REDUCTION OF 2-, 3- AND 4-QUINOLINECARBONITRILE AND 3- AND 4-QUINOLINECARBONITRILE METHYL METHOSULFATES WITH TRIETHYLAMMONIUM FORMATE*

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Whereas 2-quinolinecarbonitrile (*Ia*) is not reduced with triethylammonium formate, 3-quinolinecarbonitrile (*Ib*) affords a mixture of 1,4-dihydro-3-quinolinecarbonitrile (*IVb*) and 1-formyl-1,2,3,4-tetrahydroquinoline-3-carboxamide (*IIa*) in addition to the corresponding acid *IIb*. 4-Quinolinecarbonitrile (*Ic*) is reduced to 1-formyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (*IId*) and 1-formyl-1,2,3,4-tetrahydroquinoline (*IIc*). Reduction of 3-quinolinecarbonitrile methyl methosulfate (*Va*) at low temperature leads to 1-methyl-1,4-dihydroquinoline-3-carbonitrile (*IVc*) whereas at higher temperatures it affords, in addition to *IVc*, 1-methyl-1,2,3,4-tetrahydroquinoline-3-carboxamide (*IIf*) and the acid *IIg*. 4-Quinolinecarbonitrile methyl methosulfate (*Vb*) gives 1-methyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (*IIh*) and 1-methyl-1,2,3,4-tetrahydroquinoline (*IIe*).

In one of our previous communications[1] of this series we described the reduction of 2-, 3- and 4-quinolinecarboxylic acids with triethylammonium formate. The pyridine part of the molecule was reduced under formation of the corresponding 1-formyl-1,2,3,4-tetrahydroquinolinecarboxylic acids in the case of the 2- and 4-carboxylic acids whereas 3-quinolinecarboxylic acid afforded 1-formyl-1,2,3,4-tetrahydroquinoline. As a continuation of these studies we have now investigated the reduction of 2-, 3- and 4-quinolinecarbonitriles with triethylammonium formate (Table I). Since triethylammonium formate is known[2] to reduce several α,β-unsaturated nitriles at the C=C bond, we expected that the reduction of nitriles would be analogous to that of the quinolinecarboxylic acids[1].

Surprisingly, 2-quinolinecarbonitrile (*Ia*), when heated with triethylammonium formate, gave only 2-quinolinecarboxamide (*Id*). Formation of this compound can be explained either by addition of formic acid to the nitrile group and subsequent hydrolysis, or, if we admit the formation of 1-formyl-1,2-dihydroquinoline-2-carbonitrile (*IIIa*) as an intermediate, by hydrolysis of this analogue of the Reissert salt *IIIb*. Acid-catalysed hydrolysis of *IIIb* affords a mixture of products containing

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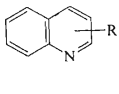
2-quinolinecarboxamide[3] whereas the mixture after reduction of *IIIb* with triethylammonium formate does not contain this amide[4]. The reduction of the nitrile *Ia* thus does not proceed *via* the intermediate *IIIa*. The reduction of 3-quinolinecarbonitrile (*Ib*) with triethylammonium formate afforded, besides the 1,4-addition product, *i.e.* 1,4-dihydroquinoline-3-carbonitrile (*IVb*)), also products of its further reduction and hydrolysis: 1-formyl-1,2,3,4-tetrahydroquinoline-3-carboxamide (*IIa*) and 1-formyl-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (*IIb*). 4-Quinolinecarbonitrile (*Ic*) was reduced to a mixture of 1-formyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (*IId*) and 1-formyl-1,2,3,4-tetrahydroquinoline (*IIc*), formed by splitting off the nitrile group. Thus, if we compare the triethylammonium formate reduction of the acids[1] with that of the corresponding nitriles, we find a parallel behaviour only for the pair 4-quinolinecarboxylic acid and its nitrile.

TABLE I

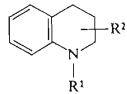
Reduction of Nitriles *Ia*—*Ic* and Methyl Methosulfates *Va*, *Vb* with Triethylammonium Formate

Nitrile	Time, h (temperature, °C)	Products %	Yield %
Ia (ref.[9])	8 (160)	*Id*[a]	74·7
Ib (ref.[7])	10 (165)[b]	*IIa* (38·6), *IIb* (12·2), *IVb* (8)	58·8
Ic (ref.[11])	8 (160)	*IId*[c] (30·5)[d], *IIc*[e] (30·2)[d]	60·7
IVd (ref.[11])	2 (165)	*IIe*[e]	48·3
Va[b]	0·25 (60)	*IVc*[f]	85·2
Va[b]	6 (160)[b]	*IIf* (52·5), *IIg* (7·8), *IVc* (14·6)	74·9
Vb[b]	4 (165)	*IIe* (30·6)[e], *IIh* (29·1)[g]	59·7

