The Formation of 2-Alkoxyquinolines from Quinoline *N*-Oxides in Alcoholic Media

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A novel transformation of certain quinoline *N*-oxides which gives rise to 2-alkoxy substituted quinolines by the action of acetic anhydride in alcoholic media is described. In the case of *t*-butyl alcohol direct formation of the carbostyril is also observed. A mechanism is advanced to explain the observed phenomena.

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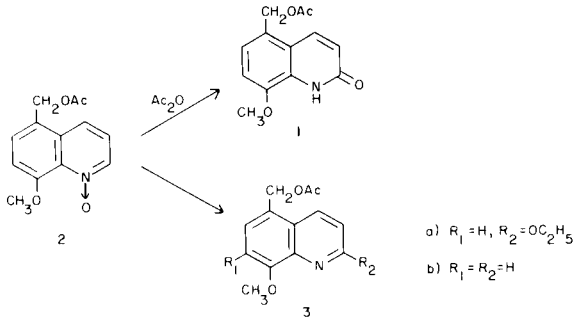
There are many reported transformations of quinoline and other heterocyclic *N*-oxides induced by acid anhydrides and chlorides. Such reactions have recently been reviewed by Oae and Ogino (1). A novel variant of the classical rearrangement of certain quinoline *N*-oxides, occurring in alcoholic media, is now described.

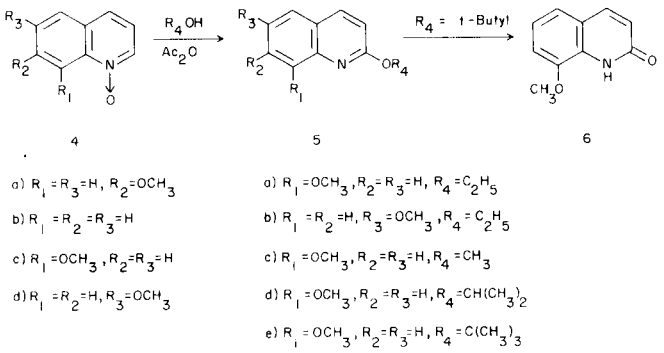
Carbostyril **1** was required as part of a synthetic program, which product it was hoped to obtain by acetic anhydride induced rearrangement of the *N*-oxide **2**. The reaction in neat acetic anhydride afforded an inseparable mixture, whilst in chloroform with one equivalent of anhydride, two products were isolated in roughly equal amounts. The less polar product proved to be the 2-ethoxy compound **3a**. The nmr of this compound in deuteriochloroform showed ethoxy peaks at 1.44 (tr) and 4.58 ppm (q); H-3 was now a doublet at 7.08 ppm (*cf.*, complex signal at *ca.* 7.5 ppm in **3b**) and there was no low field signal characteristic of H-2. Microanalysis was also consistent with this formulation.



It seemed probable that this product had formed because of the presence of ethanol in the commercial grade of chloroform used. Indeed, when one molar equivalent of acetic anhydride was added to an ethanol solution of the *N*-oxide **2**, an exothermic reaction ensued and the ethoxy compound **3a** was isolated in 85% yield.

Under the same conditions, 7-methoxyquinoline *N*-oxide **4a** and quinoline *N*-oxide **4b** were essentially unchanged, although ethyl acetate formation was noted. 8-Methoxyquinoline *N*-oxide **4c** however, reacted exactly as did *N*-oxide **2** to form the 2-ethoxy compound **5a** in 82% yield (2). The reaction occurred less readily for 6-methoxyquinoline *N*-oxide **4d** and, in this case, the ethoxy compound **5b** was isolated in 36% yield together with unreacted *N*-oxide (37%).

The transformation also took place with 8-methoxyquinoline *N*-oxide **4c** in methanol and 2-propanol to give the corresponding 2-methoxy **5c** and 2-isopropoxy **5d** compounds in 84 and 77% yields, respectively. In *t*-butyl alcohol, without external heating, the 2-*t*-butoxy analogue **5e** was isolated albeit in low yield (13%). When the solution was heated at reflux, the initially formed *t*-butoxy compound slowly disappeared at the expense of a more polar material which was also observed (tlc) in the room temperature reaction. This product proved to be the carbostyril **6** (62% yield) and was also isolated on acid hydrolysis of the 2-ethoxy compound **5a**. This compound is presumably formed by loss of isobutene from the *t*-butoxy compound in the acid medium. This reaction represents, therefore, a direct transformation of appropriately substituted *N*-oxides into carbostyrils.



