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Photochemical Studies

III. Photorearrangement of Methyl Substituted Quinoline-*N*-oxides in Aqueous Solution and in Potassium Bromide Discs

O. BUCHARDT, J. BECHER and CHR. LOHSE

Chemical Laboratory II (General and Organic Chemistry), University of Copenhagen, The H. C. Ørsted Institute, Copenhagen, Denmark

The seven monomethyl substituted quinoline-*N*-oxides were irradiated in aqueous solution and in potassium bromide discs. The 3-, 4-, 5-, 6-, 7-, and 8-methylquinoline-*N*-oxides all rearranged to give the corresponding carbostyrils. 2-Methylquinoline-*N*-oxide rearranged to 3-methylcarbostyril in solution, and gave an unidentified compound in the potassium bromide disc.

In a previous communication[1] the photorearrangement of quinoline-*N*-oxide to carbostyril was reported. Similar rearrangements for heterocyclic *N*-oxides and nitrones have been described by various workers.[2] The present paper reports an investigation of the preparative possibilities using photorearrangements of substituted quinoline-*N*-oxides, and a novel photorearrangement.

The ultraviolet spectrum of quinoline-*N*-oxide has been described by several authors,[3] who concluded that the absorption at longest wavelength (330—370 mμ) is due to a $n-\pi^*$ transition of a nonbonding electron at the oxygen atom. The ultraviolet absorption spectra of the methyl substituted quinoline-*N*-oxides are very similar to the spectrum of the unsubstituted compound (Table 1) and it may be concluded that the long wavelength absorption of the substituted *N*-oxides is due to a similar $n-\pi^*$ transition.

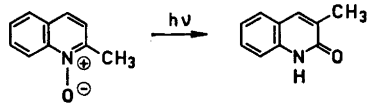
Rearrangement of 3-, 4-, 5-, 6-, 7-, and 8-methylquinoline-*N*-oxides to the corresponding carbostyrils proceeded with good yield on irradiation in aqueous solution (Table 2). 4-Methylcarbostyril was shown to be identical with an authentic sample [5] by nuclear magnetic resonance (Table 3), infrared (Table 4) and ultraviolet spectroscopy (Table 5). The rearranged products from 3-, 5-, 6-, 7-, and 8-methylquinoline-*N*-oxides were identified by their melting points (Table 2), their nuclear magnetic resonance (Table 3), and infrared (Table 4) and ultraviolet spectra (Table 5).

Table 1. Long wavelength ultraviolet absorption of quinoline-*N*-oxides.

Compound	Solvent							
	1 N HCl		H_2O		EtOH		Cyclohexane	
	mμ	log ε	mμ	log ε	mμ	log ε	mμ	log ε
Quinoline-*N*-oxide	317	3.83	313	3.89	327	4.00	351	4.05
2-Methyl- »	319	3.71	314	3.82	319	3.93	344	3.78
3-Methyl- »	320	3.84	313	3.88	317	3.87	351	3.96
4-Methyl- »	316	3.88	315	3.88	330	3.89	360	3.83
5-Methyl- »	319	3.78	328	4.00	332	3.99	351	3.73
6-Methyl- »	323	3.88	319	3.98	323	3.97	349	4.07
7-Methyl- »	328	3.81	314	3.86	318	3.92	354	4.09
8-Methyl- »	319	3.64	330	3.92	334	4.12	350	4.09

Irradiations of the series of *N*-oxides in solid form were carried out in potassium bromide discs (Table 2). The substituted quinoline-*N*-oxides all rearranged to the corresponding carbostyrils with the exception of 2-methylquinoline-*N*-oxide which formed a product (III)* not yet identified, which could also be obtained by irradiating a benzene solution of 2-methylquinoline-*N*-oxide hydrate.[10] The reactions in the solid state were followed by recording the infrared spectra of the potassium bromide discs.

By the irradiation of 2-methylquinoline-*N*-oxide in solution the authors hoped to isolate an oxaziridine intermediate, as found for the photorearrangements of 5,5-dimethyl-l-pyrroline-*N*-oxide[11] and benzaldehyde *N*-phenyloxime.[12] However, 2-methylquinoline-*N*-oxide (I) on irradiation in aqueous solution rearranged to 3-methylcarbostyril (II) in rather low yield with some decomposition (Table 2).



I II

If the irradiation of 2-methylquinoline-*N*-oxide was carried out in 96 % ethanol, a somewhat better yield of 3-methylcarbostyril was obtained.

* This compound is under investigation, and results will be reported in a subsequent communication.

Table 2. Irradiation of quinoline-*N*-oxides in aqueous solution and in KBr discs.

