The Chemistry of Pyridine. IV. The Substitution of Quinoline 1-Oxide by Mercaptans[1]

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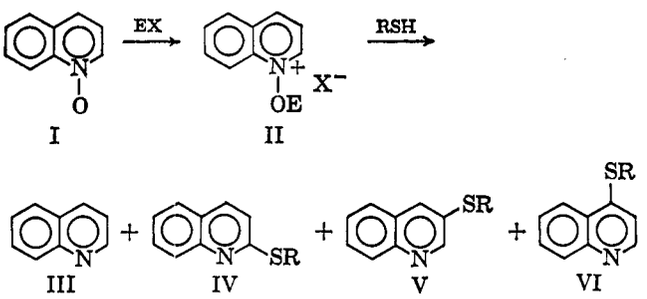
Quaternization of quinoline 1-oxide by a number of different reagents enabled the heterocyclic ring to be substituted by mercaptans. The reaction of 1-ethoxyquinolinium *p*-toluenesulfonate with sodium *n*-butylmercaptide in hot 1-butanethiol furnished a mixture of 2-, 3-, and 4-butylmercaptoquinolines, with the 3 isomer being the major product. When quinoline 1-oxide was treated with 1-butanethiol in the presence of either acetic anhydride or benzenesulfonyl chloride, a mixture of the above sulfides was obtained which consisted mainly of the 2 isomer.

In a previous study,[2,3] it was found that the substitution of pyridine 1-oxide *via* 1-alkoxy-, 1-acyloxy-, or 1-arenesulfonyloxypyridinium salts by mercaptans furnished a mixture of 2-, 3-, and 4-alkylmercaptopyridines, the yield and distribution of these isomers being a function of the group departing from the ring nitrogen atom. It was of interest to determine if the heterocyclic ring of quinoline 1-oxide could be substituted by a similar series of reactions. It was essential to quaternize quinoline 1-oxide (I) first by reagents of type EX (where E represents an electrophilic atom) prior to treatment with a mercaptan or mercaptide ion. Hence I was transformed first to the 1-ethoxy-, 1-acetoxy-, or 1-benzenesulfonyloxyquinolinium salts, II (E being C_2H_5, $COCH_3$, or $SO_2C_6H_5$, respectively), and then treated with 1-butanethiol. From each of these reactions there was isolated quinoline (III), and a mixture of 2-, 3-, and 4-butylmercaptoquinolines (IV, V, and VI, where R is n-C_4H_9). Quinoline was readily separated from the sulfides and any starting N-oxide by distillation.



The starting N-oxide was too water soluble to be extracted completely into methylene chloride during the isolation of the sulfides. However, if any N-oxide was extracted during the work-up, it codistilled with the sulfides but was separated readily during chromatography on alumina. The yields of quinoline and the sulfides are listed in Table I.

2- and 4-butylmercaptoquinolines (IV and VI) were synthesized independently by the displacement of the chlorine atom in 2- and 4-chloroquinoline by *n*-butylmercaptide ion. 4-Butylmercaptoquinoline was also prepared readily by the literature method[4] which consists of the displacement of the nitro group in 4-nitroquinoline 1-oxide to form 4-butylmercaptoquinoline 1-oxide,[5] which was then reduced to compound VI. 3-Butylmercaptoquinoline (V), which was isolated in these reactions, was readily distinguished from the other two isomers by its nmr spectrum which showed the resonance due to H-2 well separated downfield (from TMS) as a doublet with characteristic *meta* coupling to H-4 (see Experimental Section). The availability of the nmr and infrared spectra of the three isomers, IV–VI, enabled us to identify the contents of each small eluate during column chromatography.

