Mild Oxidation of Alicyclic Secondary Amines. I. On Formation of Isonitrone from Perhydroquinoline Series

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In recent years, a few papers concerning the nitrones of alicyclic secondary amines, especially piperidine[1,2] and pyrrolidine[3], have been reported. But the obtaining of isonitrone from alicyclic scondary amine has not yet been described. This paper reports on some of the isonitrones obtained from polycyclic compounds in the alicyclic secondary amine series.

Oxidation of *trans*-decahydroquinoline (I) with silver oxide in 30%-methanol solution at a temperature of 30~40°C gave a product, $C_9H_{15}ON$*, m.p. 280~282°C (IV). This product is different from a compound obtained by Witkop[5] from an air oxidation of I. Also from *cis*-decahydroquinoline (II), the same compound IV was obtained under the same condition. This compound was moreover formed by the treatment of I and II with 30%-hydrogen peroxide, perbenzoic acid, or with *N*-bromosuccinimide (NBS) although accompanied by the known hydroperoxide (XIV)[6].

This new substance (IV) was easily soluble in a polar solvent, but not in a non-polar one. In the infrared spectrum (in Nujol) of IV, the NH-stretching band at 2.96 μ which had been observed in that of *trans*-decahydroquinoline (I), disappeared. This compound IV had no unsaturated nature** and did not react with phenylisocyanate. It was reduced with sodium borohydride, sulfurous acid or with acidic potassium iodide, giving I in all cases.

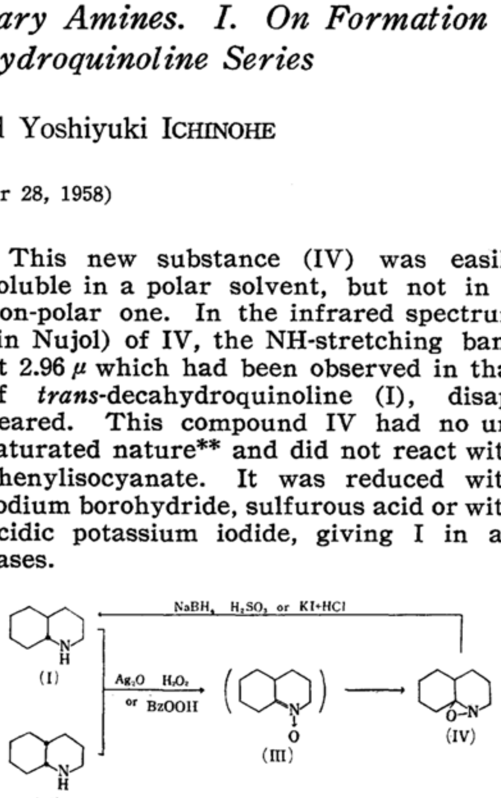

Fig. 1

When α-perhydroacridine (*trans-syn-trans*) (V)[7] was treated with 30%-hydroperoxide at room temperature for a week, it gave a crystalline product, $C_{13}H_{21}ON$*, (sublimed with decomposition at near 320°C) (VI). On the other hand, α-perhydrophenanthridine (*trans-anti-trans*) (VII)[8] reacted with silver oxide at a temperature of 90~100°C, producing a new

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1) J. Thesing and H. Mayer, *Ber.*, **89**, 2159 (1956).

2) J. Thesing and H. Mayer, *Ann.*, **609**, 46 (1957).

3) R. F. C. Brown, V. M. Clark and Sir A. Todd, *Proc. Chem. Soc.*, **1957**, 97.

* It is well known that aromatic amine oxides do not appear to form definite hydrates[4a]. Henry and Leete[4b] have recently reported that gramine oxide has hydrogen peroxide of crystallization which is determined by iodometry. These new compounds, IV, VI and VIII, had hydrogen peroxide determined by the same method (described in experimental part).

