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Ring Transformation of Heterocycles by Oxidizing Agents. A ^{14}C-Study of the Conversion of Quinolines into Indoles by Hydrogen Peroxide*

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Based on experiments with 8-nitro-[2,4-^{14}C]-quinoline and 8-nitro-[4-^{14}C]-quinoline, it has been found that during the ring transformation of 8-nitroquinoline into 7-nitrooxindole by action of hydrogen peroxide in acetic acid, the C_2-atom of the quinoline ring is expelled. A mechanism for the ring transformation is proposed.

There are several reports in the literature concerning the oxidative ring transformation of six-membered azahetarenes by hydrogen peroxide. Treatment of ammelide (**1**) with hydrogen peroxide in formic acid gives 2-amino-4,6-dioxo-3,4,5,6-tetrahydro-*s*-triazine (**2**).[2] The same compound is also formed in a reaction of xanthopterin peroxide (**3**) with an excess of hydrogen peroxide.[3,4] It was observed[2] that 2,4,6-trisubstituted and 2,4,5,6-tetrasubstituted pyrimidines, containing an electron-donating substituent in position 2, in general undergo conversion into 2-substituted 4,6-dioxo-3,4,5,6-tetrahydro-*s*-triazines by action of hydrogen peroxide and by hydrogen peroxide in formic acid.

Hydrogen peroxide in an alkaline medium shows a somewhat different behaviour: from **3** the *s*-triazine-carboxylic acid (**4**) is obtained[5] and from guanine (**5**) the same compound is recently reported to be formed.[6]

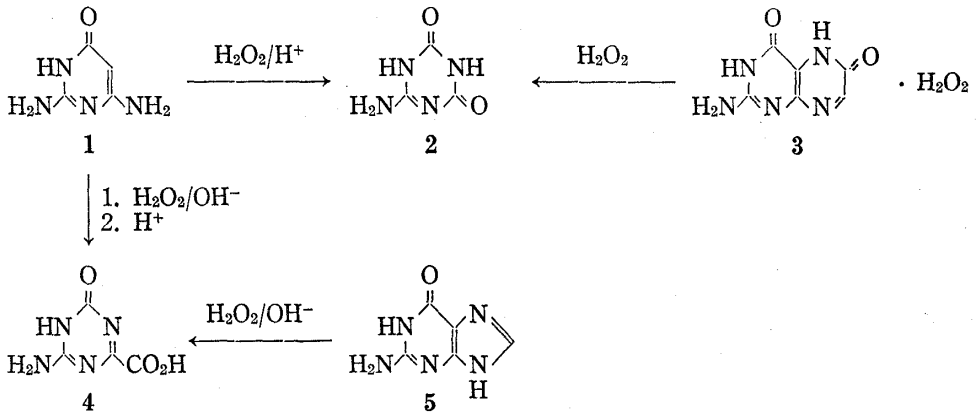


Chart 1

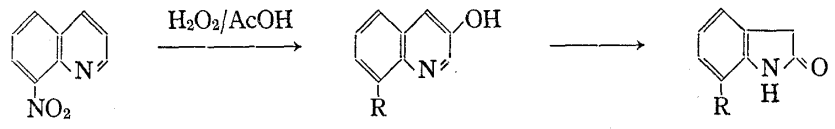
With hydrogen peroxide interesting ring contraction reactions were also observed. On treatment of 8-nitroquinoline (**6**) with hydrogen peroxide in acetic acid, 7-nitrooxindole (**8**,

* Dedicated to the memory of Prof. Eiji Ochiai.

1) Location: *Wageningen, the Netherlands.*

2) H. Yamamoto and W. Pfleiderer, *Chem. Ber.*, **106**, 3194 (1973).
3) H. Wieland and R. Parrmann, *Ann. Chem.*, **539**, 179 (1939).
4) B. Barlin and W. Pfleiderer, *Chem. Ber.*, **104**, 3069 (1971).
5) S.I. Zav'yalov and G.V. Pokhvisneva, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **1973**, 630.
6) R.C. Moschel and E.J. Behrmann, *J. Org. Chem.*, **39**, 1985, 2699 (1974).

R=NO_2) is formed[7,8] and from 5- and 8-nitrocinnoline 4- resp. 7-nitroindazole are obtained with the same reagent.[9] It is established that in the conversion of **6** into **8** the 3-hydroxy-8-nitroquinoline (**7**, R=NO_2) and not 7-nitroindole is an intermediate.[7] Other 3-hydroxy-quinolines, having bulky and electron-withdrawing groups at position 8, *i.e.* **7** (R=CO_2H, $CO_2C_2H_5$) show the same behaviour.[7]