TABLE I

PRODUCTS FROM THE REACTION OF QUINOLINE 1-OXIDE WITH 1-BUTANETHIOL IN THE PRESENCE OF A QUATERNIZING AGENT OF TYPE EX

EX	Yield of sulfides,[a] %	% of butylmercaptoquinolines in, —sulfide mixture[b]— 2	3	4	Yield of quinoline,[a] %
p-$CH_3C_6H_4SO_3C_2H_5$	28	17	70	13	34
$(C_2H_5)_2SO_4$	21	15	76	8	36
$(CH_3CO)_2O$	23	90	10	..	28
$C_6H_5SO_2Cl$	33	81	11	8	20

[a] The yields are based on quinoline 1-oxide. [b] Separated by column chromatography on alumina.

Quaternization of quinoline 1-oxide with ethyl *p*-toluenesulfonate afforded a crystalline salt (II, E = C_2H_5, X = p-$CH_3C_6H_4SO_3^-$) which reacted with sodium *n*-butylmercaptide in 1-butanethiol[2] to give the 2-, 3-, and 4-butylmercaptoquinolines, the 3 isomer predominating. When ethyl sulfate was used instead of ethyl *p*-toluenesulfonate as the quaternizing agent, a similar reaction yielded a comparable mixture of IV–VI. The substitution of the 1-ethoxyquinolinium ion paralleled that of the pyridine counterpart, both in yield and isomer distribution.[3]

The reaction of I in boiling acetic anhydride assumed that 1-acetoxyquinolinium acetate (II, E = CH_3CO; X = CH_3CO_2) was formed first, *in situ*,[6] which was then attacked by 1-butanethiol. The sulfides isolated consisted mainly of 2-butylmercaptoquinoline and a very small amount of the 3 isomer. The best over-all yield in this substitution reaction was realized when

(1) This work was supported in part by the National Science Foundation (G-22191) and the National Institutes of Health, U. S. Public Health Service (General Research Grant, 1-S01-FR-5564-01).

(2) L. Bauer and L. A. Gardella, *J. Org. Chem.*, **28**, 1320 (1963).

(3) L. Bauer and T. E. Dickerhofe, *ibid.*, **29**, 2183 (1964).

(4) E. Profft and W. Rolle, *J. Prakt. Chem.*, [4] **11**, 28 (1960).

(5) It was of interest to note that the reaction of 4-nitroquinoline 1-oxide with *n*-butylmercaptide ion proceeded by a displacement reaction and did not involve substitution at the 3-position as was observed when the ethyl malonate anion was used: H. J. Richter and N. E. Rustad, *J. Org. Chem.*, **29**, 3381 (1964).

(6) N-Acetoxypyridinium and quinolinium salts have been isolated recently as perchlorates: C. W. Muth and R. S. Darlak, *ibid.*, **30**, 1909 (1965).

I was quaternized with benzenesulfonyl chloride (E = $C_6H_5SO_2$; X = Cl) and a suspension of this salt was heated with 1-butanethiol in benzene. The most noticeable feature of the last two experiments was that starting from I considerably less β substitution took place than in the pyridine series. When pyridine 1-oxide was treated with 1-butanethiol in the presence of acetic anhydride or benzenesulfonyl chloride, 2- and 3-butylmercaptopyridines were isolated in almost equal amounts.

Each of these reactions was accompanied by an appreciable quantity of quinoline. This reduction can be accounted for by a variety of mechanisms. The decomposition of 1-alkoxypyridinium salts by strong bases (*e.g.*, hydroxide ion, Grignard reagents) to pyridine and aldehydes is a well-known reaction.[7] It is plausible that unreacted 1-ethoxyquinolinium salt was decomposed to quinoline by hydroxide ion during the alkaline work-up. The reduction of quinoline 1-oxide in acetic anhydride or benzenesulfonyl chloride takes place probably by a number of different paths. Since in both of these reactions, the formation of the salt II from I is an equilibrium process, it is possible that some N-oxide was present during the reaction. It had been shown that hot 1-butanethiol reduced pyridine 1-oxides to pyridine[8] and it is quite possible that some of the quinoline 1-oxide is reduced by this process in the reactions under study. Furthermore, in acetic anhydride, reduction of II can take place by the mechanisms suggested recently for the reduction of N-oxides by acid anhydrides.[9-11] No attempt was made to ascertain which mechanism(s) operated since we were interested primarily in the substitution reaction.

