Preparation and Properties of 4-Nitrosoquinolines

Martine Demeunynck, Najat Tohme, Marie-France Lhomme and Jean Lhomme*

Laboratoire de Chimie Organique Biologique, ERA CNRS 827,
Université de Lille I, 59655 Villeneuve d'Ascq Cédex, France

Received April 31, 1983

4-Nitrosoquinoline (**2a**) and 4-nitroso-7-chloroquinoline (**2b**) were prepared from the parent hydroxylamines. Their characteristic nmr spectrum were recorded. These highly reactive compounds condense readily with 2,3-dimethyl-1,3-butadiene and with aniline.

J. Heterocyclic Chem., **21**, 501 (1984).

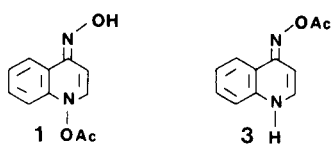
Aromatic nitroso compounds have been known since the very beginning of organic chemistry [1]. However in the π-deficient heterocyclic series (*i.e.* the azines) only a limited number of compounds have been described so far. This situation is due mainly to the lack of general synthetic routes to this class of compounds. For example direct electrophilic attack such as nitrosation or nitration followed by reduction are precluded due to the lack of reactivity of those systems. The consequence is that even very simple nitroso derivatives are still unknown. A few have been quite recently reported by Taylor *et al.* who developed an original access involving the transformation of an amino into a nitrosoheterocycle [2]. We describe here the preparation and some properties of 4-nitrosoquinolines which we happened to obtain in the course of a program devoted to the study of carcinogenic substances.

1-Acetoxy-4-hydroxyimino-1,4-dihydroquinoline (**1**) was prepared as potential metabolite of the carcinogenic 4-nitroquinoline 1-oxide [3]. This compound, which was obtained as its crystalline hydrochloride (by selective acid hydrolysis of the corresponding diester 1-acetoxy-4-acetoxyimino-1,4-dihydroquinoline) turned out to be exceedingly reactive. It eliminates the acetate group to furnish the 4-nitrosoquinoline **2a** (*p*H 7, yield about 50%). This conversion is instantaneous at all *p*H values above 1, *i.e.* when the compound is liberated from its salt [4]. The nitrosoquinoline thus obtained is itself highly unstable and depending upon the reaction conditions and notably the *p*H, complex reaction mixtures can result.

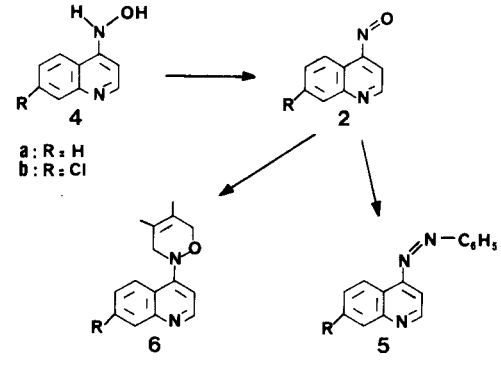
In addition we also observed that the same nitrosoquinoline **2a** was formed with an average yield of 40% in the peracid (MCPBA) treatment of 4-hydroxyaminoquinoline acetate **3** [5].

To determine unambiguously the structure of the nitrosoquinoline **2a** and study its reactivity we examined the preparation by a non ambiguous route, starting from 4-chloroquinoline. Treatment of the latter with hydroxylamine hydrochloride in the presence of potassium carbonate furnished with a quantitative yield the crystalline 4-hydroxyaminoquinoline (**4**), which was smoothly transformed into the desired 4-nitrosoquinoline (**2a**) by mild oxidation using celite impregnated with silver carbonate in a methylene chloride solution at 0°. The yield of the conversion amounts to 60%.

Scheme 1



Scheme 2



This preparation was extended to the homologous quinoline substituted at the 7-position by a chlorine atom. The same sequence of reactions gave the nitroso derivative **2b** with an overall yield of 60% starting from 4,7-dichloroquinoline.