In aqueous solution									In KBr	
Yield				M.p.		Analysis[a]			Temp. °C	Time required for total change of infrared spectrum h
						C	H	N		
Compound	Irradiated in h.	Compound	%	Found °C	Lit. °C	Found %	Found %	Found %		
Quinoline-*N*-oxide	15	Carbostyril	91 [1]							
2-Methyl- »	84	3-Methyl- »	10	238–39	235 [4]	75.40	5.68	8.78		
3-Methyl- »	19	3-Methyl- »	90	238–39	»	75.20	5.39	8.89		
4-Methyl- »	24	4-Methyl- »	80	221–22	222–24 [5]	75.20	5.77	8.84		
5-Methyl- »	24	5-Methyl- »	88	227–28	228 [6]	75.40	5.55	8.69	35	6
6-Methyl- »	24	6-Methyl- »	80	236–38	237 [7]	75.02	5.28	8.56		
7-Methyl- »	24	7-Methyl- »	98	198–99	198 [8]	75.40	5.84	9.10		
8-Methyl- »	24	8-Methyl- »	80	221–22	218–19 [9]	75.40	5.82	8.93		

[a] Calc.: C 75.45; H 5.70; N 8.80.

Table 3. Nuclear magnetic resonance spectra of carbostyrils.[a]

Compound	$-CH_3$	Center of aromatic protons	Olefinic protons	Ratio
Carbostyril	—	2.0	2.55[b] $j = 9$; 1.23[b] $j = 9$	4:1:1
3-Methyl- »	7.45	2.1	1.50	3:4:1
4-Methyl- »	7.03	2.0	2.67	3:4:1
5-Methyl- »	7.22	2.2	2.65[bc] $j = 9$; 1.13[b] $j = 9$	3:3:1:1
6-Methyl- »	7.37	2.3	2.60[b] $j = 9$; 1.33[b] $j = 9$	3:3:1:1
7-Methyl- »	7.37	2.3	2.75[b] $j = 9$; 1.43[b] $j = 9$	3:3:1:1
8-Methyl- »	7.22	2.2	2.63[b] $j = 9$; 1.37[b] $j = 9$	3:3:1:1

[a] All spectra were recorded in trifluoroacetic acid with tetramethylsilane as internal standard. Chemical shifts are in τ ppm, coupling constants are in cps.
[b] Center of doublet.
[c] Center of doublet, partly covered by the absorption of aromatic protons.

Table 4. Carbonyl absorption frequencies in the infrared (in KBr).

Compound	cm^{-1}
Carbostyril	1665
3-Methyl- »	1655
4-Methyl- »	1655
5-Methyl- »	1662
6-Methyl- »	1655
7-Methyl- »	1650
8-Methyl- »	1660

Table 5. Ultraviolet spectra of carbostyrils (in ethanol).

Compound	mμ	log ε	mμ	log ε	mμ	log ε
Carbostyril	229	4.54	268	3.86	329	3.81
3-Methyl- »	220	4.25	269	3.91	324	3.91
4-Methyl- »	230	4.58	268	3.82	327	3.84
5-Methyl- »	234	4.51	281	3.97	333	3.76
6-Methyl- »	233	4.61	271	3.88	337	3.81
7-Methyl- »	232	4.61	276	3.95	329	3.99
8-Methyl- »	233	4.64	276	4.05	332	3.88

RESULTS AND DISCUSSION

The photorearrangement of quinoline-*N*-oxides in aqueous solution appears to be a suitable synthetic method, giving good yields of carbostyrils (Table 2).

It is well documented that nitrones photoisomerize to oxaziridines, which are thermally unstable and rearrange to amides.[11-12] Another type of photochemical reaction has been recorded for pyridine-*N*-oxides in the gas phase. Pyridine- and 3-methylpyridine-*N*-oxides yield pyridine[13] and 3-methylpyridine,[14] respectively, while 2-methylpyridine-*N*-oxide gave 2-pyridylmethanol[15] as the major product with long wavelength irradiation. Several authors have reported that purine-*N*-oxides on irradiation in aqueous solution either rearrange to amide-type compounds or lose oxygen.[16-17]

In the quinoline-*N*-oxide series no deoxygenated products have been isolated, and an oxaziridine intermediate is possible. The quinoline-*N*-oxides form hydrates very easily, however, and it seems plausible that the reactive species in aqueous solution as well as in potassium bromide discs were hydrates

rather than the free *N*-oxides. This would also explain why the gas phase experiments with pyridine-*N*-oxides [13–15] proceeded in a different way than the present experiments with quinoline-*N*-oxides. Furthermore, the failure of adenine-1-*N*-oxide to yield exclusively rearranged products could be due to intramolecular hydrogen bonding of the oxygen atom.[16–17] This indicates that the photoreactions of quinoline-*N*-oxides should be markedly dependent on the solvent, and preliminary experiments support this conclusion.

EXPERIMENTAL

Microanalyses were carried out in the microanalysis department of this laboratory by Mr. Preben Hansen and his staff.

Melting points (uncorrected) were determined on a Reichert melting point microscope.

Infrared spectra for identification were recorded on a Perkin Elmer "Infracord" and infrared spectra for tabulation were recorded on a Perkin Elmer model 21 double beam spectrophotometer. Ultraviolet spectra were recorded on a Perkin Elmer model 137 UV spectrophotometer, and nuclear magnetic resonance spectra on a Varian A 60.

The light source was a medium pressure mercury lamp and in all the experiments pyrex glass was used to filter out light of wavelength shorter than 280 mμ.

