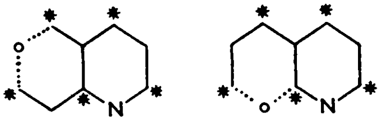
182. *Electrophilic Substitution. Part IX.* The Anomalous Nitrations of Quinoline.*

By M. J. S. Dewar and P. M. Maitlis.

Quinoline has been observed to be nitrated in the 3-, 6-, and 8-position under certain conditions, and an explanation of this anomaly is offered. The nitration with pernitrous acid to give 5-, 6-, 7-, and 8-nitroquinolines is also discussed.

ELECTROPHILIC substitution in heterocyclic systems [1] is governed by (*a*) the relative ease of substitution of the different positions in the corresponding hydrocarbon and (*b*) the effect of the heterocyclic atom. In quinoline effects due to (*a*) should favour substitution, as in naphthalene, at α-positions, *i.e.*, at position 4, 5, or 8. The effect of the ring-nitrogen atom in electrophilic substitution should be two-fold: it should strongly deactivate the *Py*-ring and only favour substitution when the nitrogen occupies an unstarred position in the transition state, as shown:



One would therefore expect substitution in the 5-, 6-, and 8-positions in quinoline, the relative amounts depending on the magnitude of the various effects; and in fact nitration of quinoline in sulphuric acid gives a mixture of 5- and 8-nitroquinoline. Nevertheless nitrations of quinoline have been reported in which 7-nitroquinoline was stated to be the main product. Bacharach, Haut, and Caroline [2] reported that heating quinoline with lithium nitrate, copper nitrate, and acetic anhydride gave 7-nitroquinoline; Schorigin and

---

* Part VIII, *J.*, 1957, 345.

[1] Cf. Dewar, " Progress in Organic Chemistry," Butterworths, London, 1953, p. 21.

[2] Bacharach, Haut, and Caroline, *Rec. Trav. chim.*, 1933, **52**, 413.

Toptchiev[3] obtained the same material (together with a substance, m. p. 170—180°, which they suspected of being the 5 : 7-dinitroquinoline) by dripping nitrogen dioxide on hot quinoline. Laville and Waters,[4] investigating the action of pernitrous acid on quinoline, isolated 6- and 7-nitroquinilines in roughly equal amounts. These reactions needed further investigation, for they seemed contrary to existing theory.

EXPERIMENTAL

Materials.—The quinoline used was Hopkin and Williams's puriss. grade, which had been redistilled under a vacuum and stored over alumina. With one exception (as mentioned) the nitric acid used was of *d* 1·5. Spectra were measured in spectroscopically pure *cyclo*hexane on a Unicam S.P. 500 spectrophotometer. 5- and 7-Nitroquinoline used as reference compounds were synthesised by Bradford, Elliot, and Rowe's method;[5] commercial specimens of the 6- and 8-nitroquinoline were crystallised and sublimed *in vacuo* to constant m.p. Except where stated otherwise, the light petroleum used had b. p. 40—60°. Aqueous ammonia (*d* 0·880) was used for neutralising acid solutions.

Analytical Methods.—Chromatography proved unsuitable for quantitative analysis of mixtures of mononitroquinolines; however preliminary chromatography with benzene–light petroleum (b. p. 60—80°) on alumina was used to separate mixtures of quinoline with mononitroquinolines from the crude products. Quinoline was then removed by partial basification, the mononitroquinolines being extracted from a weakly acid solution (pH 2·1) with chloroform. Any 3-nitroquinoline was separated by virtue of its insolubility in N-hydrochloric acid. The detailed procedure used and the efficiency of the method are indicated by the following experiment with an artificial mixture.

3-Nitroquinoline (880 mg.), 6-nitroquinoline (59 mg.), 8-nitroquinoline (59 mg.), and quinoline (7·39 g.) were dissolved in acetic anhydride (100 ml.), hydrolysed with ice and water, and neutralised to litmus with ammonia. The volume of liquid was about 600 ml. This solution was extracted with chloroform (5 × 200 ml.), and the aqueous solution then discarded. The chloroform solution was next extracted with N-hydrochloric acid (4 × 200 ml.); the *Bz*-nitroquinolines and quinoline passed into the aqueous layer. The chloroform solution was then dried (Na_2SO_4) and filtered and the solvent distilled off. The residue, fraction I (3-nitroquinoline), a pale yellow solid (840 mg., 95%), had m. p. (crude) 121—125°; after one crystallisation it had m. p. 129—130°.