These nitrosoquinolines **2** are obtained as pale yellow solids. They are quite unstable and could not be characterized by elemental analysis. However their mass spectrum shows the expected molecular ion at 158 and 194 respectively for **2a** and **2b**. The nmr spectrum (which exhibits well resolved peaks in the case of **2b**) is characterized by considerable deshielding of the H-5 proton (δ = 9.6) and concommittant shielding for H-3 (δ = 6.1) as compared to the corresponding values observed for quinoline (δ = 7.6 and 7.2 respectively). Comparable chemical shifts variations are observed for **2a** (Table I).

Table I

Proton Chemical Shifts (ppm) for Quinoline [a], 4-Nitrosoquinoline (**2a**), and 7-Chloro-4-nitrosoquinoline (**2b**)

	[c] H-2	[c] H-3	H-4	H-5	H-6	H-7	H-8
[a] Quinoline	8.81	7.26	8.00	7.68	7.43	7.61	8.05
2a	9.10	6.10	—	9.70	7.5-8.5	7.5-8.5	7.5-8.5
2b	9.15	6.10	—	9.65	7.90	—	8.30

[a] L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, 1972, p 211. [b] The spectra were measured in deuteriochloroform. [c] $J_{2,3}$ = 4.5 Hz.

These unusual changes correspond to the expected shifts due to the large magnetic anisotropy of the nitroso group. According to Okazaki and Inamoto [6], who suggested for the N=O bond a model comparable to that proposed for the carbonyl group, protons situated along the N=O bond axis are deshielded, while positions perpendicular to the bond direction are shielded. Using this model and assuming restricted rotation of the nitroso group in **2a** and **2b**, with a large preference for the conformers in which N=O is anti to the peri C_5-H position, the observed shifts are clearly interpretable. The anti H-5 protons are deshielded by a value close to 2 ppm, while the syn H-3 proton exhibits a 1 ppm high field shift.

As expected for nitroso derivatives possessing electro-attracting aryl systems [7], compounds **2** behave as good electrophiles and react with aromatic amines such as aniline to give the corresponding phenylazoquinolines **5**.

They also are good dienophiles, oxazines **6** are rapidly formed by reaction with 2,3-dimethyl-1,3-butadiene, as evidenced by the rapid disappearance of the characteristic yellow colour when the reagents are mixed. The corresponding crystalline derivatives **6** are obtained with good yields (70%).

A number of aryl nitroso compounds have been shown to be involved in the metabolic pathways of carcinogenic aromatic amines [11]. We are presently studying the possible involvement of 4-nitrosoquinoline **2a** and its reactivity towards nucleic acid bases.

EXPERIMENTAL

Melting points were determined on a Totoli apparatus. All melting points are uncorrected. Infrared spectra (ir) were obtained on Perkin-Elmer Model 157G and 237 Spectrophotometers. The ^{1}H nmr spectra were recorded on a Brucker WP 60 (60 MHz). Chemical shifts are reported in ppm (δ) relative to hexamethyldisiloxane as an internal standard. Mass spectra were recorded on Riber-Mag 10-10 spectrophotometer. Elemental analysis was performed by "Service Central de microanalyses du CNRS" (France).

4-Hydroxyaminoquinoline (**4a**).

To a stirred mixture of 10 g (71 mmoles) of potassium carbonate and 10 g (143 mmoles) of hydroxylamine hydrochloride in 120 ml of methanol, 2 g (12 mmoles) of 4-chloroquinoline was added. The mixture was stirred at 60° for 3 hours. The hot solution was then filtered to remove potassium chloride and allowed to stand at room temperature. Compound **4a** crystallized as the hydrochloride in quantitative yield, mp 260-262° dec (lit [8] 262-263°); ir (nujol): 3160, 1640, 1620, 1600, 1145, 1120, 1010, 805, 760 cm^{-1}; nmr (tetradeuteriomethanol): δ 7.1 (d, H-3, 1H, $J_{2,3}$ = 6.8 Hz), 7.5-8 (m, 3H), 8.2 (m, 1H), 8.4 (d, H-2, 1H, $J_{2,3}$ = 6.8 Hz); ms: 160 (M$^+$, 64), 144 (M-18, 100), 129 (37).