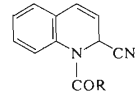
[a] M.p. 126·5—127·5°C (reported[10] m.p. 126—128°C). For $C_{10}H_8N_2O$ (172·2) calculated: 69·76% C, 4·68% H, 16·27% N; found: 69·46% C, 4·86% H, 16·42% N. [b] See Experimental. [c] M.p. 74—75°C (pentane–ethyl acetate). For $C_{11}H_{10}N_2O$ (186·2) calculated: 70·95% C, 5·41% H, 15·04% N; found: 70·86% C, 5·65% H, 15·14% N. IR spectrum ($CHCl_3$) cm^{-1}: 2250, ν(CN); 1670, ν(C=O) in NCHO. ^{1}H-NMR spectrum ($CDCl_3$), ppm: 2·00—2·42 (m, 2 H) CH_2 (3); 3·85—4·16 (m, 3 H) CH_2 (2) and CH (4); 7·10—7·56 (m, 4 H) benzene ring; 8·80 (s, 1 H) CHO. [d] Based on the nitrile *Ic*. [e] Identical with an authentic compound. [f] M. p. 95·5—96·5°C (ethyl acetate–hexane). For $C_{11}H_{10}N_2$ (170·2) calculated: 77·62% C, 5·92% H, 16·46% N; found: 77·74% C, 5·99% H, 16·36% N. IR spectrum ($CHCl_3$), cm^{-1}: 2840, $\nu(CH_3)$ in NCH_3; 2200, ν(CN); 1645, ν(C=C). UV spectrum (methanol): 333 nm, ε = 10400. ^{1}H-NMR spectrum ($CDCl_3$), ppm: 3·17 (s, 3 H) CH_3; 3·69 (s, 2 H) CH_2 (4); 6·66 (s, 1 H) CH (2); 6·67—7·29 (m, 4 H) benzene ring. [g] B.p. 112—114°C/0·1 Torr. For $C_{11}H_{12}N_2$ (172·2) calculated: 76·71% C, 7·02% H, 16·26% N; found: 76·95% C, 7·11% H, 16·36% N. IR spectrum ($CHCl_3$), cm^{-1}: 2840, $\nu(CH_3)$ in NCH_3; 2250, ν(CN). ^{1}H-NMR spectrum ($CDCl_3$), ppm: 2·22 (q, 2 H, J = 6) CH_2 (3); 2·88 (s, 3 H) NCH_3; 3·29 (m, 2 H) CH_2 (2); 3·90 (t, 1 H, J = 6) CH (4); 6·64 (t, 2 H, J = 10) CH (6,7); 7·00—7·26 (m, 2 H) CH (5,8).



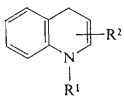
Ia, R = 2-CN
Ib, R = 3-CN
Ic, R = 4-CN
Id, R = 2-$CONH_2$



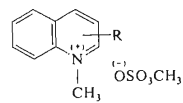
IIa, R^1 = CHO, R^2 = 3-$CONH_2$
IIb, R^1 = CHO, R^2 = 3-COOH
IIc, R^1 = CHO, R^2 = H
IId, R^1 = CHO, R^2 = 4-CN
IIe, R^1 = CH_3, R^2 = H
IIf, R^1 = CH_3, R^2 = 3-$CONH_2$
IIg, R^1 = CH_3, R^2 = 3-COOH
IIh, R^1 = CH_3, R^2 = 4-CN



IIIa, R = H
IIIb, R = C_6H_5



IVa, R^1 = CH_3, R^2 = H
IVb, R^1 = H, R^2 = 3-CN
IVc, R^1 = CH_3, R^2 = 3-CN
IVd, R^1 = CH_3, R^2 = 4-CN



Va, R = 3-CN
Vb, R = 4-CN

We investigated further also the reduction of 3-quinolinecarbonitrile and 4-quinolinecarbonitrile methyl methosulfates (*Va* and *Vb*, respectively). From the reduction of *Va* with triethylammonium formate at 60°C we obtained 1-methyl-1,4-dihydroquinoline-3-carbonitrile (*IVc*) as the sole product. This compound was reduced further (at 160°C) to 1-methyl-1,2,3,4-tetrahydroquinoline-3-carboxamide (*IIf*) and the corresponding acid *IIg*. The amide *IIf* was formed also in the reduction of the quaternary salt *Va* with potassium formate and formic acid[5].