The acid solution was then basified to pH 2·2 and extracted with chloroform (4 × 150 ml.), giving fraction II in the chloroform layer. Since a mixture of chloroform and quinoline is hard to separate, the aqueous solution was washed with ether (2 × 50 ml.), then neutralised with ammonia and extracted with ether (5 × 200 ml.); this on drying (Na_2SO_4) and evaporation gave fraction III (quinoline; 6·35 g., 86%).

The chloroform solution containing fraction II was then evaporated to give a small amount of oil, smelling somewhat of quinoline. This was again dissolved in N-hydrochloric acid (100 ml.), partially basified to pH 2·2, and extracted with chloroform (4 × 50 ml.). The chloroform solution was dried and the solvent distilled off, to give fraction II, a quinoline-free oil which slowly crystallised (121 mg.; 102% recovery; contains some 3-nitroquinoline).

Thus the recovery of both the 3-nitroquinoline and of the 6- + 8-nitroquinoline fraction is virtually quantitative. However, owing to the considerable solubility of quinoline in water, the amount of quinoline recovered is only a rough guide to the amount present.

Nitrations.—The results quoted are for a selection of typical experiments.

*N.*1. *Reaction between quinoline and metal nitrates in acetic anhydride.* A mixture of lithium nitrate (anhyd.; 12 g.), copper nitrate (0·2 g.), and quinoline (10 g.) was dissolved as far as possible in acetic anhydride (100 ml.). This was heated on a steam-bath for 1 hr. under reflux (until the evolution of nitrous fumes ceased). The solution was then cooled, hydrolysed with ice and water, and neutralised with ammonia. On extraction of a solution at pH 2·1 with chloroform and purification of the resultant nitroquinoline fraction, a pale yellow solid was obtained. This was crystallised from light petroleum–ether and from alcohol-water, yielding three substances. The major product, " X," had m. p. 130—131° and gave correct analyses for a

---

[3] Schorigin and Toptchiev, *Ber.*, 1936, **69**, 1874.

[4] Laville and Waters, *J.*, 1954, 400.

[5] Bradford, Elliot, and Rowe, *J.*, 1947, 442.

mononitroquinoline (Found: C, 62·2; H, 3·6; N, 16·2. Calc. for $C_9H_6O_2N_2$: C, 62·0; H, 3·5; N, 16·1%) but depressed the m. p. of synthetic 7-nitroquinoline (m. p. 135—136°) to 110—125°. It formed a picrate, m. p. 162—163°, whereas the picrate of 7-nitroquinoline had m. p. 217—218°. The ultraviolet spectra were also different; 7-nitroquinoline had peaks at (log ε values in parentheses) 248 (4·37), 256·5 (4·3), and a plateau at about 284 mμ (3·97); " X " had peaks at 242·5 (4·45) and 295 mμ (4·0). 3-Nitroquinoline, prepared by Colonna's method,[6] had properties identical with those of " X " and did not depress its m. p. in admixture.

Material in the mother-liquors from " X " crystallised from light petroleum–ether to give, first, needles, m. p. 146—148° (raised to 151—152° on admixture with 6-nitroquinoline), and then needles, m. p. 89—90° (mixed m. p. with synthetic 8-nitroquinoline 90°).

*N.*2—6. *Nitrations with nitric acid–acetic anhydride.* These experiments were carried out under similar conditions. In N.2—5 quinoline (10 g.), acetic anhydride (120 c.c.), and nitric acid were heated at 100° for 1 hr. Experiment N.4 differed from N.3 only in that glass wool (10 g.) was added. In N.6, a solution of fuming nitric acid (7 ml.) in acetic anhydride (200 ml.) was added dropwise to the quinoline–acetic anhydride mixture during 7 hr. at 85—90°. The products were separated as previously described and fraction II was fractionally crystallised. The results are shown in Table 1.

TABLE 1.

Expt.	HNO_3 (ml.)	Yield (%) of nitroquinolines 3-	(6 + 8)-	Quinoline recovered (%)
N.2	3	1·9	0·8	55
N.3	5	6·6	0·9	—
N.4	5	6·2	0·7	—
N.5	7	3·8	0·9	47
N.6	7	6·2	0·7	14

*N.*7—9. *Reactions with nitrogen dioxide.* The nitration with nitrogen dioxide was repeated according to Schorigin and Toptchiev's method,[3] except that the nitrogen dioxide was not dropped on the hot quinoline as described but a current of the gas was bubbled through the quinoline. Nitrogen dioxide, made by heating lead nitrate in a steel tube, was dried by passage over phosphoric oxide and condensed in a small cooled flask. A stream of the gas mixed with air was bubbled through a pool of quinoline (25 g.) in the bottom of a 3-necked flask. A filter-pump at one end of the system of traps and condensers connected to one neck of the flask slowly drew the gases through the system. Three experiments were run, about 30—35 g. of nitrogen dioxide being used each time. The durations of the experiments were varied by bubling the gases through at different rates. Finally, the whole apparatus was washed out with 17% hydrochloric acid and chloroform. These solutions were then worked up as usual. Results were as in Table 2.