3-Chloro-4-(hydroxyamino)quinoline (**4b**).

Compound **4b** was prepared as described above. After reaction and filtration of the hot solution, methanol was concentrated under reduced pressure and the residue was poured into water cooled near 0°. Compound **4b** precipitated as a yellow solid, mp 145-147° dec; nmr (dimethylsulfoxide-d_6): δ 6.0 (d, H-3, 1H, $J_{2,3}$ = 7.7 Hz), 6.8-7.05 (m, H-2, H-6 and H-8, 3H), 7.75 (d, H-5, 1H, $J_{5,6}$ = 8.3 Hz), 9.8 (s, N-H or O-H, 1H), 9.95 (s, O-H or N-H, 1H); ms: 196 (M$^+$+2, 35), 194 (M$^+$, 100), 180 (19), 178 (M$^+$−16, 92), 164 (11), 163 (77), 151 (35), 142 (11), 129 (19).

Anal. Calcd. for $C_9H_7ClN_2O$: C, 55.5; H, 3.6; N, 14.4. Found: C, 55.6; H, 3.7; N, 14.2.

4-(Acetoxyamino)quinoline (**3**).

To a stirred solution of 1 g (5.1 mmoles) of **4a** and 0.4 g (6.2 mmoles) of imidazole in 10 ml of dimethylformamide, was added 1 ml (14 mmoles) of acetic anhydride. The mixture was stirred under inert atmosphere at room temperature for 3 hours and then poured into a saturated aqueous solution of sodium bicarbonate cooled at 0°. Compound **3** precipitated as a white solid which was filtered, washed with water and dried. Recrystallization from methylene chloride gave 0.7 g (70%) of **3**, mp 176-177° (lit [9] 175-178°); ir (nujol): 3440 (N-H), 1730 (C=O), 1620, 1590, 1550, 1350, 1250, 790 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 2.15 (s, $COCH_3$, 3H), 6.1 (d, H-3, 1H, J = 7.5 Hz), 7.1-7.6 (m, 4H), 8.05 (m, 1H), 10.9 (broad, N-H, 1H); ms: 202 (M$^+$, 23), 160 (54), 144 (100), 129 (27), 117 (39).

4-Nitrosoquinoline (**2a**). Method A.

To a solution of 0.5 g (2.5 mmoles) of **4a** in 250 ml of chloroform, was added 5 g of freshly prepared silver carbonate on celite [10]. The mixture was stirred at room temperature in the dark for 3 hours. After filtration on celite to remove silver carbonate, the solution was evaporated under reduced pressure to give 0.32 g (60%) of a yellow powder, mp 82° dec; nmr (deuteriochloroform): δ 6.1 (d, H-3, 1H, $J_{2,3}$ = 4.2 Hz), 7.5-8.5 (m, aromatic, 3H), 9.1 (d, H-2, 1H, $J_{2,3}$ = 4.2 Hz), 9.7 (m, H-5, 1H); ms: 158 (M$^+$, 76), 156 (51), 139 (47), 128 (100).

Method B.

A solution of 0.3 g (1.48 mmoles) of **3** in 75 ml of methylene chloride was cooled near 0° in an ice bath, 0.37 g (2.1 mmoles) of *meta*-chloroperbenzoic acid was added under nitrogen in three equal parts at 20 minutes intervals. The mixture was stirred in the dark for 2 hours, then cooled near −20° and washed with an aqueous solution of sodium bicarbonate (0.18 g in 50 ml of water). The organic layer was collected, dried on 4 Å molecular seives and evaporated to dryness. The crude product was eluted over silica gel (elution with ether) to give 0.096 g (41%) of **2a**.