The mechanisms suggested to explain similar reactions in the pyridine series[3] can be applied to the substitution of the quinolinium salts, II. However, no satisfactory arguments can be advanced at present to explain why 1-acetoxy- and 1-benzenesulfonyloxypyridinium salts are substituted to a larger extent at the β positions than the quinolinium counterparts. Nor, is it clear why β substitution predominates when the leaving group is ethoxy, while α substitution predominates when acetate and benzenesulfonate are the departing groups.

Experimental Section[12]

Materials.—Quinoline 1-oxide, bp 130–134° at 0.2 mm, mp 59–60° (lit.[13] mp 62°), was prepared by the oxidation of quinoline in the fashion outlined for pyridine 1-oxide.[14] 2- and 4-chloroquinoline were purchased from Aldrich Chemical Co., 4-nitroquinoline 1-oxide from Beacon Chemical Industries, sodium hydride (53% dispersion in mineral oil) from Metal Hydrides, Inc., and activated alumina from Alcoa (Grade F-20). Petroleum ether used in this work refers to the fraction boiling at 30–60°. The generous gifts of 1-butanethiol from Pennsalt Chemical Co. and Phillips Petroleum Co. are gratefully acknowledged.

Synthesis of Reference Compounds. 2-Butylmercaptoquinoline.—Sodium hydride (9.1 g of dispersion, 0.2 mole) was added in divided portions to a cold solution of 1-butanethiol (21 ml, 0.2 mole) in N,N-dimethylformamide (50 ml). A solution of 2-chloroquinoline (16.4 g, 0.1 mole) in N,N-dimethylformamide (30 ml) was then added dropwise. The mixture was heated at 100° for 2.0 hr and then acidified with 10% hydrochloric acid; the solution was concentrated *in vacuo*. The solid residue was extracted with petroleum ether and then treated with 10% sodium hydroxide solution. The basic mixture was extracted with methylene chloride (four 50-ml portions). Distillation of the extract gave an oil (10.0 g), bp 123–134° at 0.2 mm, which was chromatographed on alumina (150 g). Elution with petroleum ether (1.1 l.) and redistillation gave the product (8.3 g, 45%), bp 120–122° at 0.1 mm. The very strong infrared absorption bands at 1085 and 1136 cm^{-1} readily distinguished this isomer from 3- and 4-butylmercaptoquinoline. Its nmr spectrum showed the aromatic protons as a doublet at δ 8.14 ($J_{3,4}$ = 8 cps)[15] for H-4 and as a multiplet from δ 7.02 to 7.82 for the remaining five protons. The *n*-butyl group showed the $-CH_2-S$ as a triplet, δ 3.37 (J = 7 cps), the terminal CH_3 as a triplet at δ 0.86 (J = 6 cps), and the remaining CH_2 groups as a multiplet centered at δ 1.62.

Anal. Calcd for $C_{13}H_{15}NS$: C, 71.84; H, 6.97; N, 6.45. Found: C, 71.89; H, 7.04; N, 6.54.

4-Butylmercaptoquinoline. A. From 4-Chloroquinoline.—This was prepared in 55% yield, as above, using 4-chloroquinoline and 1-butanethiol. The sulfide was distilled and then chromatographed on alumina. It was eluted with benzene–ether (1:1, 600 ml) and was redistilled, bp 144–145° at 0.05 mm. Infrared absorption characteristic of this isomer appeared as a medium band at 985 cm^{-1}. Its nmr spectrum showed a resonance furthest downfield, δ 9.05 ($J_{2,3}$ = 5 cps),[15] which was assigned to H-2, coupled to H-3, which was seen as a doublet at δ 7.10. The remaining four aromatic protons appeared as two sets of multiplets centered at δ 7.85 and 8.45. The *n*-butyl group showed three sets of signals, the CH_2S at 2.92, the terminal CH_3 at 0.90, and the two CH_2 groups from δ 1.15 to 1.85.