The mechanisms shown in Schemes I and II are advanced to explain these observations. Attack by the most abundant nucleophile (the alcohol) at C-2 of the *N*-acetoxyquinolinium salt **7** known (3) to be formed initially in reactions of *N*-oxides with anhydrides, affords the adduct **8**, which can react further by two possible routes: either elimination of acetic acid and formation of the 2-alkoxy-

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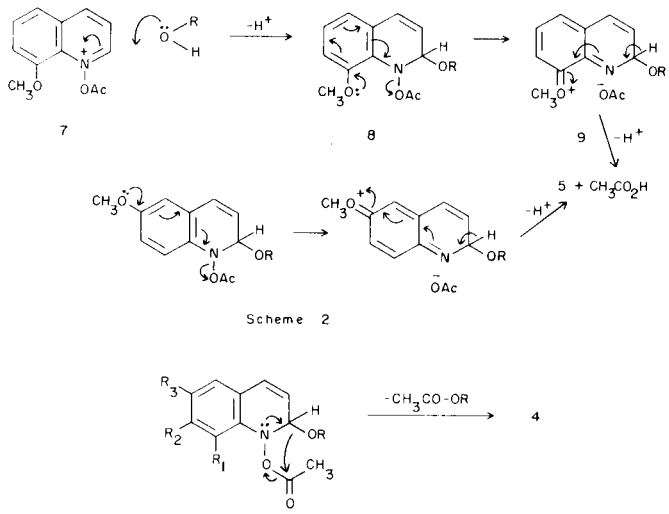
quinoline (Scheme I) or elimination of alkyl acetate with reformation of the *N*-oxide (Scheme II).

Scheme 1



Scheme 2

It is proposed that the presence of the 8-methoxy function mesomerically facilitates elimination of acetate ion from adduct **8**, followed by proton elimination to give the 2-alkoxyquinoline. Such mesomeric assistance is also possible in the case of the 6-methoxy isomer but not the 7-isomer (which *vide supra* does not undergo the reaction). The greater reactivity of the 8-isomer is probably due to an increased facility for acetate ion elimination engendered by the subsequent *peri* ion-pair stabilisation of the intermediate **9**, not available in the case of the 6-isomer, which consequently reacts also by the mechanism shown in Scheme II.

Generalisation of this transformation to other heteroaromatic *N*-oxides remains to be investigated, as does the influence of other substituent types in the quinoline ring.

EXPERIMENTAL

Melting points were determined on a Büchi SMP 20 (Tottoli) apparatus and are uncorrected. ^{1}H-nmr spectra were recorded on either a Perkin Elmer R12 or an R24 instrument. Ir spectra were recorded on a Perkin Elmer 297 spectrophotometer. Microanalyses were performed by the Service Analytique of L. E. R. S. Synthelabo.

General Method of preparation of *N*-oxides.

The *N*-oxides were prepared by oxidation of the parent quinolines with *m*-chloroperbenzoic acid in chloroform by the method of Cymerman Craig and Purushothaman (4). Although these compounds, with the exception of compound **2**, are reported in the literature, they have, for the most part, been ill-characterised and hence their characteristics are summarised in Table I.

General Method of *N*-Oxide Transformation.

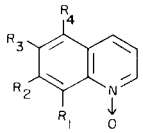
The appropriate *N*-oxide (0.01 mole) was dissolved or suspended in the alcohol (10 ml.) and acetic anhydride (1.02 g. 0.01 mole) was added. In most cases, the solution became hot and darker in colour. When this initial, exothermic reaction had subsided, the mixture was heated for 0.5 hour at reflux before dilution with water. The products subsequently crystallised from the solution, or were extracted into ether or dichloromethane and were purified by crystallisation or distillation. Their properties are summarised in Table II.

8-Methoxy-5-hydroxymethylquinoline.

8-Hydroxy-5-hydroxymethylquinoline (5) (35 g., 0.2 mole) in dry DMF (150 ml.) was slowly added to sodium hydride (10.6 g., 0.22 mole 50% oil dispersion) suspended in DMF (75 ml.) under nitrogen. The resultant, dark-tan solution was cooled in an ice bath and methyl iodide (15 ml.) in dry DMF (35 ml.) was rapidly added. An exothermic reaction occurred and the reaction mixture was stirred 0.75 hour in the ice bath. The mixture was evaporated to dryness *in vacuo*; the residue was taken up with a minimum amount of water and was continuously extracted with chloroform.

The crude product crystallised in the extraction flask and was filtered

Table I

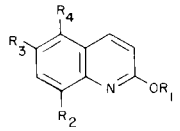


Quinoline *N*-Oxides

R_1	R_2	R_3	R_4	Yield %	M.p.	Crystallisation Solvent	Compound No.	Microanalysis % (a) C	H	N	Literature Reference
CH_3O	H	H	CH_2OAc	83	147-148°	Ethyl Acetate	**2**	63.11 (63.15)	5.28 (5.30)	5.62 (5.66)	
CH_3O	H	H	H	57	86-87.5° (b)	Ethyl Acetate/Hexane	**4c**	65.04 (65.21)	5.58 (5.47)	7.42 (7.60)	(7)
H	CH_3O	H	H	45 (c)	142.5-143.5°	Ethyl Acetate/Hexane	**4a**	68.44 (68.56)	5.11 (5.18)	7.83 (8.00)	(8)
H	H	CH_3O	H	74	110-112° (d)	Benzene	**4d**	68.57 (68.56)	5.08 (5.18)	7.94 (8.00)	(9)

(a) Values required shown in parenthesis. (b) Rapid heating-analysis corresponds to the hemihydrate. (c) From quinoline contaminated with the 5-isomer formed concomitantly in the Skraup reaction with *m*-methoxyaniline. (d) After drying at 60° *in vacuo*.