7-Chloro-4-nitrosoquinoline (**2b**).

Compound **2b** was prepared as described above from 0.4 g (2.06 mmoles) of **4b** and 2.9 g of silver carbonate on celite (Method A) to give 0.25 g (63%) of a pale yellow powder, mp 141-142° dec; nmr (deuteriochloroform): δ 6.1 (d, H-3, 1H, $J_{2,3}$ = 4.7 Hz), 7.9 (dd, H-6, 1H, $J_{5,6}$ = 9 Hz and $J_{6,8}$ = 2.2 Hz), 8.3 (d, H-8, 1H, $J_{6,8}$ = 2.2 Hz), 9.15 (d, H-2, 1H, $J_{2,3}$ = 4.7 Hz), 9.65 (d, H-5, 1H, $J_{5,6}$ = 9 Hz); ms: 194 (M$^+$ + 2, 26), 192 (M$^+$, 100), 164 (38), 162 (93), 149 (6), 137 (15), 135 (52), 127 (27).

4,5-Dimethyl-3,6-dihydro-*N*-(4-quinolinyl)-1,2-oxazine (**6a**).

To a solution of 0.067 g (0.43 mmole) of 4-nitrosoquinoline (**2a**) in 10 ml of methylene chloride, 0.5 ml (4.4 mmoles) of 2,3-dimethyl-1,3-butadi-

ene was added under a nitrogen atmosphere. The mixture was stirred at room temperature for 2 hours. After removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica, eluting with a 1:1 mixture of petroleum ether-ether. The compound was recrystallized from hexane giving 0.072 g (71%) of crystals, mp 100-101° dec; nmr (deuteriochloroform): δ 8.75 (d, H-2, 1H, $J_{2,3}$ = 4.9 Hz), 7.9-8.1 (m, H-5 and H-8, 2H), 7.4-7.7 (m, H-6 and H-7, 2H), 7.13 (d, H-3, 1H, $J_{2,3}$ = 5 Hz), 4.36 (s, OCH_2, 2H), 3.69 (s, NCH_2, 2H), 1.65 (s, $2CH_3$, 6H); ms: 240 (M^+, 66), 222 (M − 18, 74), 221 (58), 207 (38), 206 (15), 195 (6), 158 (27), 144 (17), 129 (20), 128 (100), 103 (14), 101 (46).

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.9; H, 6.7; N, 11.6. Found: C, 74.8; H, 6.9; N, 11.5.

4,5-Dimethyl-3,6-dihydro-*N*-(7-chloro-4-quinolinyl)-1,2-oxazine (**6b**).

Compound **6b** was prepared as described above for **6a**, from 0.2 g (1.04 mmoles) of **2b** to give 0.16 g (56%) of **6b**, mp 146.5-148°; nmr (deuteriochloroform): δ 1.6 (s, CH_3, 6H), 3.65 (s, N-CH_2, 2H), 4.35 (s, O-CH_2, 2H), 7.05 (d, H-3, 1H, $J_{2,3}$ = 5 Hz), 7.35 (dd, H-6, 1H, $J_{5,6}$ = 9 Hz and $J_{6,8}$ = 2.2 Hz), 7.95 (d, H-5, 1H, $J_{5,6}$ = 9 Hz), 8.0 (d, H-8, 1H, $J_{6,8}$ = 2.2 Hz), 8.7 (d, H-2, 1H, $J_{2,3}$ = 4.9 Hz); ms: 276 (M^+ + 2, 8), 274 (M^+, 28), 258 (34), 257 (39), 255 (100), 221 (27), 206 (18), 194 (6), 192 (11), 164 (10), 162 (32), 137 (6), 135 (20), 127 (14).

