OXIDES OF HETEROCYCLIC QUINONES. N-OXIDES AND EPOXIDES OF QUINOLINE- AND ISOQUINOLINE-5,8-DIONE

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Abstract - The syntheses of 6,7-epoxides and N-oxides of quinoline- and isoquinoline-5,8-diones and of their 6,7-dichloro derivatives are described. The key step of synthesis is oxidation of quinoline or isoquinoline N-oxides bearing the hydroxy or amino groups in the position 5 and 8.

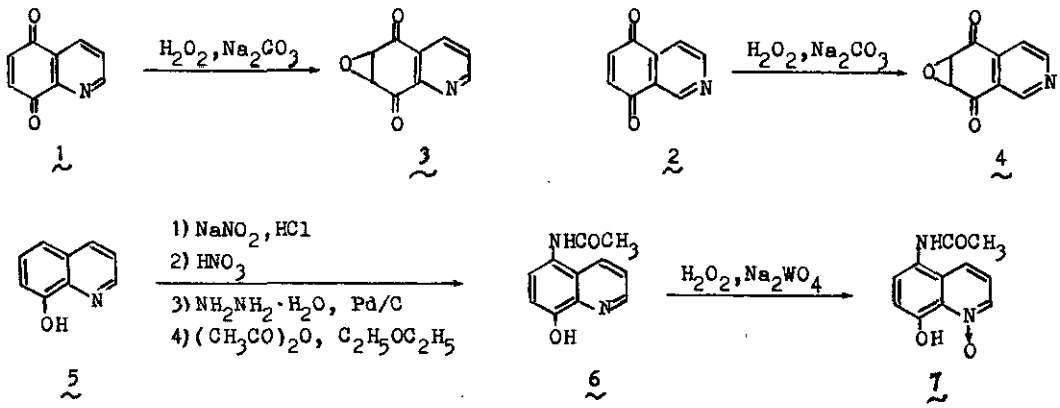
The chemistry and pharmacology of heterocyclic quinones is a subject of continuing interest. A generalized review has been reported recently[1] and it has been shown that various simple derivatives of azaaromatic quinones (particularly quinoline-5,8-dione) bearing substituents in the carbocyclic ring exhibit potent activity against bacteria, protozoa, amoebas and cancer cells.[2] On the other hand, in earlier works carried out in our laboratory[3] we have found that introduction of N-oxide function into azaaromatic molecules increases biological activity in comparison with parent bases. Thus, we hoped that introduction of this function into azaaromatic quinones also could increase their activity.

Contrary to their carbocyclic analogues, epoxides of heterocyclic p-quinones have been previously unknown. N-Oxides of heterocyclic quinones have also been unknown except 6,7-dibromoquinoxaline-5,8-dione 1,4-dioxide reported as product of oxidation of 6,7-dibromo-5,8-dimethoxyquinoxaline with nitration mixture.[4]

The aim of present work was to elaborate the convenient methods of syntheses of quinoline-5,8-dione N-oxide, isoquinoline-5,8-dione N-oxide and their 6,7-dichloro- and 6,7-epoxy derivatives being suitable substrates for syntheses of various derivatives substituted in the carbocyclic ring.

N-Oxides of quinoline- and isoquinolinequinones could not be obtained in usual way by direct oxidation with peracids or hydrogen peroxide due to a low basicity

of the nitrogen atom[5] and tendency to 6,7-epoxidation. When quinones 1 and 2 were oxidized with hydrogen peroxide in the alkaline medium (similarly as naphthoquinone[6]) corresponding epoxides 3 and 4 could be isolated in good yields. Our method of synthesis of quinoline or isoquinolinequinone N-oxides was based on the N-oxidation of quinoline or isoquinoline having electron releasing substituents in the positions 5 and 8 and successive oxidation of the carbocyclic ring. When ferric chloride or potassium dichromate were used as oxidants unsubstituted quinones were formed. Oxidation of 8, 13 or 16 according to Shellhammer and Petersen[7] gave desired 6,7-dichloro derivatives 11, 15 and 17. However, when amide 7 whose hydrolysis is more difficult than 16, was oxidized in the same manner, tetrachloroquinolinequinone N-oxide 9 was formed.



