[Contribution from the National Institutes of Health]

CONVERSION OF BENZOXAZINE HYDROPEROXIDES TO THE PARENT BENZOXAZINES (1)

JAMES BURNS PATRICK and BERNHARD WITKOP

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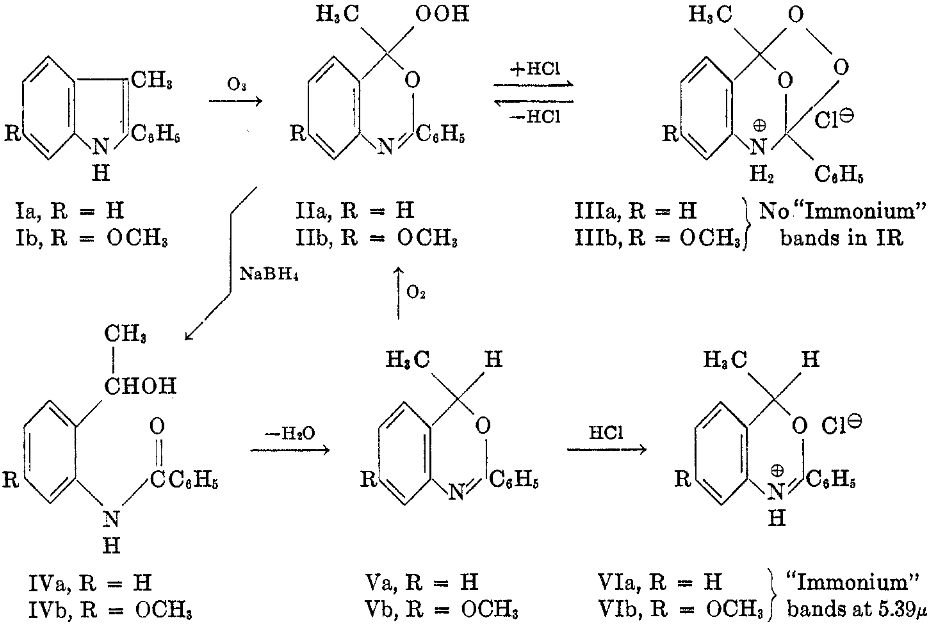
Ozonolysis of the easily accessible phenylskatoles (Ia, Ib) (2) yields 2-phenylbenzoxazine hydroperoxides (IIa, IIb) which have been shown to be in equilibrium with the ring-tautomeric isozonide (IIIa, IIIb) on the basis of the hypsochromic shift observed on salt formation (3). The present paper describes the conversion of the oxazine hydroperoxides (IIa, IIb) to the parent oxazines (Va, Vb). Since the tertiary hydrogen atom at 4 is in a benzyl position and labilized by the adjacent oxygen atom, the autoxidation of such oxazines, which will be the subject of a more detailed investigation, should lead back to the oxazine hydroperoxides (IIa, IIb). A similar synthesis of an isozonide by autoxidation has been achieved in the furan series (4).



The hydroperoxide (IIa) is smoothly reduced by sodium borohydride to *o*-benzamidophenylmethylcarbinol (IVa) (5). Concentrated sulfuric acid under special precautions effects the dehydration of this carbinol in good yield. The oxazine (Va), characterized by the crystalline picrate and hydrochloride, failed to yield the crystalline hydroperoxide (IIa) under the following conditions (i) irradiation of its solution in diethyl and diisopropyl ether with ultraviolet and sunlight for several hours or weeks at room temperature or on refluxing; (ii) shaking under oxygen in ethyl acetate containing freshly reduced platinum