TABLE 2.

Expt.	Time of expt. (hr.)	Yields (%) of nitroquinolines 3-	(6 + 8)-	Quinoline recovered (%)
N.7	0·75	0·5	—	54
N.8	1·5	1·5	—	75
N.9	3·0	2·8	0·8	—

Nitration at the b. p. of quinoline gave the same products as well as a considerable amount of quinoline nitrate. No dinitro-compound could be isolated.

Miscellaneous Reactions.—*N.*10. Nitrogen dioxide was bubbled through a solution of quinoline in acetic anhydride (4 g. in 80 ml.) for 2½ hr. at 25°. This gave 200 mg. of 3-nitroquinoline but no 6- or 8-nitroquinoline.

*N.*11. A solution of quinoline (10 g.) in acetic anhydride (100 ml.) and nitric acid (*d* 1·42; 10 ml.) was left at *ca.* 20° for 5 months. It gave only 508 mg. of 3-nitroquinoline, and no 6- or 8-isomer.

*N.*12. Quinoline (1·1 g.) was dissolved in trifluoroacetic anhydride[7] (13 ml.) and trifluoroacetic acid (1 ml.). Nitric acid (0·7 ml.) was added and the solution was left at room temperature for 42 hr., after which the excess of anhydride was distilled off under reduced pressure and

---

[6] Colonna, *Boll. Sci. Fac. Chim. ind. Bologna*, 1941, 91.

[7] Bourne, Stacey, Tatlow, and Tedder, *J.*, 1949, 2977.

the residue hydrolysed. Working this up gave 170 mg. of crystals in fraction II and none in fraction I. Fraction II was then crystallised from ether–light petroleum to give, first, needles, m. p. 90—120° (which recrystallised from hot water in long needles, m. p. 150—152°, mixed m. p. with 6-nitroquinoline 151—152°); the mother-liquors then gave fine needles which on recrystallisation had m. p. 86—88° (mixed m. p. with 8-nitroquinoline, 88—89°). No other isomers could be detected.

N.13. Nitric oxide, made by dripping sulphuric acid (50%) on potassium iodide (34 g.) and sodium nitrite (14 g.) in water (50 ml.), was bubbled through a solution of quinoline (2·5 g.) in acetic anhydride during 1·5 hr. Fraction I contained 31 mg. of white solid, crystallising in needles, m. p. 162—163° from alcohol (Found : C, 57·2; H, 3·2; N, 22·1. $C_9H_5O_2N_3$ requires C, 57·7; H, 2·7; N, 22·5%). Thus the compound has the composition of a *dinitrosoquinoline*. It was also occasionally formed in reactions of type N.10, presumably owing to the use of impure nitrogen dioxide. If this reaction is carried out with gas containing a high proportion of dinitrogen trioxide, then only 3-nitroquioline is formed (as in N.10).

This " dinitrosoquinoline " has absorption max. (log ε in parentheses) at 226 (4·0), 262 (4·3), and 347·5 mμ (3·75).

Nitrations with pernitrous acid. Since Laville and Waters[4] reported recovery of large quantities of quinoline we used only one-fifth of their amount of quinoline while keeping the amounts of the other reactants constant. Quinoline (20 g.) was dissolved in sulphuric acid (2 ml.), acetic acid (3 ml.), and water (16 ml.) at 0°. Solutions were made up containing (i) sodium nitrite (48 g.) in water (140 ml.) and (ii) 100-vol. hydrogen peroxide (120 ml.) in sulphuric acid (3 ml.) and water (20 ml.). These two solutions were dripped separately into the base–acid mixture with stirring during 2 hr. No material was obtained in fraction I. After chromatography, fraction II was obtained as a pale yellow solid of low m. p.; about 6·4 g. of quinoline were recovered. In several runs, yields of fraction II varied from 1·7 to 3·4 g.

Fraction II (2·1 g.) was separated into three parts: (A) (600 mg.; m. p. 105—130°) by crystallisation from ether; (B) (250 mg.; m. p. 78—100°) by addition of light petroleum to the mother-liquors from (A); and (C) (1·11 g.) by evaporation of the remaining solution.