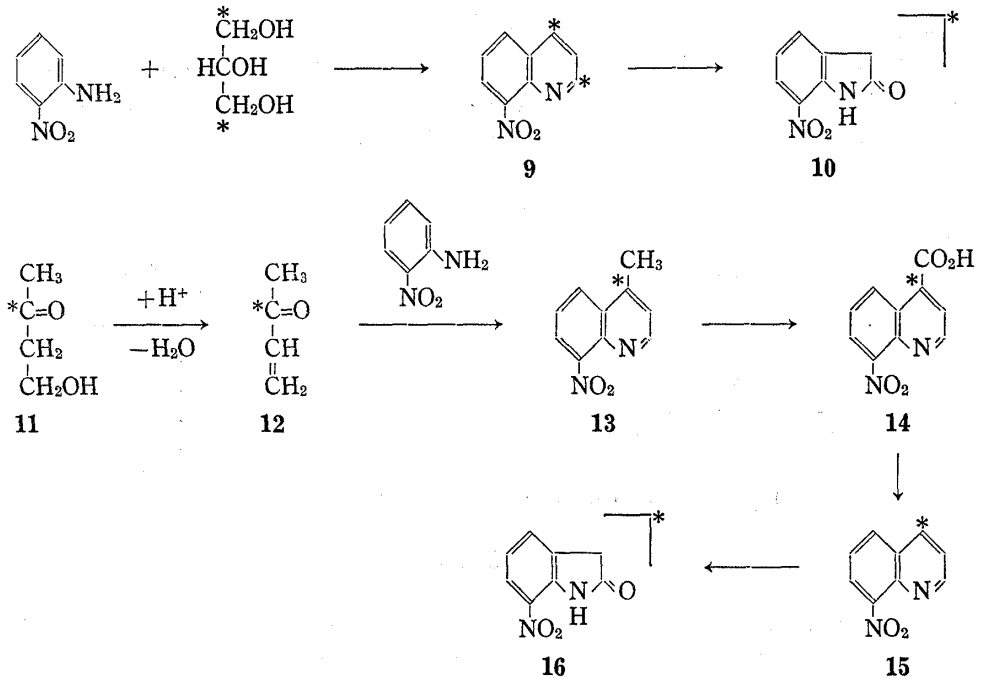


6 **7** **8**

Chart 2

Because of our continuing interest in the mechanism of ring transformation reactions[10] with heterocycles, we have tried to elucidate the oxidative conversion of **6** into **8** (R=NO_2) by ^{14}C-labelling experiments. The problem to be solved is which C-atom of the pyridine ring of the 8-nitroquinoline is lost during the ring contraction. We decided to synthesize the rather readily accessible 8-nitro-[2,4-^{14}C]-quinoline (**9**). If loss of C_3 should occur, it could be easily detected—the specific radioactivity in the 7-nitrooxindole should then be the same as in **9**—and might give us a useful hint as to which mechanism the ring contraction might occur.

Compound **9** was obtained by a Skraup reaction of *o*-nitroaniline with [1,3-^{14}C]-glycerol, following the procedure given in the literature for the unlabelled compound[11] (Chart 3). Treatment of **9** with hydrogen peroxide in acetic acid gave us radioactive 7-nitrooxindole (**10**); the specific radioactivity of **10** was found to be *half* of that of the starting substance **9** (see Table I). This result clearly indicates that it is not the C_3-atom which is lost during the ring contraction,



9 **10** **11** **12** **13** **14** **15** **16**

Chart 3

7) T. Nakashima and I. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **17**, 2293 (1969).
8) R.T. Coutts, K.W. Hindmarsh and E. Mah, *Can. J. Chem.*, **48**, 3747 (1970).
9) I. Suzuki, T. Nakashima and N. Nagasawa, *Chem. Pharm. Bull.* (Tokyo), **13**, 713 (1965).
10) H.C. van der Plas, "Ring transformations of Heterocycles," Vol. 1 and 2, Academic Press, London and New York, 1973.
11) Chr. A. Knueppel, *Chem. Ber.*, **29**, 703 (1896).

but one of the remaining C-atoms, C_2 or C_4. In order to establish which of these two C-atoms, is expelled we were obliged to synthesize either [2-^{14}C]- or [4-^{14}C]-8-nitroquinoline. We prepared 8-nitro-[4-^{14}C]-quinoline (**15**) by the synthetic route as shown in Chart 3. A Skraup reaction was performed of *o*-nitroaniline with the ^{14}C-labelled methylvinylketone (**12**)— prepared from [2-^{14}C]-acetone by the procedure given in the literature[12]—leading to the 4-methyl-8-nitro-[4-^{14}C]-quinoline (**13**). Oxidation of **13** with selenium dioxide gave 8-nitro-[4-^{14}C]-4-quinolinecarboxylic acid (**14**), which on heating decarboxylated into the desired compound **15**. The 7-nitrooxindole (**16**), obtained after treatment of **15** with hydrogen peroxide in acetic acid, was found to have the same specific radioactivity as **15**.

The results obtained with both compounds **9** and **15** unequivocally show that the oxidative ring contraction of **6** into **8** (R=NO_2) must occur with an almost exclusive loss of the C_2-atom of the quinoline ring.