4a) T. W. J. Taylor and W. Baker, "The Organic Chemistry of Nitrogen by Sidgwick", Oxford University Press, London (1937), p. 167.

4b) D. W. Henry and E. Leete, *J. Am. Chem. Soc.*, **79**, 5254 (1957).

5) B. Witkop, *Experientia*, **10**, 419 (1954).

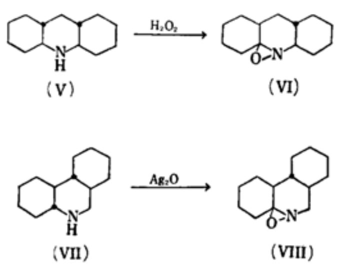
6) L. A. Cohen and B. Witkop, *J. Am. Chem. Soc.*, **77**, 6575 (1955).

** The compound IV gave a negative test to bromine or tetranitromethane and decolorized only permanganate.

7) T. Masamune and S. Wakamatsu, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **77**, 1145 (1956); *J. Fac. Sci. Hokkaido Univ. Ser. III. Chem.*, **5**, 47 (1957).

8) T. Masamune and Y. Kubota, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **77**, 1468 (1956).

substance, $C_{13}H_{21}ON$*, (sublimed with decomposition at near 325°C) (VIII), although it did not react with hydrogen peroxide. Both compounds, VI and VIII, showed extreme susceptibility to reduction as well as IV, and the infrared absorption spectrum similar to that of IV. On the basis of these data, it seems reasonable to assume that these two products were derived by the reaction of the same type as that which occurred in decahydroquinoline.

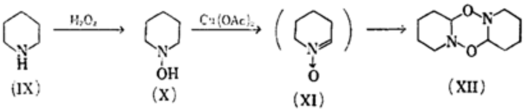


(V) (VI) (VII) (VIII)

Fig. 2

In order to confirm the constitution of IV, VI and VIII, the compound IV was mainly examined since many oxidation products of decahydroquinoline have already been prepared and characterized in detail. *cis*-*N*-Benzoyldecahydroquinoline could be recovered unchanged after attempting silver oxide oxidation of it under various conditions, hence it would be expected that basic nitrogen is concerned in this reaction. On the other hand, the same product (IV) was obtained not only from *trans*(I), but also from *cis*(II) as described above. Therefore, it is considered that this reaction involves change in the nitrogen $C_{(9)}$ atoms.

As to the conversion of the bond between nitrogen and $C_{(9)}$ atom in decahydroquinoline, four possibilities are considered. The first is the formation of an *N*-hydroxyl derivative corresponding to that obtained from piperidine (IX)[9]. The second is the formation of a dimer corresponding to that produced from *N*-hydroxyl piperidine (X)[1]. The third is the formation of a nitrone and the fourth is the formation of an isonitrone***.



(IX) (X) (XI) (XII)

Fig. 3

(i) The new compounds, IV, VI and VIII, had no characteristic absorption of the hydroxyl group in the infrared spectra and IV did not react with phenylisocyanate as has been above mentioned. Therefore, no *N*-hydroxyl group is present in these compounds.

(ii) 1, 4, 2, 5-Dioxa-diazine ring formed in the dimer (XII) has been reduced only by catalytic hydrogenation giving X, but not so with lithium aluminum hydride or with sulfurous acid. On the contrary, these compounds, IV, VI and VIII, were readily reduced with sodium borohydride or even with acidic potassium iodide. Hence the dimer as mentioned under the second possibility is not considered.

(iii) The new compounds, IV, VI and VIII, are similar to a nitrone in physical properties (i.e., in higher melting point or insolubility to non-polar solvents, etc.). These compounds however showed no ultraviolet absorption maxima at near 220∼230 mμ[3,11,12] and no infrared absorption band at 6.25μ[12] probably due to the CN-double bond of nitrone. Therefore, it is not needful to consider the structure of nitrone for these compounds.