Fraction (A) crystallised from ether–light petroleum or alcohol–water in needles, m. p. 151—152°, undepressed on admixture with 6-nitroquinoline. Fractional crystallisation of (B) from ether–light petroleum gave a small amount of 6-nitroquinoline; the mother-liquors gave 7-nitroquinoline, m. p. 131—132°, raised to 132—133° on admixture with 7-nitroquinoline (admixture with 3-nitroquinoline lowered the m. p. sharply).

From part of the oil (C) a small amount of 8-nitroquinoline, m. p. and mixed m. p. 90—90·5°, separated. Further crystallisation of the mother-liquors yielded only a small amount of solid, m. p. *ca.* 50°, which was not raised by recrystallisation. This was probably the eutectic of 5- and 8-nitroquinoline described by Dufton.[8] The remainder of the oil (C) (330 mg.) was reduced in acetic acid (10 ml.) by iron powder (200 mg.) at the b. p. for 6 min. It was then poured into water, neutralised, and extracted with chloroform (3 × 150 ml.). The chloroform solution was dried and gave a brown oil on evaporation. This was extracted with boiling light petroleum (10 × 10 ml.), to give 173 mg. of light yellow oil. On careful crystallisation from light petroleum needles were obtained which on recrystallisation had m. p. 108·5—109·5°. 5-Aminoquinoline made from 5-nitroquinoline by the same procedure had m. p. 109—110°; there was no change of m. p. on mixture of the two samples. The picrates had m. p. and mixed m. p. 214—215°.

The results are summarised in Table 3.

TABLE 3. *Summary of results.*

Reagent	Nitroquinolines formed			Reagent	Nitroquinolines formed			
$LiNO_3$–$Cu(NO_3)_2$–Ac_2O; 100°	3	6	8	N_2O_4–Ac_2O; 20°	3			
HNO_3–Ac_2O; 100°	3	6	8	HNO_3–$(F_3C{\cdot}CO)_2O$; 20°		6		8
HNO_3–Ac_2O; 20°	3			Pernitrous acid; 0°	5	6	7	8
N_2O_4; 100°	3	6	8	NO–Ac_2O; 20°	$C_9H_5O_2N_3$			

The common feature of these reactions is the low yield of product; indeed it is usually possible to recover 50—70% of the quinoline. No other products could be isolated from any of the reactions investigated, all by-products being intractable tars.

---

[8] Dufton, *J.*, 1892, **61**, 783.

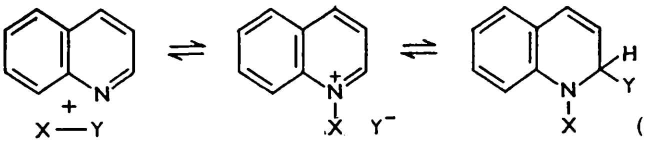
DISCUSSION

(a) *Nitrations not involving Pernitrous Acid.*—The most surprising feature of these experiments was the isolation of 3-nitroquinoline as the major mononitration product; it seems clear that the material described previously by two independent groups of investigators as 7-nitroquinoline must in fact have been the 3-isomer as the melting points are very similar. We could not find any evidence for the formation of 7-nitroquinoline and were also unable to confirm the special virtue claimed for metal nitrates in acetic anhydride as nitrating agents; we obtained the same products, in rather better yield, by using equivalent amounts of nitric acid.

We consider that the formation of 3-nitroquinoline (and of the 6- and the 8-isomer), despite the small amount, is significant and presents an interesting theoretical problem since its formation is even more unexpected than would have been that of the 7-nitroquinoline. In the first place, 3-nitroquinoline would not be expected to be formed in detectable amount by direct nitration of quinoline; the reactivity of this position would not be expected to be greatly different from the 3-position in pyridine, the inertness of which to normal nitration is well known.[9]

We have also studied the rates of destruction of the *Bz*-mononitroquinolines when heated with a large excess (*ca.* 7 mols.) of nitric acid under the conditions of a typical nitration. The results show that the rates of destruction of the 5-, 6-, and 7-isomers were similar while that of the 8-isomer was rather less. Thus there is no reason to suppose that the 5-isomer, a major product of the straightforward nitration of quinoline in sulphuric acid, is formed here and then selectively destroyed by oxidation.

A likely mechanism for the reaction seems to be indicated by the fact that the only other isolable products were the 6- and the 8-isomer; indeed, with nitric acid in trifluoroacetic anhydride these alone could be isolated. This suggests that the entity being nitrated is not quinoline itself but a 1 : 2-dihydroquinoline derivative, formed by addition of the reagent to the 1 : 2-bond. This adduct (I) would be an aniline derivative and would be expected to be nitrated *ortho* and *para* to the nitrogen atom (*i.e.*, in the 6- and 8-position); while addition of oxides of nitrogen to the styrene-like double-bond of (I) followed by elimination could give the 3-isomer. It is interesting that the 3-nitroquinoline was formed only under conditions where oxides of nitrogen were present initially or could have been formed by reduction of nitric acid; in trifluoroacetic anhydride, a non-reducing solvent, only 6- and 8-nitroquinoline were formed.