Anal. Found: C, 72.30; H, 7.15; N, 6.43.

B. From 4-Nitroquinoline 1-Oxide.—A suspension of sodium *n*-butyl mercaptide (as described for 2-butylmercaptoquinoline) was added to a stirred suspension of 4-nitroquinoline 1-oxide (19.0 g, 0.1 mole) in N,N-dimethylformamide (100 ml) over a period of 0.5 hr. The mixture was heated at 100° for 3 hr, cooled, acidified with 10% hydrochloric acid and concentrated at 100° and 30 mm. The residue was dissolved in acetic acid (35 ml) and heated to 100°, and iron powder (7 g) was added to the solution in small portions over 2 hr. The mixture was cooled, acidified with 10% hydrochloric acid (150 ml), filtered, extracted with ether, and made basic by the addition of sodium hydroxide pellets. The slurry so obtained was filtered and the residue was triturated with ether several times. The filtrate was extracted with methylene chloride. Both organic extracts were combined, dried (Na_2SO_4), and distilled to give the thio ether (6.1 g, 36% based on the N-oxide), bp 135–140° at 0.2 mm, identical with the one prepared from 4-chloroquinoline.

1-Ethoxyquinolinium *p*-Toluenesulfonate.—Quinoline 1-oxide (7.3 g, 0.05 mole) was heated with ethyl *p*-toluenesulfonate (10.0 g, 0.05 mole) at 100° for 1.0 hr. The dark gum was cooled and washed with ether, then tetrahydrofuran. Crystallization from acetonitrile–tetrahydrofuran afforded the salt (10.0 g, 60%) as a colorless solid, mp 71°.

Anal. Calcd for $C_{18}H_{19}O_4NS$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.37; H, 5.60; N, 4.34.

The Reaction of 1-Ethoxyquinolinium Salts with Sodium *n*-Butyl Mercaptide. A. The *p*-Toluenesulfonate.—Sodium hydride (9.1 g of dispersion, 0.2 mole) was added in small portions to 1-butanethiol (150 ml) at 0° with stirring. Then 1-ethoxyquinolinium *p*-toluenesulfonate (15.9 g, 0.05 mole) was added to the suspension of the mercaptide. The mixture was heated at

(7) These and related mechanisms have been discussed recently by R. Eisenthal and A. R. Katritzky, *Tetrahedron*, **21**, 2205 (1965).

(8) D. I. Relyea, P. O. Tawney, and A. R. Williams, *J. Org. Chem.*, **27**, 477 (1962).

(9) C. Rüchardt, S. Eichler, and O. Krätz, *Tetrahedron Letters*, 233 (1965).

(10) T. Cohen, I. H. Song, and J. H. Fager, *ibid.*, 237 (1965).

(11) T. Koenig, *ibid.*, 3127 (1965).

(12) All melting and boiling points are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill. The nitrogen analyses were obtained using a Coleman nitrogen analyzer, Model 29. The infrared spectra were determined in $CHCl_3$ solution with a Perkin-Elmer spectrophotometer (Model 337); the nmr spectra were obtained neat with a Varian A-60 spectrometer. All signals are recorded downfield from TMS (internal reference) in parts per million (δ); the number of protons was assigned to each area by means of integration.

(13) J. Meisenheimer, *Ber.*, **59**, 1850 (1926).

(14) H. S. Mosher, L. Turner, and A. Carlsmith, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 828.

(15) M. H. Palmer and B. Semple [*Chem. Ind.* (London), 1766 (1965)] report the following coupling constants for quinolines are typical: $J_{3,4}$ = 8.3 cps, $J_{2,3}$ = 4.2 cps.

