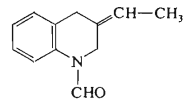
III



IVa, R = 3-CH_2CH_3
IVb, R = 4-CH_2CH_3



V



VI

with formic acid to above 150°C. In keeping with this are the separate reductions of 1-(3-quinolyl)ethanol and 3-ethylquinoline. The former gave a mixture of *IIb*, *IVa* and *VI*, the latter a mixture of *IIb* and *IVa* (ref.[1]), also identified in the reduction of 3-acetylquinoline (*Ib*).

EXPERIMENTAL

Gas chromatography was carried out with an apparatus Chrom II (column length 170 cm, I.D. 0·6 cm, 15% of poly(1,4-butanediol succinate) on Chromatone N-AW), the FID detection being used. The carrier was nitrogen. Thin-layer chromatography ran on Silufol plates UV 254 and 366 (macroporous silica gel Silpearl with a luminiscence indicator for UV 254 and 366 nm on an aluminium foil with starch as binder). The spots were detected with the aid of a Universal UV-Lampe Camag (Muttenz, Switzerland) at 254 and 366 nm. Column chromatography was carried out on silica gel Silpearl UV 254. The infrared spectra were measured with a spectrophotometer Perkin–Elmer, Model 325. The absorption maxima are given in cm^{-1}. ^{1}H-NMR spectra were measured with an apparatus Varian XL-100-15 (100·1 MHz) at 37°C using tetramethylsilane as internal standard, or an apparatus Jeol JNM-PS-100 at 22°C with hexamethyldisiloxane as the standard. The chemical shifts are given in δ(ppm) units and the interaction constants in Hz. The ultraviolet spectra were measured with a spectrophotometer UV Specord Zeiss, Jena, in ethanol, the absorption maxima are given in nm. The mass spectra were measured with a Gas Chromatograph, Mass Spectrometer LKB 9 000. The ionic species are given in units *m/e* (% of relative intensity). The boiling points and melting points are uncorrected.

The amount of triethylammonium formate[3] used for the reduction of 2-, 3-, and 4-acetylquinolines is expressed in mol per mol of formic acid.

Reduction of 2-Acetylquinoline (*Ia*)

A mixture of 5 g (0·029 mol) of *Ia* (ref.[4]) and 38 g (0·438 mol) of triethylammonium formate was heated under stirring for 12 h at 165—170°C. The unreacted triethylammonium formate was distilled off, the residue was treated with 30 ml of a saturated solution of sodium bicarbonate and a portion of ether was added. The separated solid product was collected on a filter; yield 0·7 g (16·6%) of 2-quinolone (*III*), m.p. 198—199°C (ethanol–ethyl acetate), reported[5] 195°C. For C_9H_7NO (145·2) calculated: 74·47% C, 4·86% H, 9·65% N; found: 74·50% C, 4·92% H, 9·44% N. IR spectrum (KBr): 3 600—3 300ν(NH), 1 640ν(CO), was identical with the reported[6] spectrum of 2-quinolone. ^{1}H-NMR spectrum (hexadeuteriodimethyl sulphoxide): 6·45 (d, 1 H, J = 9) CH(3); 7·00—7·68 (m, 4 H) benzene ring; 7·81 (d, 1 H, J = 9) CH(4); 11·66 (11·48 at 70°C) (s, 1 H) NH; CH(3) and CH(4) were calculated as the AB system. Mass spectrum: $M^+_{\bullet}$ = = 145.