Anal. Calcd. for $C_{15}H_{15}ClN_2O$: C, 65.5; H, 5.5; N, 10.1. Found: C, 65.5; H, 5.5; N, 10.1.

4-(Phenylazo)quinoline (**5a**).

Aniline (0.15 ml, 1.64 mmoles) was added to a suspension of 0.06 g (0.38 mmole) of **2a** in 3 ml of acetic acid. The mixture was stirred at room temperature under nitrogen for 12 hours. Acetic acid was evaporated *in vacuo* at 40° and **5a** was purified by chromatography over silica gel (elution with a 1:1 mixture of hexane-ether) and recrystallized from pentane to give 0.017 g (20%) of red crystals, mp 63.5-64.5°; nmr (deuteriochloroform): δ 7.4-8.2 (m, 9H), 8.7 (m, H-5, 1H), 9.0 (d, H-2, 1H, $J_{2,3}$ = 4.8 Hz); ms: 233 (M^+, 12), 128 (22), 105 (16).

Anal. Calcd. for $C_{15}H_{11}N_3$: C, 77.2; H, 4.7; N, 18.0. Found: C, 77.3; H, 4.8; N, 18.0.

7-Chloro-4-(phenylazo)quinoline (**5b**).

Compound **5b** was prepared from 0.25 g (1.29 mmoles) of **2b** and 0.25 ml (2.7 mmoles) of aniline by the procedure described for **5a**. The yield was 25% after chromatography and recrystallization from hexane, mp 117-118°; nmr (deuteriochloroform): δ 7.4 (d, H-3, 1H, $J_{2,3}$ = 4.8 Hz), 7.5-7.7 (m, 4H), 7.9-8.2 (m, 3H), 8.65 (d, H-5, 1H, $J_{5,6}$ = 9 Hz), 8.95 (d, H-2, 1H, $J_{2,3}$ = 4.8 Hz); ms: 269 (M^+ + 2, 4), 267 (M^+, 15), 164 (4), 162 (11), 137 (4), 134 (13), 127 (4), 105 (28).

Anal. Calcd. for $C_{15}H_{10}ClN_3$: C, 67.3; H, 3.7; N, 15.7. Found: C, 67.5; H, 3.8; N, 15.6.

Acknowledgement.

This research was supported by the DGRST and the INSERM (cancérogenèse chimique, 78.7.2628 and 77.79.109). M. D. is fellow of the "Ligue Française contre le cancer" which is gratefully acknowledged.

REFERENCES AND NOTES

[1] S. Patai, "The Chemistry of Nitro and Nitroso Groups", John Wiley and Sons, New York, 1969.

[2] E. C. Taylor, C. P. Tseng and J. B. Rampal, *J. Org. Chem.*, **47**, 552 (1982).

[3] M. Demeunynck, M. F. Lhomme and J. Lhomme, *Tetrahedron Letters*, 3189 (1981).

[4] The reaction is still more rapid above *p*H 10, *i.e.*, when the oximate is formed. However in such conditions a number of secondary reactions are observed.

[5] The peracid oxidation of 4-hydroxylaminoquinoline acetate was conducted in an attempt to oxidise the heterocyclic nitrogen to prepare the corresponding *N*-oxide.

[6] R. Okazaki and N. Inamoto, *J. Chem. Soc. (B)*, 1584 (1970).

[7] G. Kresze, J. Firl, H. Zimmer and U. Wollnik, *Tetrahedron*, **20**, 1605 (1964).

[8] M. Hamana and K. Funakoshi, *Yakugaku Zasshi*, **84**, 42 (1964).

[9] O. Ogawa, Y. Kawazoe and H. Sawanishi, *Chem. Pharm. Bull.*, **28**, 3029 (1980).

[10] M. Fetizon and M. Golfier, *Compt. Rend.*, **267**, 900 (1968).