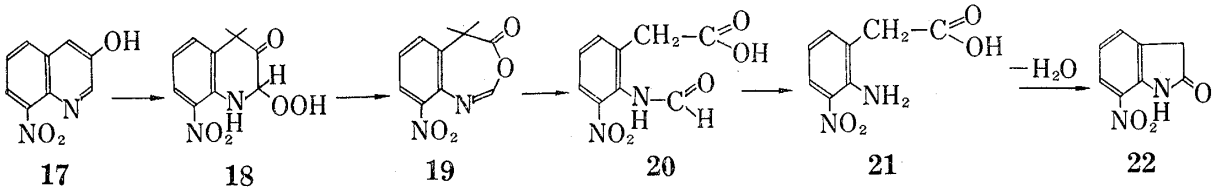


Chart 4

The following mechanism, based on our measurements and the findings of the Japanese investigators, can be advanced. As initial step the hydrogen peroxide adds to the C=N bond of the 3-hydroxy-8-nitroquinoline (**17**), yielding the peroxide **18**. A Baeyer-Villiger-type reaction leads to ring expansion into the seven-membered 5H-3,1-benzoxazepin-4-one (**19**). Hydrolytic ring opening of this seven-membered lactone yields the formyl derivative **20**, which subsequently hydrolyses into 2-amino-3-nitrobenzeneacetic acid (**21**). Dehydration of **21** gives ring closure into the 7-nitrooxindole (**22**). The last-mentioned step has been found[13] to occur with great ease with *o*-aminobenzeneacetic acid.

TABLE I

Compound	Measured radioactivity[a] μC/mmole
8-Nitro-[2,4-^{14}C]-quinoline (**9**)	0.196
7-Nitrooxindole (**10**)	0.090
8-Nitro-[4-^{14}C]-quinoline (**15**)	0.025
7-Nitrooxindole (**16**)	0.029

a) measured with a liquid scintillation counter

Experimental

Melting points are uncorrected. Radioactivity measurements were carried out with a Mark I liquid scintillation counter (Nuclear–Chicago). The samples are dissolved in 10 ml of a scintillation solution of 5 g of PPO and 0.5 g of POPOP in 1 litre of an ethanol–toluene mixture (volume 1: 9).

Preparation of Starting Compounds

4-Methyl-8-nitro-[4-^{14}C]-quinoline (**13**)——18.4 g (133 mmole) of *o*-nitroaniline were heated with 17.6 g of arsenic pentoxide in 20.4 ml of concentrated sulfuric acid at 80°. During 1.5—2 hr 16.0 g (228 mmole) of ^{14}C labelled methylvinylketone (**12**) were dropped into the mixture. After heating for an additional hour at 120° the reaction–mixture was poured out onto 500 ml of crushed ice. With ammonia the solution

12) T. White and R.N. Haward, *J. Chem. Soc.*, **1943**, 25.
13) G. Hahn and H.J. Schultz, *Chem. Ber.*, **72**, 1308 (1939).

was neutralized; **13** precipitated as a dark brown mass. Recrystallization from petroleum–ether (b.r. 60—80°)–benzene gave 2.4 g of **13** (10%); mp. 124—125° (lit:[14] 126—127°).

8-Nitro-[4-^{14}C]-4-quinolinecarboxylic Acid (14)——2.4 g (12.8 mmole) of **13** were refluxed with 2.7 g of selenium oxide in 3 ml of pyridine for 2 hr. After cooling, the mixture was diluted with 50 ml of water. Evaporation to a small volume gave 1.65 g of **14** (60%); mp 258—259° (lit.[14] 254—255°).

8-Nitro-[4-^{14}C]-quinoline (15)——1.65 g (7.6 mmole) of **14** were heated for 0.5 hr at 240° in 30 ml of Dowtherm. After ceasing of the evolution of carbon dioxide the mixture was diluted with *n*-hexane; 0.5 g (38%) of **15** crystallized, mp 87—88° (lit:[14] 90—91.5°).

General Procedure for the Oxidation of 8-Nitro-[2,4-^{14}C]-quinoline (9) and 8-Nitro-[4-^{14}C]-quinoline (15) The oxidation and the work-up procedure were carried out according to the prescription as given for the unlabelled compound.[7] 0.65 g (3.7 mmole) of **9** (or **15**) were dissolved in 4 ml of acetic acid and 1.3 ml of 30% hydrogen peroxide and heated for 4 hr at 70°. Then 1.3 ml of 30% hydrogen peroxide was added and the mixture was heated again for 4 hr at 70°. After cooling, crystals separated, which were collected and recrystallized from methanol. Yield 0.13 g of **10** (or **16**) (20%); mp 220—225° (decomp.).

Acknowledgement We wish to express our sincere thanks to Dr. D. A. de Bie for his assistance with the measurements of the ^{14}C-radioactivity.

14) M. Ishikawa and I. Kikkawa, *Yakugaku Zasshi*, **75**, 33 (1955).