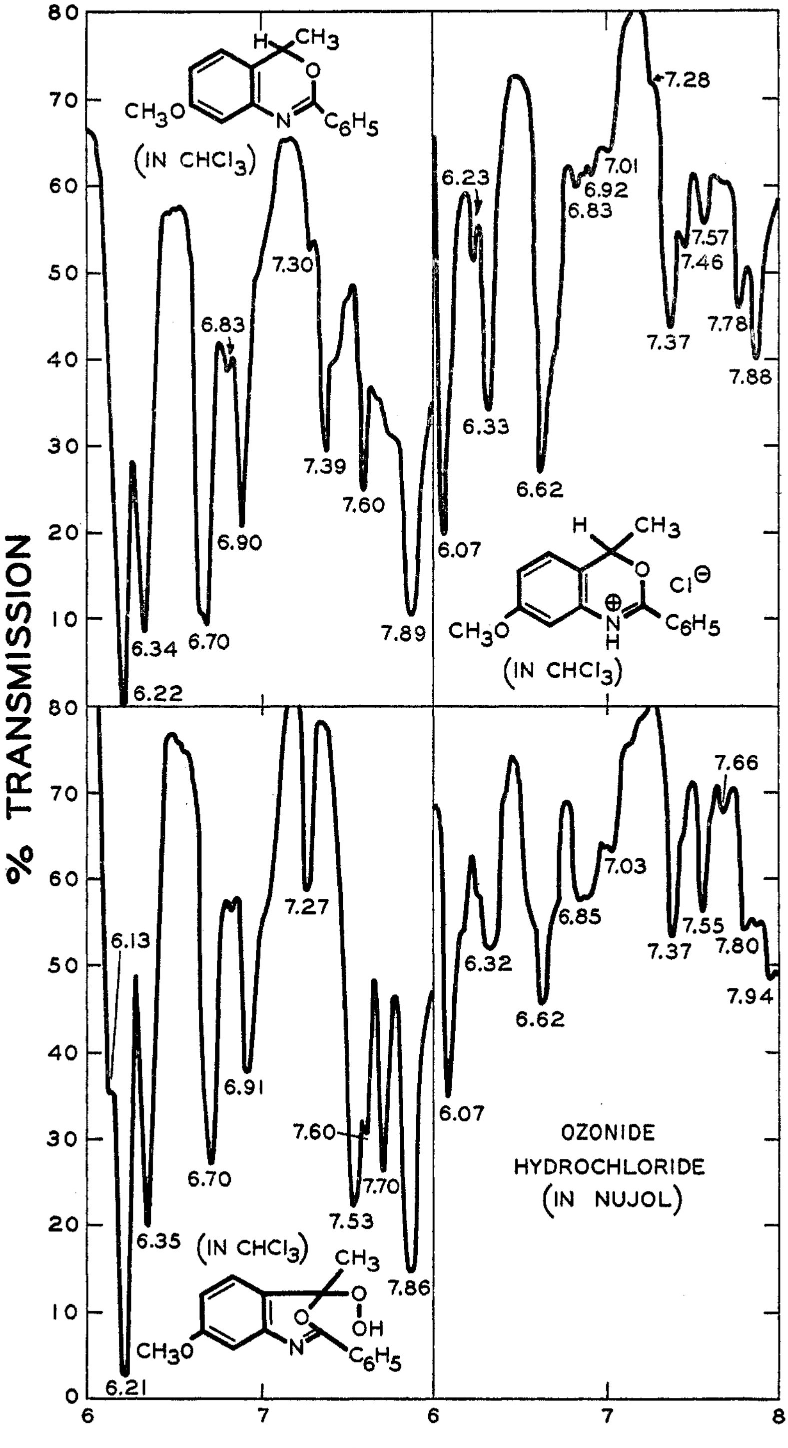


FIG. 1. CHANGES IN THE 6–8μ REGION OF THE INFRARED SPECTRA OF THE 4-METHYL (VB) and 4-hydroperoxy (IIb) derivative of 2-phenyl-7-methoxy-1,3,4a-benzoxazine on salt formation.

oxide (6); (iii) bubbling oxygen through the oxazine as such or in a solution of technical ligroin at room or elevated temperature. In no case was hydroperoxide detected. Traces of the expected *o*-benzamidoacetophenones point to the possibility that small amounts of hydroperoxides underwent rearrangement in the process of formation. The methoxy compounds IIb, IVb and Vb in which autoxidation should be facilitated by the 7-methoxy group in *para*-position of the benzyl hydrogen atom in the oxazine Vb were also prepared. The autoxidizability of 5,6-dimethoxyindoles (7) and tetrahydrocarbazoles (8) occurs with remarkable ease. However, methoxyoxazine (Vb) did not form a hydroperoxide under the above-mentioned variety of conditions.