After drying ($MgSO_4$) the ethereal solution gave 4 g of a product, which was then separated on a column of silica gel (chloroform). Fractions: *a*) b.p. 109—110°C/0·01 Torr, 1·4 g (25·5%), 2-ethyl-1-formyl-1,2,3,4-tetrahydroquinoline (*IIa*). For $C_{12}H_{15}NO$ (189·3) calculated: 76·16% C, 7·99% H, 7·40% N; found: 76·38% C, 8·01% H, 7·19% N. IR spectrum ($CHCl_3$): 1 660 (s) ν(C=C) in NCHO. ^{1}H-NMR spectrum ($CDCl_3$): 0·80 (t, 3 H, J = 7) CH_3; 1·10—2·18 (m, 4 H) CH_2(3) and C$\underline{H}_2$CH$_3$; 2·60—2·80 (q, 2 H) CH_2(4); 4·44—4·76 (m, 1 H) CH(2); 6·96—7·20 (m, 4 H) benzene ring; 8·60 (s, 1 H)CHO. *b*) m.p. 49—50°C (light petroleum 30—60°C), 0·4 g of the product was identified by its IR spectrum and melting point as *Ia*. Reported[4] m.p. 47 to 48°C. *c*) m.p. 82—83°C (n-hexane), 0·4 g (8%) of 1-(2-quinolyl)ethanol (*Id*). Reported[7] m.p. 81—82°C. For $C_{11}H_{11}NO$ (173·2) calculated: 76·27% C, 6·40% H, 8·09% N; found 76·30% C, 6·70% H, 7·95% N. IR spectrum ($CHCl_3$): 3 400ν (OH), 1 370δ (CH_3). Mass spectrum 158 (100), 130 (81), 129 (48), 128 (42), 156 (41), 172 (23), 77 (21), 102 (20). ^{1}H-NMR spectrum ($CDCl_3$): 1·56 (d, 3 H, J = 7) CH_3; 3·27 (s, 1 H) OH; 5·03 (q, 1 H, J = 7) C$\underline{H}$CH$_3$; 7·33—8·27 (m, 6 H) benzene ring and CH (3, 4).

Reduction of 3-Acetylquinoline (*Ib*)

Like in the reduction of *Ia*, 5 g (0·029 mol) of 3-acetylquinoline (*Ib*, ref.[8]) was reduced with 38 g (0·438 mol) of triethylammonium formate for 10·5 h. The distillation residue was alkalized, extracted with ether (nothing was isolated from the extract) and acidified with dilute hydrochloric acid (1 : 1). The product was washed with water and dried over P_2O_5. TLC on Silufol (ethyl acetate–light petroleum) showed it to be a mixture of several compounds. Crystallization gave 1·6 g 3-acetyl-1,4-dihydroquinoline (*V*), m.p. 187—188°C (ethyl acetate–ethanol); reported[9] m.p. 177—181°C. For $C_{11}H_{11}NO$ (173·2) calculated: 76·28% C, 6·40% H, 8·09% N; found: 76·55%C, 6·05% H, 8·10% N. IR spectrum ($CHCl_3$): 3460 and 3 300ν(NH), 1 640 (s) and 1 610 (m) ν(N—C=C—COCH$_3$). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulphoxide): 2·08 (s, 3 H) CH_3; 3·48 (s, 2 H) CH_2(4); 6·62—7·06 (m, 4 H) benzene ring; 7·33 (d, 1 H, $^3J_{NH,CH(2)}$ = 6) CH(2); 9·00 (bd, 1 H) NH. UV spectrum (ethanol): 355. After distilling off the solvents from the mother liquor the residue (3·6 g) was resolved on a column of silica gel (ethylacetate–cyclohexane). Fractions: *a*) b.p. 117°C/0·1 Torr, 0·6 g, identified by GLC with standards[1] as a mixture of 3-ethyl-1-formyl-1,2,3,4-tetrahydroquinoline (*IIb*, 87%) 3-ethyl-1-formyl-1,2-dihydroquinoline (*IVa*, 7%) and 3-ethylidene-1-formyl-1,2,3,4-tetrahydroquinoline (*VI*, 6%). Catalytic hydrogenation (0·26 g of a mixture of *IIb*, *IVa* and *VI*, 9 ml of acetic acid, 50 mg of Adams catalyst, atmospheric pressure, 20°C) gave *IIb*, identical with an authentic sample[1]. *b*) m.p. 81—82°C (ethyl-acetate–n-hexane), 0·1 g, 3-acetyl-1-formyl-1,2,3,4-tetrahydroquinoline (*IId*). For $C_{12}H_{13}NO_2$ (203·2) calculated: 70·91% C, 6·45% H, 6·89% N; found: 70·86% C, 6·45% H, 6·75% N. IR