(iv) On the basis of these considerations three of the four possibilities described above are excluded; then the fourth is the most reasonable. It has been reported that isonitrone is readily reduced by acidic potassium iodide[11-13] and these compounds, IV, VI and VIII, also were reduced by the reagent as above mentioned. These compounds formed stable chloroplatinates although they did not form stable salts with some of the usual acids. The compound IV showed instability to any acidic reagent**** and to alkaline potassium ferricyanate[14]. As shown by these chemical behaviors, these new compounds were considered to be analogous with isonitrone. Krimm[12] reported recently that a characteristic band of isonitrone appears at near 7μ in the infrared

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[9] R. Wolffenstein, *Ber.*, **25**, 2777 (1892).

*** The isonitrone has a three membered ring consisting of nitrogen, oxygen and carbon atoms, and was recently named by Krimm[10]. Although the presence of this ring has been discussed for a long time, it has recently been synthesized from the Schiff base by means of hydrogen peroxide or peracetic acid. Emmons[11] suggested the name "oxazirane" for this compound.

[10] H. Krimm and K. Hammann, cf. *Chem. Abstr.*, **51**, 3656 (1957).

[11] W. D. Emmons, *J. Am. Chem. Soc.*, **78**, 6208 (1956).

[12] H. Krimm, *Ber.*, **91**, 1057 (1958).

[13] L. Horner and E. Jürgens, ibid., **90**, 2184 (1957).

**** When IV was treated with acetic anhydride it gave oily products which could not yet be characterized.

[14] Oxidation of IV with alkaline potassium ferricyanate gave a neutral product, m. p. 56∼57°C, which has not been characterized.

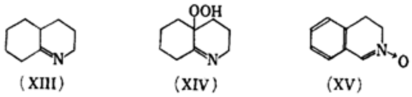
spectrum. Similar absorption was observed in these compounds, IV, VI and VIII. However, the settlement of the absorption[15] (due to near 7μ) will be deferred until more evidences are available on the various isonitrones.

In the course of the oxidation of decahydroquinoline, two pathways are considered reasonable.

i) Carbinol amine (as initial intermediate) is converted to the Schiff base by dehydration and then is further changed to isonitrone by the addition of oxygen.

ii) *N*-Hydroxyl amine (as initial intermediate) is converted to nitrone by dehydrogenation and then changed to isonitrone.

In the first case, the formation of carbinol amine has usually been observed in a reaction of tertiary amine with silver oxide[16a,b] or NBS reagent[16b]. It has been reported that the formed C(OH)-NH group is readily dehydrated to C=N-group[17]. Cohen and Witkop[6] have reported that 10 - hydroperoxy - $\Delta^{1(9)}$ - octahydroquinoline (XIV) is formed by the oxidation of $\Delta^{1(9)}$-octahydroquinoline (Schiff base) (XIII). Moreover, isonitrones have been obtained directly by oxidation of the Schiff base[10,11]. Accordingly, it is considered that the reaction of decahydroquinoline with silver oxide or NBS may proceed through the Schiff base stage (XIII) since the isonitrone (IV) was produced together with the hydroperoxide (XIV) in NBS oxidation as above mentioned.



(XIII) (XIV) (XV)

Fig. 4

In the second case, the formation of *N*-hydroxyl amine has commonly been observed in an oxidation of secondary amine with hydrogen peroxide[9] or perbenzoic acid[18]. It has been reported that further oxidation of *N*-hydroxylamine led to the corresponding nitrone by dehydrogenatian. If the nitrone (III) arose from the reaction of decahydroquinoline with hydrogen peroxide or perbenzoic acid, it has no stability because there is no conjugated double bond with nitrone group as shown in 3, 4-dihydroisoquinoline-*N*-oxide (XV)[2]. Consequently, the nitrone (III) is converted to the corresponding isonitrone (IV). In this case, no formation of a dimer will result from a steric effect, although that point is not sure.

Further study of the other compounds related to isonitrone derived from alicyclic secondary amine series is in progress.