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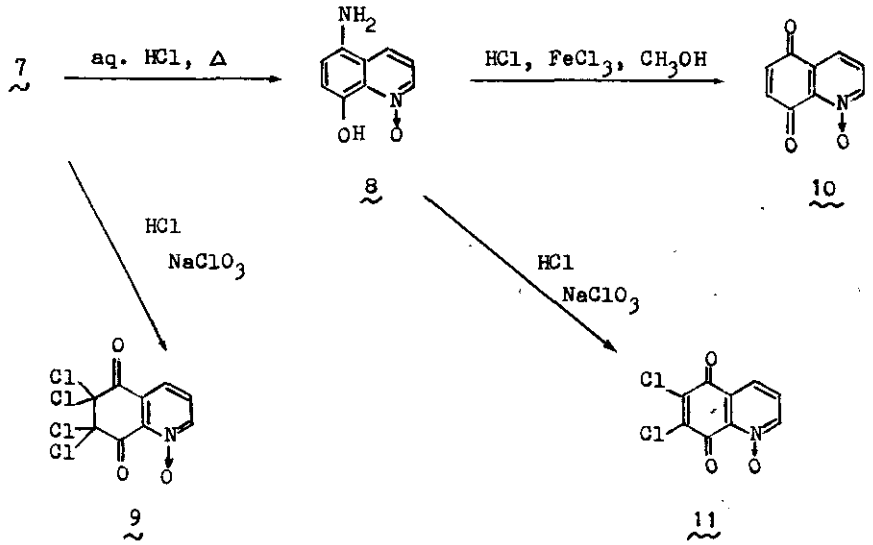

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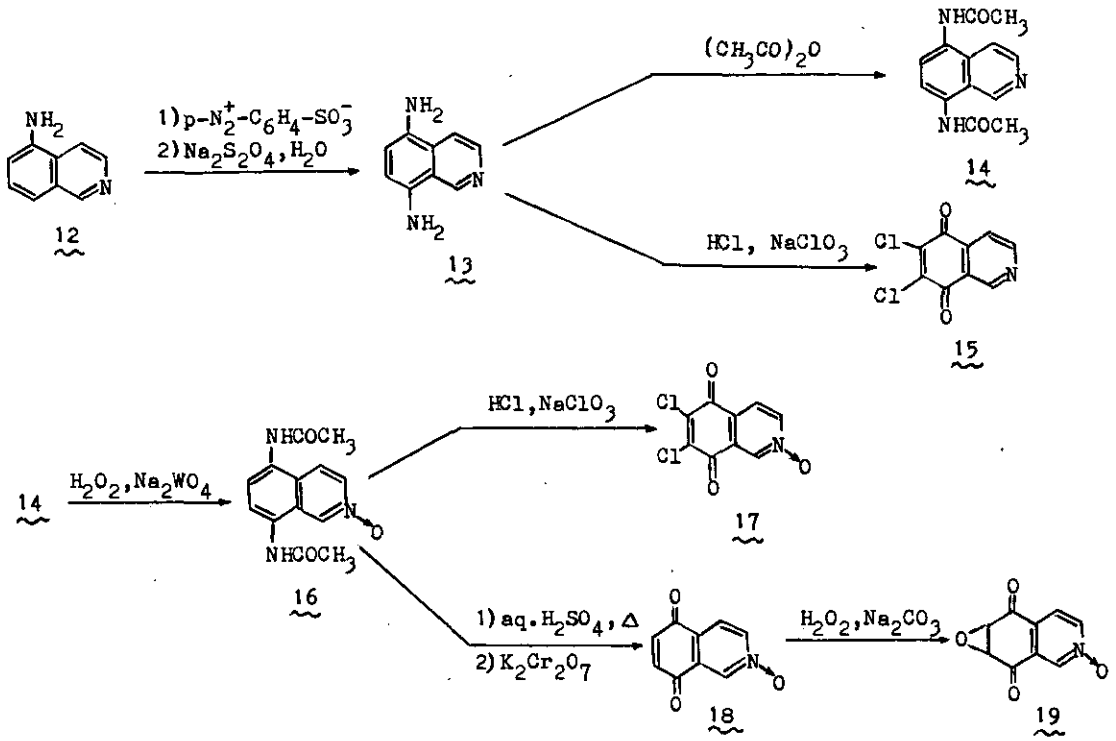

Quinones 1, 2 and 18 were easily converted into epoxides. Thus, to vigorously stirred a suspension of the corresponding quinone (6.5 mmole) in water (20 ml), a solution of sodium carbonate(0.432g, 4.0 mmole) in water (10 ml) and 30% hydrogen peroxide (2.0 ml) was added in small portions with cooling on the ice-water bath for 2h. Then the reaction mixture was extracted with chloroform. The extract was dried over $MgSO_4$, and evaporated to give desired epoxides 3, 4 and 19.