spectrum ($CHCl_3$): 1712ν(C=O) v $COCH_3$, 1670 ν(C=O) in NCHO. ^{1}H-NMR spectrum ($CDCl_3$): 2·20 (s, 3 H) CH_3; 2·80–3·04 (m, 3 H) CH_2(4) and CH(3); 3·44–3·72 (m, 1 H) 2-Ha; 4·10–4·34 (m, 1 H, ^2J = 13) 2-He; 7·02–7·24 (m, 4 H) benzene ring; 8·69 (s, 1 H) CHO. Mass spectrum: 160 (100), 132 (61), 130 (33), 203 (31), 156 (19), 117 (19), 77 (19) and 128 (18). *c*) m.p. 102–105°C (ethylacetate–hexane) 0·8 g, 1-formyl-3-(1-formyloxyethyl)-1,2,3,4-tetrahydroquinoline (*IIe*). For $C_{13}H_{15}NO_3$ (233·3) calculated: 66·93% C, 6·48% H, 6·00% N; found: 67·03% C, 6·64% H, 6·00% N. IR spectrum ($CHCl_3$): 1723ν(C=O) in OCHO, 1670ν(C=O) in NCHO. Mass spectrum: 158 (100), 130 (71), 233 (60), 144 (26), 117 (25), 160 (24), 132 (24), 186 (23), 77 (21), 187 (20). ^{1}H-NMR spectrum ($CDCl_3$): 1·33 (d, 3H, J = 6·5) $CHCH_3$; 1·84–2·22 (m, 1 H) 3-Ha; 2·38–2·60 (m, 1 H, ^2J = 16, $^3J_{4a,3a}$ = 10) 4-Ha; 2·60–2·96 (m, 1 H, $^3J_{4e,3a}$ = 5·5) 4-He; 3·04–3·33 (m, 1 H, ^2J = 13, $^3J_{2a,3a}$ = 10) 2-Ha; 4·08–4·36 (m, 1 H, $^3J_{2e,3a}$ = 4)2-He; 4·80–5·10 (m, 1 H) C<u>H</u>CH_3; 7·08 (s, 4 H) benzene ring; 7·98 (s, 1 H) OCHO; 8·68 (s, 1 H) CHO. The ^{1}H-NMR spectrum is not consistent with the presence of a mixture of diastereoisomers. Even in the use of shift agent Yb $((CH_3)_3CCOCH_2COC_3F_7)_3$ (Yb(Fod)$_3$) up to R_p = 0·147 there was no change indicating a mixture of two diastereoisomers. *d*) b.p. 145–150°C/0·05 Torr, 1·3 g, a mixture of two compounds resolved by preparative TLC (Silpearl, ethyl acetate–light petroleum 1 : 1). The product, 80 mg, melted at 99°C (ethylacetate–n-hexane) without depression with *Ib* (ref.[8] m.p. 97·5–98·5°C); also obtained was 0·6 g of 1-formyl-3-(1-hydroxyethyl)-1,2,3,4-tetrahydroquinoline (*IIf*), b.p. 140–142°C/0·05 Torr. For $C_{12}H_{15}NO_2$ (205·3) calculated: 70·22% C, 7·37% H, 6·82% N; found: 70·52% C, 7·50% H, 7·08% N. IR spectrum ($CHCl_3$): 3630, 3450ν(OH), 1660ν(C=O) in NCHO. ^{1}H-NMR spectrum ($CDCl_3$): 1·33 (d, 3 H, J = 6·5) $CHC\underline{H}_3$; 1·93 (m, 1 H) 3-Ha; 2·28 (bs, 1 H) OH; 2·50–3·12 (m, 2 H) CH_2(4), AB system; 3·20–3·62 (m, 1 H) 2-Ha; 3·78 (m, 1 H) $C\underline{H}CH_3$; 4·20 (m, 1 H) 2-He; 7·14 (s, 4 H) benzene ring; 8·76 (s, 1 H) CHO. Gradual addition of the shift agent Yb(Fod)$_3$ (R_p = 0·0182 and 0·0451) effected resolution of two doublets, corresponding to the methyl group signals, and other protons of the two diastereoisomers.