Experimental

Formation of Isonitrone (IV) from *trans*-Decahydroquinoline (I).—(i) *Oxidation with silver oxide.*—To a solution of 1 g. of *trans*-decahydroquinoline in 20 cc. of 30% aqueous methanol, silver oxide which was freshly prepared from 5 g. of silver nitrate was added. When the resulting suspension was warmed at 30~40°C, a silver mirror gradually formed. After 6 hr. the mixture was cooled and filtered. The methanol of the filtrate was removed under reduced pressure and the resulting aqueous solution was extracted with chloroform after being made alkaline with sodium hydroxide solution. Drying and concentration of the extract left a residue, from which 170 mg. of the product crystallized readily after the addition of ether. Unreacted *trans*-decahydroquinoline could be removed readily by means of addition of ether followed by filtration because of its great solubility in the solvent. The product insoluble in ether was recrystallized from a mixture of ethanol and ether as white needles, m.p. 280~282°C. This substance was readily soluble in polar solvents, i.e., alcohol, water or chloroform, but insoluble in non-polar solvents, i.e., ether, benzene or tetrahydrofurane. It could also be purified by sublimation at 200°C at 5 mm. and had hygroscopic property under high moisture, but did not show any change in the melting point even in that case. It could be heated over its melting points, and recovered unchanged. It formed an aurichloride, m.p. 126~127°C, and a chloroplatinate, m.p. 176~177°C.

In the infrared absorption spectrum (in Nujol) the substance showed peaks at 7.32, 7.46, 7.61, 7.80, 7.94, 8.27, 9.36, 9.53, 10.27, 10.35, 10.48, 10.81, 11.06, 11.30, 11.57, 11.86 and 12.04 μ.

Anal. Found: C, 60.72; H, 9.58; N, 7.43; H_2O_2, 13.70. Calcd. for $C_9H_{15}ON\cdot {}^3/_4\, H_2O_2$: C, 60.48; H, 9.31; N, 7.84; H_2O_2, 14.27%.

ii) *Oxidation with hydrogen peroxide.*—When a suspension of 1 g. of *trans*-decahydroquinoline in 20 cc. of 30%-hydrogen peroxide solution was left at room temperature, *trans*-decahydroquinoline dissolved during the course of the reaction and a deep orange-yellow color gradually developed. After 3 days the reaction mixture was made alkaline with concentrated ammonium hydroxide solution under cooling with water. The alkaline

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[15] It has been reported that the N-O-stretching vibration in amine oxide shows at near 10.6~10.8μ [R. Mathis Noel et al. *Compt rend.*, **242**, 1873 (1956)], and the characteristic absorption of grouping -O-C-N in oxazolidine ring displays at 8.63, 8.92 and 9.06μ, respectively [E. D. Bergmann, *Chem. Rev.*, **53**, 326 (1953)].

[16a] H. Suginome and K. Ohno, *J. Fac. Sci. Hokkaido Univ. Ser. III Chem.*, **4**, 36 (1950).

[16b] O. E. Edwards, F. H. Clarke and B. Douglas, *Can. J. Chem.* **32**, 235 (1954).

[17] D. H. R. Barton, *J. Chem. Soc.*, **1953**, 1027.

[18] M. A. T. Rogers, ibid., **1955**, 769.

solution obtained was extracted with chloroform in as short a time as possible; the extract was washed with water and then dried with sodium sulfate. The residue that remained after evaporation of the solvent crystallized on the addition of ether. The product (185 mg.) was recrystallized from a mixture of ethanol and ether and melted at 280~282°C. It was proved to be identical (mixed melting point and comparison of infrared absorption spectra) with the product from the silver oxide oxidation.

iii) *Oxidation with perbenzoic acid.*—A solution of 100 mg. of *trans*-decahydroquinoline in 100 cc. of chloroform was treated with 150 mg. of perbenzoic acid for a day at room temperature. After this treatment, the chloroform solution afforded 13 mg. of a product which melted at 280~282°C after recrystallization and was proved to be identical also with the product obtained by the oxidation with silver oxide.