The reduction of 4-quinolinecarbonitrile methyl methosulfate (*Vb*) with triethylammonium formate afforded 1-methyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (*IIh*) and, similarly as in the case of compound *Ic*, the corresponding product without the nitrile group, *i.e.* 1-methyl-1,2,3,4-tetrahydroquinoline (*IIe*). The compound *IIe* was also obtained by reduction of 1-methyl-1,4-dihydroquinoline-4-carbonitrile (*IVd*) with triethylammonium formate, as well as with potassium formate and formic acid[5].

Our results show that the reduction of the quaternary salts *Va* and *Vb* with triethylammonium formate proceeds *via* the 1,4-dihydro derivatives *IVc* and *IVd*. Under the reaction conditions employed, the nitrile *IVd*, as a vinylogue of an α-amino nitrile, loses the nitrile group to give the compound *IVa* which is then reduced to *IIe*.

EXPERIMENTAL

Gas–liquid chromatographic analyses were performed on a Chrom II instrument (170 cm column, diameter 0·6 cm, filled with 15% poly(butane-1,4-diol succinate) on Chromaton N-AW), flame ionisation detector, carrier gas nitrogen. Thin-layer chromatography was carried out on Silufol UV 254 and 366 plates (Kavalier, Czechoslovakia); spots were detected using a Universal UV-Lampe Camag (Muttenz, Switzerland) in the 254 and 366 nm regions. Column chromatography was performed on a Silpearl UV 254 adsorbent. The IR spectra were taken on a Perkin–Elmer 325 spectrophotometer, ^{1}H-NMR spectra on a Varian XL-100-15 (100·1 MHz) instrument at 37°C with tetramethylsilane as internal standard. The UV spectra were measured in ethanol on a UV Specord (Zeiss, Jena) spectrometer, mass spectra were taken on a Gas Chromatograph — Mass Spectrometer 9000 LKB instrument (AB Stockholm, Sweden). The temperature data are uncorrected. The amount of triethylammonium formate[6], used in the reductions, is expressed in moles, corresponding to the amount of formic acid.

Reduction of 3-Quinolinecarbonitrile (*Ib*)

A stirred mixture of the nitrile[7] *Ib* (6·2 g; 0·04 mol) and triethylammonium formate[6] (51·8 g; 0·6 mol) was heated to 165—170°C for 10 h. After cooling, ethyl acetate (60 ml) was added and the mixture was allowed to stand at −20°C for 10 h. The product was filtered and washed with water; yield 2·7 g (33·1%) of 1-formyl-1,2,3,4-tetrahydroquinoline-3-carboxamide (*IIa*), m.p. 195—196°C (ethyl acetate–ethanol). For $C_{11}H_{12}N_2O_2$ (204·2) calculated: 64·69% C, 5·92% H, 13·72% N; found: 64·63% C, 6·08% H, 13·97% N. IR spectrum (KBr), cm^{-1}: 3380, 3200, ν(NH$_2$); 1660, ν(C=O in NCHO); 1640, ν(C=O + δ(NH$_2$) in CONH$_2$; 1615, ν(CN + δ(NH$_2$). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide), ppm: 2·60—2·70 (m, 1 H) CH(3); 2·76—2·96 (m, 2 H) CH$_2$(4); 3·18—3·44 (m, 1 H) 2-H$_a$; 3·92—4·20 (m, 1 H) 2-H$_e$; 6·80—7·52 (m, 6 H) benzene ring and CONH$_2$; 8·76 (s, 1 H) in CHO. ^{1}H-NMR spectrum (pentadeuteriopyridine), ppm: 2·80—3·40 (m, 3 H), CH$_2$(4) and CH(3); 3·44—3·94 (m, 1 H) 2-H$_a$; 4·64—4·96 (m, 1 H) 2-H$_e$, 6·90—7·30 (m, 4 H benzene ring; 7·66—8·06 (bs, 1 H) and 8·1—8·5 (bs, 1 H) CONH$_2$; 8·98 (s, 1 H) CHO. The filtrate from the isolation of the amide *IIa* was taken down, the residue made alkaline with saturated sodium hydrogen carbonate solution (25 ml), the separated product filtered, washed with water and dried (1·3 g). Chromatography on silica gel (light petroleum–ethyl acetate–ethanol) afforded following fractions: *a*) 1,4-Dihydroquinoline-3-carbonitrile (*IVb*) (0·5 g; 8%), m.p. 132—133°C (ethyl acetate–light petroleum); reported[8] m.p. 131·5°C. IR spectrum (KBr), cm^{-1}: 3300, ν(NH); 2190, ν(CN); 1645, ν(C=C). UV spectrum: 327 nm. ^{1}H-NMR spectrum (trideuterioacetonitrile), ppm: 3·66 (s, 2 H) CH$_2$(4); 6·68 (d, 1 H, $J_{NH,CH(2)} = 8$); 6·82—7·18 (m, 4 H) benzene ring. *b*) Amide *IIa* (0·3 g), m.p. 194—195°C, undepressed on admixture with an authentic sample of *IIa*.