Reduction of 3-Acetyl-1,4-dihydroquinoline (*V*)

In analogy to the reduction of *Ib*, 1·3 g (0·0075 mol) of *V* was treated with 9·7 g (0·113 mol) of triethylammonium formate. After alkalization the ethereal extract gave 40 mg of the product melting at 186°C, with authentic *V* the m.p. was undepressed. After evaporation the residue (1·3 g) was chromatographed on a column of silica gel (ethylacetate–cyclohexane). Fractions: *a*) b.p. 108°C/0·05 Torr, 0·25 g identified by GLC with an authentic mixture as a mixture of *IIb* (75%), *IVa* (11%) and *VI* (14%). *b*) m.p. 82–83°C, 0·17 g of *IId* (no m.p. depression with an authentic sample, identity of IR spectra). *c*) 0·5 g, b.p. 148–152°C 0·05 Torr; preparative TLC (Silpearl, benzene–methanol 10 : 1) gave 20 mg of a product identical with *Ib* and 0·25 g of a product identical with *IIf* (identity of IR spectra).

3-Acetyl-1,4-dihydroquinoline (*V*)

A mixture of *Ib* (2·5 g, 0·015 mol,) ethanol (300 ml) and Raney nickel (2 g) was hydrogenated at room temperature and atmospheric pressure. The stoichiometrical amount of hydrogen was absorbed in 2 h. The catalyst was filtered off, the filtrate was taken to dryness *in vacuo* and the residue was crystallized. Yield 1·4 g of *V*, m.p. 187°C (ethyl acetate–ethanol) without depression with an authentic sample.

3-Acetyl-1-formyl-1,2,3,4-tetrahydroquinoline (*IId*)

A solution of *V* (1·4 g, 0·008 mol) in 98% formic acid (3·5 ml) was heated to 140°C for 12 h. The formic acid was removed by distillation and the residue was alkalinized with a solution of potassium carbonate and extracted with ether. After drying with $MgSO_4$ the extract gave 1·3 g of crude product, melting at 55–60°C. Recrystallization gave 1·1 g of the ketone *IId*, m.p. 81–82°C (ethylacetate–ethanol). For $C_{12}H_{13}NO_2$ (203·2) calculated: 70·91% C, 6·45% H, 6·89% N; found: 70·62% C, 6·37% H, 6·72% N. The IR spectrum was identical with that of an authentic sample.

Reduction of 3-Acetyl-1-formyl-1,2,3,4-tetrahydroquinoline (*IId*)

Like in the reduction of *Ib*, a mixture of *IId* (1·35 g, 0·0066 mol) and triethylammonium formate (13·5 g, 0·156 mol) was kept at 160°C for 12 h. The distillation residue was alkalinized with a solution of potassium carbonate and extracted with chloroform, the extract was dried with $MgSO_4$. The solvent was distilled off and the residue (1·1 g) was chromatographed on a column of silica gel (ethyl acetate–n-hexane). Fractions: *a*) 60 mg of a product identified by GLC as a mixture of *IIb* (68%), *IVa* (23%) and *VI* (9%). *b*) 150 mg, m.p. 81°C (ethyl acetate–n-hexane), without depression with the starting ketone *IId*. *c*) 0·6 g, b.p. 135–137°C/0·01 Torr, identified by comparison with an authentic sample as 1-formyl-3-(1-hydroxyethyl)-1,2,3,4-tetrahydroquinoline (*IIf*).