3 was recrystallized from chloroform-ether; white prisms, yields 66%, m.p.136-138°C (dec.), NMR ($CDCl_3$) δ(ppm) 4.06 (2H, s, 6-H and 7-H), 7.63 (1H, dd, 4.5 Hz and 8 Hz, 3-H), 8.26 (1H, dd, 2 Hz and 8 Hz, 4-H), 9.00 (1H, dd, 2 Hz and 4.5 Hz, 2-H), ir (KBr, cm^{-1}) 1690 (CO).

4 was recrystallized from chloroform-hexane; bright-yellow prisms, yield 43%, m.p. 98-99°C (dec.), NMR ($CDCl_3$) 4.00 (2H, s, 6-H and 7-H), 7.65 (1H, d, 4.5 Hz, 4-H), 9.00 (1H, d, 4.5 Hz, 3-H), 9.08 (1H, s, 1-H), ir (KBr, cm^{-1}) 1695 (CO).

19 was recrystallized from chloroform-hexane; yellow prisms, yield 45%, m.p.147°C (dec.), NMR (DMSO) 4.47 (2H, s, 6-H and 7-H), 7.93 (1H, d, 7 Hz, 4-H), 8.76 (1H, s, 1-H), 8.80 (1H, d, 7 Hz, 3-H), ir (KBr, cm^{-1}) 1690 (CO), 1250 (NO).

8-Hydroxyquinoline 5 was nitrosated and then oxidized to nitro derivative.[8,9] The nitro group was reduced with hydrazine and the resulting amine was acetylated

in usual way gave 6 in total yield of 48%, m.p. 222°C (ref.[10] 219-220°C). A suspension of the compound 6 (6.07 g, 30 mmole), 30% hydrogen peroxide (30 ml) and $Na_2WO_4 \cdot 2H_2O$ (0.06g) was heated with vigorous stirring at 60°C for 4h. After this period the reaction mixture was cooled to 0°C, the product was filtered and washed with a small volume of water and dried on the air. Crude N-oxide 7, recrystallized from ethanol, gave yellow needles,[11] yield 77%, m.p. 212-214°C (dec.), ir ($CHCl_3$, cm^{-1}) 3680 (OH), 3440 (NH), 1690 (CO), (KBr, cm^{-1}) 1250 (NO). N-Oxide 7 (6.55 g, 30 mmole) was heated at 50-60°C with hydrochloric acid (conc. HCl 25 ml and H_2O 40 ml) for 5h. After hydrolysis water (300 ml) was added to a reaction mixture and the solid filtered off. The filtrate was adjusted to pH 6.5 - 7.0 with sodium hydrogen carbonate and extracted with chloroform. From extract amine 8 was isolated and recrystallized from benzene to give, in 75% yield, dark orange needles, m.p. 182-183°C (dec.) (ref.[8] 180-182°C).

Quinoline-5,8-dione N-oxide 10 was obtained in the following way: To an ice-cooled and vigorously stirred solution of 8 (1.06 g, 6.0 mmole) in methanol (100 ml), anhydrous ferric chloride (4.83 g, 30.0 mmole) and hydrochloric acid (3 ml) were added within 1 min. Then chloroform (300 ml) was poured into reaction mixture, agitated for 30 sec and water (300 ml) was added. The chloroform layer was separated and extraction repeated four times within a short time period (10-15 min). The combined extracts were washed with saturated aq. NaCl, water and dried over $MgSO_4$. Chloroform was removed from the extract, on rotatory evaporator at room temperature and 10 remained as a residue in 20% yield. Crystalline yellow compound 10 was unstable and m.p. could not be taken. NMR ($CDCl_3$) 7.40 (2H, s, 6-H and 7-H), 7.95 (1H, dd, 6 Hz and 8 Hz, 3-H), 8.29 (1H, dd, 2 Hz and 8 Hz, 4-H), 8.88 (1H, dd, 2 Hz and 6 Hz, 2-H); ir (KBr, cm^{-1}) 1665 (CO), 1260 (NO).