(I)

The formation of adducts such as (I) is reasonable and there are many analogies;[10] similar intermediates (X = Bz; Y = CN) are postulated for the Reissert reaction. The nature of the reagent XY in our case is not clear, but we believe it to be an acyl nitrate (X = NO_2, Y = AcO, $CF_3 \cdot CO \cdot O$; or $\cdot NO_2$ in the case of nitrogen peroxide). We could obtain no evidence for a direct addition of acetic anhydride itself to quinoline; for example, the ultraviolet spectrum of quinoline in acetic anhydride is very similar to that in *cyclo*hexane. Kosower[11] has shown that an equilibrium exists between 1-methylpyridinium iodide and 1 : 2-dihydro-2-iodo-1-methylpyridine. We think it likely therefore, that

---

[9] den Hertog and Overhoff, *Rec. Trav. chim.*, 1930, **49**, 552.

[10] Doering and McEwen, *J. Amer. Chem. Soc.*, 1951, **73**, 2104; Gilman, Argersinger, and McEwen, *ibid.*, 1954, **76**, 41; Schofield and Simpson, *J.*, 1946, 472.

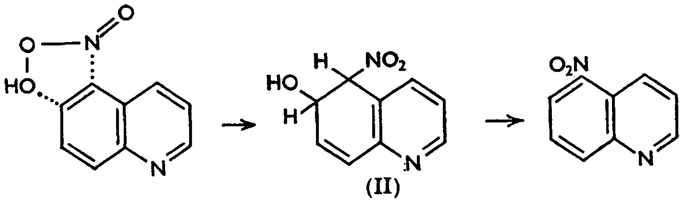
[11] Kosower, *J. Amer. Chem. Soc.*, 1955, **77**, 3883.

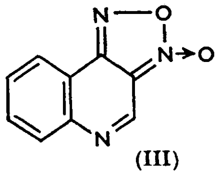
similar equilibria exist in other heterocyclic systems and that other polar molecules (*e.g.*, acetyl nitrate) can form similar adducts.

Experiments similar to those on quinoline were also carried out with *iso*quinoline and pyridine. In the former case only a small amount of intractable red tar was isolated, while nitration of pyridine in acetic anhydride and nitric acid at 100° gave a small amount (<1%) of 3-nitropyridine.[12]

It is possible that bromination of quinoline, by heating quinoline perbromide,[13] proceeds by an analogous though more efficient mechanism, addition of bromine to the intermediate (I; X = H, Y = Br) at the 3 : 4-bond being followed by elimination of two molecules of hydrogen bromide.

Nitration with Pernitrous Acid.—This clearly follows an entirely different path, since the products are quite different; unlike Laville and Waters,[4] we isolated comparable amounts of all four *Bz*-substituted isomers, but no 3-nitroquinoline was formed. Since in an experiment with nitrous acid under the same conditions there was no reaction whatever, and since free radicals would be expected to attack quinoline selectively in the 2-position (cf. high-temperature bromination [14]), it seems to us that the attacking entity must be pernitrous acid itself. Pernitrous acid may, like ozone, act as a double-bond reagent; ozone in fact selectively attacks the 5 : 6- and 7 : 8-bonds.[15]


(II)


(III)

The intermediate (II) could undergo a variety of alternative elimination reactions, leading to phenols, etc.; this would account well for the copious formation of tarry and phenolic by-products.[16]

The " dinitrosoquinoline " isolated from the reaction of quinoline with nitric oxide may possibly have the structure of a quinolinofuroxan, *e.g.*, (III).

We thank the Central Research Fund of London University for a grant towards the cost of materials, and D.S.I.R. for a maintenance grant (to P. M. M.).

QUEEN MARY COLLEGE, UNIVERSITY OF LONDON,
MILE END ROAD, LONDON, E.1.

[*Received, March* 20*th*, 1956.]

---

[12] Dewar and Maitlis, *Chem. and Ind.*, 1955, 685.

[13] Claus and Collischon, *Ber.*, 1886, **19**, 2765.

[14] Jansen and Wibaut, *Rec. Trav. chim.*, 1937, **56**, 699.

[15] Wibaut and Boer, *ibid.*, 1955, **74**, 241.

[16] Cf. Halfpenny and Robinson, *J.*, 1952, 928, 939.