Table II



2-Alkoxyquinolines

R_1	R_2	R_3	R_4	Yield %	M.p./B.p.	Crystallisation Solvent	Compound No.	Microanalysis % (a) C	H	N
C_2H_5	OCH_3	H	CH_2OAc	85	97-98.5°	Ether/Hexane	**3a**	65.29	6.27	5.03
								(65.44)	(6.22)	(5.09)
C_2H_5	OCH_3	H	H	82	58-59°	Methanol/Water	**5a**	70.89	6.31	6.84
								(70.92)	(6.45)	(6.89)
CH_3	OCH_3	H	H	84	36°	Methanol/Water	**5c**	69.72	5.93	7.35
					160°/0.5 mm			(69.83)	(5.86)	(7.40)
$(CH_3)_2CH$-	OCH_3	H	H	77	150°/0.4 mm (b)		**5d**	71.97	6.96	6.38
								(71.87)	(6.96)	(6.45)
$(CH_3)_3C$- (c)	OCH_3	H	H	13	150°/0.1 mm (b)		**5e**	72.71	7.83	6.06
								(72.70)	(7.41)	(6.06)
C_2H_5	H	OCH_3	H	36	63-63.5°	Methanol/Water	**5b**	71.10	6.57	6.94
								(70.92)	(6.45)	(6.89)

(a) Values required are shown in parenthesis. (b) Bath temperature, bulb to bulb distillation. (c) Oxygen analysis Calcd: 13.83. Found: 13.88.

and recrystallised from water as long off-white crystals, m.p. 182-184° (21.78 g.). A second crop was obtained on evaporation of the water (2.04 g.) (total yield 23.82 g.) (63%).

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.38; H, 5.94; N, 7.17.

8-Methoxyquinoline was prepared from oxine by the above method in 92% yield.

8-Methoxy-5-acetoxymethylquinoline (**3c**).

8-Methoxy-5-hydroxymethylquinoline (27.2 g., 0.144 mole) was heated for 1 hour at 80-100° in acetic acid (50 ml.) and acetic anhydride (50 ml.). The solvent was removed *in vacuo* and the residue was treated with excess sodium bicarbonate. The separated oil was extracted into dichloromethane, dried (magnesium sulfate) and evaporated. The residual oil was short path distilled to give a colourless oil (b.p. 190-200°/0.1 mm, bath temperature) which rapidly crystallised. On recrystallisation from ethyl acetate/hexane, the compound was obtained as colourless crystals, m.p. 91-92° (28.87 g.). A second crop (3.25 g. m.p. 85.5-89.5°) was obtained on concentration of the mother liquors (total yield 32.12 g,) (96.6%); nmr (deuteriochloroform): 2.17 (3H, s, CH_3CO), 4.10 (3H, s, CH_3O), 5.50 (2H, s, CH_2O), 7.14 (1H, d, H7), 7.35-7.80 (2H, d + m, H3 + H6), 8.40 (1H, dd, H4), 9.17 (1H, dd, H2).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.53; H, 5.78; N, 6.02.

8-Methoxycarbostyril.

i.

Acetic anhydride (1.02 g., 0.01 mole) was added to a suspension of 8-methoxyquinoline *N*-oxide (1.75 g., 0.01 mole) in *t*-butyl alcohol (10 ml.) and the mixture was heated for 1.5 hours under reflux. The mixture was poured onto ice and was diluted with water to 150 ml. The crystalline product was filtered, washed well with water and dried *in vacuo* (yield 1.08 g.) (61.7%). The compound recrystallised from ethyl acetate/hexane as tan needles (0.80 g.), which readily hydrated (m.p. rather indefinite before drying at 50° under vacuum when it was 109-110.5° (lit (6) m.p. 108-109°).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00; O, 18.26. Found: C, 68.63; H, 5.40; N, 7.82; O, 18.13.

ii.

2-Ethoxy-8-methoxyquinoline **5a** (0.2 g., 0.001 mole) was heated at reflux for 14 hours in dilute (*ca.*, 5*N*) hydrochloric acid (10 ml.). The solution was evaporated to dryness *in vacuo* and the residue was treated with aqueous sodium bicarbonate. The oil so formed crystallised on trituration, was filtered, washed well with water and dried at the pump (0.16 g., 91%). On recrystallisation from ethyl acetate/hexane it formed colourless needles, m.p. 108-109° (mixed m.p. with the product obtained in *i* above, 109-111°, identical also by ir and tlc).

REFERENCES AND NOTES

(1) S. Oae and K. Ogino, *Heterocycles*, **6**, 583 (1977).

(2) Nmr spectra were consistent for this and for all other transformation products.

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(4) J. C. Craig and K. K. Purushothaman, *J. Org. Chem.*, **35**, 1721 (1970).

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