Reduction of 4-Acetylquinoline (*Ic*)

In analogy to the reduction of *Ia*, 4·8 g (0·028 mol) of 4-acetylquinoline (*Ic*, ref.[10]) was treated with 38 g (0·44 mol) of triethylammonium formate. The distillation residue was diluted with water, alkalinized with 40% sodium hydroxide and extracted with ether. After drying ($MgSO_4$) there was obtained 2·4 g of a liquid, b.p. 104–122°C/0·1 Torr, which was chromatographed on a column of silica gel (ethyl acetate–cyclohexane). Fractions: *a*) b.p. 110–112°C/0·1 Torr, 1·7 g, identified by GLC and ^{1}H-NMR spectrum as a mixture of 4-ethyl-1-formyl-1,2,3,4-tetrahydroquinoline (*IIc*, 86%) and 4-ethyl-1-formyl-1,2-dihydroquinoline (*IVb*, 14%). Catalytic hydrogenation of the mixture in acetic acid on PtO_2 gave *IIc*. The percentual composition of the mixture was read from the NMR spectrum. ^{1}H-NMR spectrum of *IVb* ($CDCl_3$): 4·32–4·44 (m) CH_2(2); 5·72–5·84 (bs) CH(3); 8·50 (s) CHO. *b*) b.p. 85–87°C/0·5 Torr, 0·35 g, identified as 4-ethylquinoline (*Ie*). Reported[11] b.p. 134°C/9 Torr. For $C_{11}H_{11}N$ (157·2) calculated: 84·04% C, 7·05% H, 8·91% N; found 83·89% C, 7·36% H. 8·87% N. ^{1}H-NMR spectrum ($CDCl_3$): 1·38 (t, 3 H, $J = 7$) CH_3; 3·10 (q, 2 H, $J = 7$) $C\underline{H}_2CH_3$; 7·21 (d, 1 H, $J = 4$) CH(3); 7·40–8·20 (m, 4 H) benzene ring; 8·79 (d, 1 H, $J = 4$) CH(2).

4-Ethyl-1-formyl-1,2,3,4-tetrahydroquinoline (*IIc*)

A solution of *IIc* and *IVb* (0·45 g of the mixture from the preceding reduction) in 98% acetic acid (8·5 ml) was hydrogenated on PtO_2 (60 mg) at room temperature and atmospheric pressure until the absorption of hydrogen had ceased (30 min). After distillation *in vacuo* the residue was alkalinized and extracted with ether. The extract was dried ($MgSO_4$); yield 0·3 g of a liquid, b.p. 106°/0·01 Torr. For $C_{12}H_{15}NO$ (189·3) calculated: 76·16% C, 7·99% H, 7·40% N; found: 75·96% C, 7·92% H, 7·64% N. IR spectrum (substance): 1670ν(C=O) in NCHO. ^{1}H-NMR spectrum ($CDCl_3$): 0·92 (t, 3 H, $J = 7$) CH_3; 1·14–2·08 (m, 4 H) CH_2(3) and $C\underline{H}_2CH_3$; 2·46–2·76 (m, 1 H) CH(4); 3·70 (t, 2 H, $J = 7$) CH_2(2); 7·00–7·28 (m, 4 H) benzene ring; 8·70 (s, 1 H) CHO.

The elemental analyses were carried out at the analytical laboratory of our department (head Dr L. Helešic). The IR *spectra (head Dr P. Adámek) and mass spectra (head Dr V. Kubelka) were measured at the service departments of the Institute. The* UV *spectra were measured at the Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague. The* ^{1}H-NMR *spectra were measured at our Institute under the direction of Dr P. Trška, who helped us to interpret them, and at the Institute of Macromolecular Chemistry, Czechoslovak Academy of Sciences, Prague, by Dr J. Lövy.*

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