100° for 2 hr and cooled, and the reaction was quenched with cold 10% hydrochloric acid (120 ml). The phases were separated and the organic layer was extracted with a portion of 10% hydrochloric acid. The combined acid fractions were extracted with four portions of 1:1 benzene–ether (50 ml), then made basic with 20% sodium hydroxide solution. Extraction with methylene chloride (five 75-ml portions) and subsequent distillation gave quinoline (2.2 g, identified by its infrared spectrum), bp 75–85° at 0.2 mm, followed by the major fraction (3.2 g), bp 131–134° at 0.2 mm. The latter was chromatographed on alumina (100 g). Elution with petroleum ether–benzene (9:1, 900 ml) gave 2-butylmercaptoquinoline, 0.5 g. Further elution with petroleum ether–benzene (4:1, 150 ml; 7:3, 900 ml; 3:2, 450 ml; 1:1, 450 ml; 1:3, 450 ml) and benzene (450 ml) gave 3-butylmercaptoquinoline, 2.1 g, bp 132° at 0.1 mm. Its nmr spectrum showed H-2 as a doublet at δ 9.07 ($J_{2,4}$ = 2.5 cps) and the remaining five aromatic protons as a complex multiplet between δ 8.40 and 7.50. The aliphatic protons gave the expected triplet at 3.01 (CH_2S), a multiplet between 1.85 and 1.15 (CH_2 groups), and a triplet at δ 0.90 (CH_3).

Anal. Found: C, 71.89; H, 7.03; N, 6.49.

Continued elution with benzene–ether (99:1, 150 ml; 49:1, 450 ml; 9:1, 450 ml; 3:1, 150 ml) gave 4-butylmercaptoquinoline, 0.4 g. No quinoline 1-oxide could be detected upon elution with ether or methanol.

B. The Ethyl Sulfate Salt.—Quinoline 1-oxide (14.5 g, 0.1 mole) was heated with ethyl sulfate (15.4 g, 0.1 mole) at 100° for 1.5 hr. The mixture was cooled, washed with dry ether, and used without further purification. A suspension of sodium *n*-butylmercaptide in butanethiol was prepared as in A, using 4.6 g (0.1 mole) of sodium hydride dispersion. The gummy quinolinium salt, prepared above, was then added to the suspension of the mercaptide in 1-butanethiol. The mixture was heated at 100° for 2 hr, then worked up as in part A. Distillation of the basic fraction gave quinoline (4.7 g), bp 62–70° at 0.2 mm, and a 2-, 3-, and 4-butylmercaptoquinoline mixture (5.5 g) together with quinoline 1-oxide, bp 131–134° at 0.2 mm. The high-boiling mixture was chromatographed on alumina (90 g). Elution with petroleum ether–benzene (20:1, 300 ml; 10:1, 300 ml) gave 2-butylmercaptoquinoline (0.6 g). Further elution with petroleum ether–benzene (9:1, 150 ml; 3:1, 75 ml) gave a mixture (0.2 g), shown (nmr) to consist of equal parts of 2- and 3-butylmercaptoquinoline. Further elution with petroleum ether–benzene (3:1, 150 ml; 1:1, 600 ml), benzene (600 ml), and benzene–ether (99:1, 150 ml; 20:1, 150 ml; 9:1, 75 ml) gave 3-butylmercaptoquinoline (3.4 g), identified by its nmr spectrum. Continued elution with benzene–ether (1:1, 150 ml) and ether (225 ml) gave 4-butylmercaptoquinoline (0.3 g) and with methanol (150 ml) furnished quinoline 1-oxide (0.21 g).

The Reactions of Quinoline 1-Oxide with 1-Butanethiol. C. In the Presence of Acetic Anhydride.—Quinoline 1-oxide (14.5 g, 0.1 mole) was dissolved in acetic anhydride (100 ml), and 1-butanethiol (32 ml, 0.3 mole) was added slowly. The mixture warmed spontaneously and was then heated under reflux for 2 hr and cooled, and the solvents were removed under reduced pressure. The residue was treated with 10% hydrochloric acid, and the mixture was worked up as under A. The basic fraction was boiled down with several portions of benzene, then chromatographed on alumina (140 g) without prior distillation. Elution with petroleum ether (400 ml) gave 2-butylmercaptoquinoline (4.5 g). Further elution with petroleum ether (150 ml) gave a mixture (0.2 g), shown to be composed of equal amounts of the 2- and 3-butylmercaptoquinolines (nmr). Pure 3-butylmercaptoquinoline (0.5 g) was eluted by petroleum ether (375 ml) and petroleum ether–benzene (9:1, 100 ml). Continued elution with benzene (600 ml) furnished quinoline (3.6 g) and then with methanol (100 ml) to give quinoline 1-oxide (0.9 g).