iv) *Oxidation with N-bromosuccimide (NBS).*—A solution of 1 g. of *trans*-decahydroquinoline in 40 cc. of acetone containing 10 cc. of water was treated with 1.28 g. of NBS overnight in an atmosphere of nitrogen at room temperature. The solution was then refluxed in a stream of nitrogen for 20 min. After removal of the acetone under reduced pressure the aqueous solution was extracted with ether. The ethereal extract was subjected successively to drying, removal of the solvent and distillation in vacuo. The distillate obtained at 52~53°C at 5 mmHg consisted mainly of unreacted *trans*-decahydroquinoline. The distillate obtained above the temperature of 52~53°C deposited as needle crystals on being allowed to stand in an ice box cooled at −5°C. Separation by filtration and recrystallization from ethyl acetate led to a product which melted at 96~98°C, and was positive to the starch-potassium iodide test. Its crystal form changed from needle to plate on standing. From these properties the product appeared to be identical with 10-hydroperoxy-$\Delta^{1(9)}$-octahydroquinoline, but it was necessary to carry out a further investigation for the identification because of the shortage of the material. On standing for several weeks the mother liquor of the above crystals deposited a further amount of crystals. This compound had m.p. 280~282°C after recrystallization from a mixture of ethanol and ether. It showed no depression on admixture with isonitrone (IV) obtained by the oxidation with silver oxide.

Formation of Isonitrone (IV) from *cis*-Decahyhdroquinoline (II).—When *cis*-decahydroquinoline was treated with silver oxide or hydrogen peroxide under the same conditions as *trans*-decahydroquinoline was, it produced the same isonitrone (IV) which was confirmed by the mixed melting point method and the comparison of infrared spectra.

Action of Silver Oxide on *cis-N*-Benzoyldecahydroquinoline.—*cis-N*-Benzoyl-decahydroquinoline was nearly inert to the reagent at 30~40°C under the conditions as described under oxidation of *trans*-decahydroquinoline. Furthermore, the compound proved to be inert to silver oxide even at 80~90°C in aqueous methanol.

Reduction of Isonitrone (IV).—i) *Reduction with sodium borohydride.*—A solution of 10 mg. of sodium borohydride in 2 cc. of methanol was added to a solution of 40 mg. of isonitrone (IV) in 2 cc. of methanol under cooling with water. After having been heated for 30 min. on a steam bath, the solution was concentrated to near dryness under reduced pressure. The residue was then taken up in ether, washed with water, dried and evaporated to dryness. There were thus obtained 34 mg. of crystals which were recrystallized from petroleum ether, m.p. 46~48°C, and proved identical with *trans*-decahydroquinoline[19] by mixed melting point not only as free base but also as hydrochloride.

ii) *Reduction with sulfurous acid.*—Sulfur dioxide was saturated into a solution of 50 mg. of isonitrone (IV) in 5 cc. of water under cooling with water. After being kept for two days the resulting solution was alkalized with sodium carbonate solution and extracted with chloroform. After drying, evaporation of the extract left a residue which crystallized on standing for a few hours, giving 23 mg. of the product. On recrystallization from petroleum ether the product melted at 46~48°C and was proved identical with *trans*-decahydroquinoline.

iii) *Reduction with acidic potassium iodide.*—To a solution of 82 mg. of isonitrone (IV) in 1 cc. of 2 N-hydrochloric acid was added 1 cc. of an aqueous solution saturated with potassium iodide. On standing at room temperature iodine was gradually separated. After being kept overnight the mixture was concentrated to a syrup in a desiccator under reduced pressure and methanol was then added. Evaporation of the methanolic solution from which inorganic salt was removed by filtration left 12 mg. of a product. On washing with ether and recrystallization from a mixture of ethylacetate and chloroform, the product melted at 274~278°C and showed no depression of the melting point by admixture with *trans*-decahydroquinoline hydrochloride.