The alkaline filtrate was acidified with hydrochloric acid, the separated product filtered, washed with water and dried (1·8 g). Chromatography on silica gel (ethyl acetate–ethanol–acetic acid 25 : 2 : 1) afforded: *a*) 1-formyl-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (*IIb*) (1 g; 12·2%), m.p. 165—166°C (ethyl acetate–ethanol), no depression on admixture with an authentic sample[1]; *b*) amide *IIa* (0·15 g), identical (mixed m.p.) with an authentic sample.

3-Quinolinecarbonitrile Methyl Methosulfate (*Va*)

A mixture of 3-quinolinecarbonitrile (14 g; 0·091 mol), dimethyl sulfate (12·6 g; 0·1 mol) and benzene (100 ml) was refluxed for 5 h. The product was filtered and washed with benzene, m.p.

214–215°C (aqueous methanol); yield 20 g (78·6%). For $C_{12}H_{12}N_2O_4S$ (280·3) calculated: 51·42% C, 4·31% H, 9·99% N, 11·44% S; found: 51·37% C, 4·44% H, 10·09% N, 11·32% S.

4-Quinolinecarbonitrile Methyl Methosulfate (*Vb*)

This compound was prepared analogously as described for *Va*; m.p. 115–116°C (ethyl acetate–methanol). For $C_{12}H_{12}N_2O_4S$ (280·3) calculated: 51·42% C, 4·31% H, 9·99% N, 11·44% S; found: 51·41% C, 4·43% H, 9·97% N, 11·79% S.

Reduction of *Va* at 160°C

A stirred mixture of *Va* (5·6 g; 0·02 mol) and triethylammonium formate (26 g; 0·3 mol) was heated to 60°C until the evolution of carbon dioxide ceased (15 min) and then to 160°C for 6 h. The reagent was distilled off *in vacuo*, the residue made alkaline with a solution of potassium carbonate, extracted with benzene and the separated product filtered affording 1·5 g (39·4%) of 1-methyl-1,2,3,4-tetrahydroquinoline-3-carboxamide (*IIf*), m.p. 130–131°C (ethyl acetate–hexane). For $C_{11}H_{14}N_2O$ (190·3) calculated: 69·45% C, 7·42% H, 14·72% N; found: 69·42% C, 7·61% H, 14·95% N. IR spectrum ($CHCl_3$), cm^{-1}: 3 540, 3 420, $\nu(NH_2)$; 2 840, $\nu(CH_3)$ in NCH_3; 1 680, $\nu(C{=}O) + \delta(NH_2)$; 1 590, $\delta(NH_2) + \nu(CN)$. ^{1}H-NMR spectrum ($CDCl_3$), ppm: 2·60 to 3·10 (m, 3 H) CH(3) and $CH_2(4)$; 2·92 (s, 3 H) CH_3; 3·30 (d, 2 H, $J = 5$) $CH_2(2)$; 6·02 (at 60°C 5·86; bs, 2 H) $CONH_2$; 6·50–7·26 (m, 4 H) benzene ring.

The mother liquor from *IIf* was taken down and the residue (2·6 g) was chromatographed on silica gel (benzene–methanol), affording: *a*) 0·5 g (13.1%) of *IIf*, m.p. 128–129°C (no depression with an authentic sample), *b*) 0·5 g (14·6%) of *IVc*, m.p. 94°C (no depression with a standard; see Table I). The alkaline solution after benzene extraction was neutralised with hydrochloric acid, extracted with chloroform, dried over magnesium sulfate and taken down, leaving a product, melting at 94–97°C (0·5 g). This material was chromatographed on silica gel (in ethyl acetate), affording 0·3 g (7·8%) of 1-methyl-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (*IIg*), m.p. 107–108°C (ethyl acetate–hexane). For $C_{11}H_{13}NO_2$ (191·2) calculated: 69·10% C, 6·85% H, 7·32% N; found: 68·90% C, 6·92% H, 7·22% N. IR spectrum ($CHCl_3$), cm^{-1}: 2840, $\nu(CH_3)$ in NCH_3; 1710, $\nu(C{=}O)$. ^{1}H-NMR spectrum ($CDCl_3$), ppm: 2·92 (s, 3 H) CH_3; 2·96–3·14 (m, 3 H) CH(3) and $CH_2(4)$; 3·22–3·50 (m, 2 H) $CH_2(2)$; 6·54–7·24 (m, 4 H) benzene ring.

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