Quinolines. 2-Methylquinoline, 4-methylquinoline, and quinoline itself were commercial products, while 5-, 6-, 7-, and 8-methylquinolines were prepared by a method analogous to that described for quinoline,[18] 5- and 7-methylquinoline were obtained as a mixture and separated by gas phase chromatography. 3-Methylquinoline was prepared according to the procedure of Utermohlen.[19]

Quinoline-N-oxides. (Table 6). With the exception of 8-methylquinoline-*N*-oxide quinoline-*N*-oxides were all prepared analogous to the method described for quinoline-*N*-oxide below.

Quinoline (1.50 g) was mixed with 30 % hydrogen peroxide (6.0 ml). Acetic anhydride (2.0 ml) was added to the stirred solution in three portions over a 2 min interval. The solution was kept at about 30°C during the addition, after which time it was heated on a steambath for 3-6 h. The heating was discontinued when the solution turned brown. During the last 20 min of the heating, a stream of nitrogen was blown on the reaction mixture to concentrate it. This was followed by addition of water (10 ml), and 1 N sodium hydroxide (10 ml) and the mixture extracted with chloroform (30 ml). The extract was washed with 1 N sodium hydroxide, water and saturated sodium chloride solution, and filtered through anhydrous magnesium sulfate. Evaporation of the solvent gave quinoline-*N*-oxide in 90 % yield, (m.p. 59–60°C, Ref. 20, 60°C).

8-Methylquinoline-*N*-oxide was prepared with the following exceptions from the general method described above. After mixing the starting materials the reaction mixture was heated to 80°C for 2 h 25 min, after which time the mixture was cooled by the addition of ice. 2 N Sodium hydroxide (10 ml) was then added, and 8-methylquinoline-*N*-oxide isolated in the previously described way as a yellow oil, in 6 % yield. After recrystallization from ether saturated with water, 8-methylquinoline-*N*-oxide was isolated as a crystalline hydrate, m.p. 51–53°C (Table 6).

Irradiation of N-oxides in solution. (Table 2). The irradiation of *N*-oxides in solution was carried out as described in a previous paper.[1] The carbostyrils formed from 3-, 4-, 5-, 6-, 7-, and 8-methylquinoline-*N*-oxide were separated as crystals, and isolated by filtration. Irradiation of 2-methylquinoline in water precipitated a small quantity of crystals while the solution turned dark. The crystals were identified as 3-methylcarbostyril (*vide supra*). By evaporation of the solvent, and column chromatography on florisil of the resulting semicrystalline product an additional small amount of 3-methylcarbostyril was obtained, as well as starting material. In this way more than 90 % of the starting material was accounted for.

If 2-methylquinoline-*N*-oxide was irradiated in 96 % ethanol, 3-methylcarbostyril was obtained in 17 % yield.

Table 6. Methylquinoline-*N*-oxides.

Compound	Yield %	M.p.		Carbon		Hydrogen		Nitrogen	
		Found °C	Lit. °C	Found %	Calc. %	Found %	Calc. %	Found %	Calc. %
2-Methylquinoline-*N*-oxide, 2 H_2O	80	56–62		60.86	61.59	6.55	6.72	6.90	7.18
» » ½ H_2O[a]		68–69	77–78 [21]	72.40	71.49	5.92	6.00	8.36	8.34
3-Methylquinoline-*N*-oxide, ¼ H_2O[a]	81	86–87		73.75	73.46	5.53	5.84	8.62	8.54
4-Methylquinoline-*N*-oxide, 1½ H_2O	82	57–62		64.85	64.57	6.66	6.50	7.41	7.53
4-Methylquinoline-*N*-oxide, ¼ H_2O[a]		120–21	113–15 [22]	72.85	73.46	5.86	5.84	8.43	8.54
5-Methylquinoline-*N*-oxide[a]	90	122–23	115–16 [23]	75.20	75.45	5.92	5.70	8.94	8.80
6-Methylquinoline-*N*-oxide, ¼ H_2O[a]	71	80–82	75 [24]	73.50	73.46	5.84	5.84	8.62	8.54
7-Methylquinoline-*N*-oxide[a]	75	81–84	[25]	74.60	75.45	5.76	5.70	8.67	8.80
8-Methylquinoline-*N*-oxide, 2 H_2O	6	51–53		60.75	61.59	6.62	6.72	7.54	7.18
8-Methylquinoline-*N*-oxide, ¼ H_2O[b]				73.55	73.46	5.84	5.84	8.88	8.54

[a] Dried over P_2O_5 at 80°C for 4–8 h. Very hygroscopic.
[b] Dried over P_2O_5 at 24°C for 24 h. Very hygroscopic.

Irradiation of quinoline-N-oxides in potassium bromide discs. (Table 2). The light source was a 600 W sun lamp. The discs were prepared from *ca.* 2 mg of substance to be irradiated and *ca.* 300 mg potassium bromide. The irradiations lasted from 6 – 10 h (Table 5), and took place in a pyrex container at a distance of 25 cm from the light source. During irradiations the container was continuously flushed with nitrogen.

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