Action of Phenylisocyanate on Isonitrone (IV).—Isonitrone (IV) did not react with phenylisocyanate in dioxane on treatment for 16 hr. at room temperature.

Oxidation of α-Perhydroacridine with Hydrogen Peroxide.—A half g. of α-perhydroacridine was treated with an excess of 30%-hydrogen peroxide solution at room temperature for a week. The reaction mixture gradually colored orange-yellow. The solution was made alkaline with sodium hydroxide solution under cooling with cold water and extracted with chloroform as quickly as possible. The resulting chloroform extract was washed once with water, then dried (sodium sulfate) and concentrated to dryness. On treatment with ether, the crystals could be separated into soluble and insoluble parts for the solvent. The soluble

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[19] Cohen and Witkop[5] and Leonard et al. (*J. Am. Chem. Soc.*, 78, 3463 (1956)) reported that derivatives of $\Delta^{1(9)}$-octahydroquinoline were reduced to the *trans*-form of decahydroquinoline in good yields by lithium aluminum hydride reduction.

part was unchanged amine. The insoluble part was recrystallized from a mixture of chloroform-ethanol as thin plates, giving 230 mg. of the product, isonitrone (VI), which sublimed with decomposition at near 320°C. This isonitrone was completely insoluble in a non-polar solvent, less soluble in water and alcohol, and more soluble in chloroform. The VI formed a chloroplatinate, m. p. 248～250°C (decomp.) In the infrared absorption spectrum (in Nujol) the substance showed peaks at 7.32, 7.46, 7.61, 7.80, 7.96, 8.17, 8.27, 8.46, 9.12, 9.56, 9.72, 10.09, 10.35, 10.50, 10.81, 11.04 and 11.91 μ.

Anal. Found: C, 67.36; H, 10.10. Calcd. for $C_{13}H_{21}ON \cdot 3/4H_2O_2$: C, 67.06; H, 9.74%.

Oxidation of α-Perhydrophenanthridine (VII) with Silver Oxide.—A mixture of 0.5 g. of α-perhydrophenanthridine and silver oxide (freshly prepared from 2 g. of silver nitrate) in 3 cc. of methanol and 30 cc. of water was refluxed at 90～100°C on a steam bath for 3 hr. A silver mirror was gradually formed. The solids were removed by filtration and washed thoroughly with hot methanol. After removal of methanol from the combined filtrate and washings, the aqueous solution was made alkaline with sodium hydroxide solution, filtered and extracted with chloroform. On evaporation of the solvent after drying, the chloroform extract afforded crystals. Since the unchanged base (VII) was readily soluble in ether, it could be separated from the reaction product by the addition of ether. The insoluble ether part was recrystallized from a mixture of ethanol and ether as needles giving 318 mg. of the product, which sublimed with decomposition at near 325°C. The property of solubility in a polar solvent was closely like that of isonitrone (IV). This product (VIII) formed a chlorofolatinate; m.p. 228～229°C (resolidified at 121°C). In the infrared absorption spectrum (in Nujol) the substance showed peaks at 7.32, 7.46, 7.61, 7.78, 7.80, 8.17, 8.27, 8.44, 9.12, 9.58, 9.72, 10.02, 10.09, 10.35, 10.52, 10.81, 11.04 and 11.91 μ.

Anal. Found: C, 66.80; H, 9.79; H_2O_2, 11.26. Calcd. for $C_{13}H_{21}ON \cdot 3/4H_2O_2$: C, 67.06; H, 9.74; H_2O_2, 10.96%.

Reductions of Isonitrone, VI and VIII, with Sodium Borohydride.—The isonitrones, VI and VIII, were respectively reduced to the original bases, V and VII with sodium borohydride in a good yield by the same treatment as described under the reduction of isonitrone (IV).

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