6,7-Dichloroquinoline-5,8-dione N-oxide (11) was obtained from amine 8. Thus, to a stirred and heated (55-60°C) solution of 8 (1.15g, 6.5 mmole) in conc. hydrochloric acid (10 ml) sodium chlorate (0.75 g, 7 mmole) in water (3 ml) was added dropwise during 20 min. Stirring was continued for an additional 20 min, then reaction mixture was poured into ice (70 g). Crude crystalline product was filtered off, washed with water and recrystallized from acetone to give pure 11 as red prisms, yield 69%, m.p. 215-216°C (dec.), NMR (DMSO) 7.98 (1H, dd, 6 Hz and 9 Hz, 3-H), 8.22 (1H, dd, 2 Hz and 9 Hz, 4-H), 8.77 (1H, dd, 2 Hz and 6 Hz, 2-H), ir (KBr, cm^{-1}) 1690 and 1675 (CO), 1270 (NO).

When acetamide 7 was oxidized under the same reaction conditions as described above,

6,6,7,7'-tetrachloroquinoline-5,8-dione N-oxide 9 was obtained in 43% yield, after recrystallization from ethanol as yellow prisms, m.p. 177-178°C (dec.), NMR (DMSO), 8.20 (1H, dd, 6 Hz and 9 Hz, 3-H), 8.33 (1H, dd, 1.5 Hz and 9 Hz, 4-H), 9.01 (1H, dd, 1.5 Hz and 6 Hz, 2-H), ir (KBr, cm^{-1}) 1730 (CO), 1250 (NO).

Coupling of 5-aminoisoquinoline (12) with diazotized sulfanilic acid, followed by reduction with sodium dithionite, gave 5,8-diaminoisoquinoline (13)[12] which was acetylated in usual manner to give 14 in total yield 46%. Recrystallization from water gave white needles[11], m.p. 298-299°C, ir (KBr, cm^{-1}), 3260 (NH), 1675 (CO).

The compound 14 was oxidized to N-oxide 16 similarly as 6. When reaction was finished, the reaction mixture was diluted with water (10 ml) and cooled to 0°C. The product was filtered off, washed with a small amount of cold water, then with ethanol and recrystallized from methanol. After drying in the air and in dryer (105-110°C, 1h) yellow needles of 16 were obtained in 71% yield,[11] m.p. 276°C (dec.), ir (KBr, cm^{-1}), 3240 (NH), 1670 (CO), 1252 (NO).

Isoquinoline-5,8-dione N-oxide 18 was obtained from 16. Thus, 16 (0.52g, 2.0 mmole) and 5% sulfuric acid (20 ml) were stirred at 90-100° for 2h, then allowed to stand at room temperature for 20h. To a suspension of a solid formed, potassium dichromate (1.0g, 3.4 mmole), conc. sulfuric acid (2 ml) and water (10 ml) were added and the reaction mixture was vigorously stirred until all the solid dissolved. This solution was extracted with chloroform and the extract dried over $MgSO_4$, then solvent removed in vacuo. Crude 18, recrystallized from chloroform-hexane (1:1), gave orange needles (darkened in the air), decomposing above 155°C, 69% yield, NMR ($CDCl_3$) 7.00 (2H, s, 6-H and 7-H), 7.83 (1H, d, 7 Hz, 4-H), 8.33 (1H, d, 7 Hz, 3-H), 8.61 (1H, s, 1-H), ir (KBr, cm^{-1}) 1655 and 1680 (CO), 1250 (NO).

6,7-Dichloroisoquinoline-5,8-dione 15 was obtained from freshly prepared 13. Thus, to a stirred and heated (55-60°C) suspension of 13 (1.59g, 10 mmole) in conc. hydrochloric acid (20 ml), sodium chlorate (1.27 g, 12 mmole) in water (5 ml) was added dropwise for 30 min . Stirring was continued for an additional 30 min and then the reaction mixture was poured into ice (150 g). The crude crystalline product was filtered off, washed with water, and recrystallized from absolute ethanol to give pure 15, in 48% yield, as yellow prisms, m.p. 178-179°C (dec.), NMR (DMSO) 8.15 (1H, d, 5 Hz, 3-H), 9.30 (1H, d, 5 Hz, 4-H), 9.45 (1H, s, 1-H), ir (KBr, cm^{-1}) 1680 (CO).

6,7-Dichloroisoquinoline-5,8-dione N-oxide 17 was obtained from 16 in the same

manner as described above for 15. The crude 17, recrystallized from acetic acid-water (3:1) gave orange prisms, in 50% yield, m.p. 246-249°C (dec.), NMR (CF_3COOH), 8.15 (1H, d, 7 Hz, 4-H), 8.40 (1H, d, 7 Hz, 3-H), 9.07 (1H, s, 1-H), ir (KBr, cm^{-1}) 1680 (CO), 1265 (NO).

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