D. In the Presence of Benzenesulfonyl Chloride.—Benzenesulfonyl chloride (17.7 g, 0.1 mole) was added dropwise to a solution of quinoline 1-oxide (14.5 g, 0.1 mole) in benzene (100 ml). Then 1-butanethiol (32 ml, 0.3 mole) was added and the mixture was heated at 100° for 2.0 hr. The mixture was cooled and worked up as under A. Distillation of the basic fraction gave quinoline (2.6 g), bp 60–70° at 0.4 mm, and another fraction (7.4 g), bp 132–136° at 0.7 mm. A portion (3.7 g) of the latter was chromatographed on alumina (80 g). Elution with petroleum ether (1 l.), petroleum ether–benzene (19:1, 500 ml) and benzene (100 ml) gave 2-butylmercaptoquinoline (2.9 g). Elution with benzene (200 ml) gave a mixture of 3- and 4-butylmercaptoquinoline (0.5 g) in the ratio of 2:3 as determined from its nmr spectrum. Further elution with benzene–ether (19:1, 100 ml) gave 3-butylmercaptoquinoline (0.2 g), and with ether–methanol (1:1, 100 ml) gave quinoline 1-oxide (0.1 g).

2-Azaquinolizinium Oxides[1]

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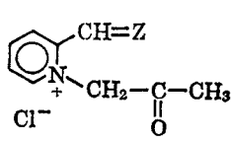
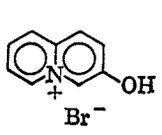
Bromoacetone reacts with picolinaldoxime or with the oxime of 2-acetopyridine to yield 2-azaquinolizinium 2-oxide salts substituted in the 3- or 1,3-positions, respectively. Benzologs of the title system were prepared by reaction of bromoacetone with 1- or 3-oximinomethylisoquinoline. The substitution of chloroacetaldoxime for bromoacetone has made possible the preparation of the parent system. 2-Azaquinolizinium 2-oxide and the 3-methyl homolog have been reduced to known 2-azaquinolizidine derivatives.

Schraufstätter[2] discovered that the salt I, obtained by quaternization of picolinaldehyde diethyl acetal with chloroacetone, readily undergoes hydrolysis and cyclization in boiling 48% hydrobromic acid affording 3-hydoxyquinolizinium ion (II). It seemed possible that through use of commercially available picolinaldoxime a quaternary salt (Ib) capable of undergoing hydrolysis and cyclization might be formed.



Ia, Z = $(OC_2H_5)_2$
b, Z = NOH



II

When picolinaldoxime in acetone or tetramethylene sulfone solution was allowed to react with bromoacetone, the resulting salt was unaffected by boiling 48% hydrobromic acid and the ultraviolet absorption spectrum of the salt was more complex than that expected for Ib. Since glutaconic dialdehyde reacts with hydroxylamine to afford pyridine 1-oxide,[3] and homophthaldehyde (III) under the same conditions yields isoquinoline 2-oxide,[4] it seemed likely that the new product was 3-methyl-2-azaquinolizinium 2-oxide

(1) This investigation was supported by Public Health Service Research Grant No. H-2170 of the National Heart Institute.

(2) E. Schraufstätter, *Angew. Chem. Intern. Ed. Engl.*, **1**, 593 (1962).

(3) P. Baumgarten, R. Marlander, and J. Olshausen, *Ber.*, **66**, 1802 (1933).

(4) C. Schöpf, A. Hartmann, and K. Koch, *ibid.*, **69**, 2766 (1936).