Fig. 1 shows the changes on salt formation observed in the 6–8 μ region with

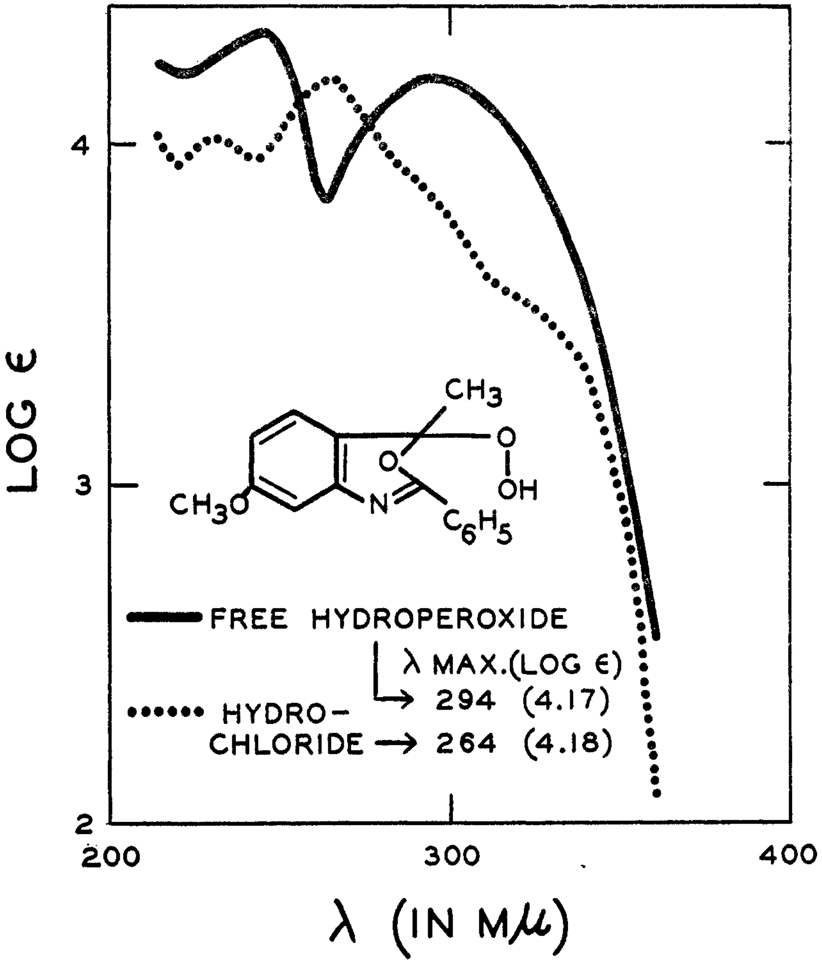


FIG. 2. HYPSOSCHROMIC SHIFT OF THE ULTRAVIOLET ABSORPTION MAXIMUM OBSERVED on salt formation of 2-phenyl-4-methyl-4-hydroperoxy-7-methoxy-1,3,4a-benzoxazine (IIb → IIIb); solvent ethanol.

the oxazine (Vb) and the oxazine hydroperoxide (IIb). The azomethine group conjugated with two phenyls in both cases shows a strong band at 6.21–6.22 μ superimposed upon any phenyl band present. This band on formation of the hydrochloride shows identical hypsochromic shifts to 6.07 μ (3, 9). If the hydrochloride of IIb consisted of, or contained, some of the ring tautomer (IIIb) the molar extinction coefficient of the band at 6.07 μ should disappear or decrease (10). A proper comparison is impossible in this case, since the hydrochloride of IIb proved to be insoluble in chloroform and had to be mulled in Nujol. The hydrochlorides (presumably IIIa, IIIb) showed only saturated ammonium bands near 4 μ, whereas VIa and VIb displayed both ammonium bands (4.10) and immonium bands (5.39 μ) typical of the unsaturated azomethine cation $—\overset{\oplus}{\mathrm{N}}\mathrm{H}{=}\mathrm{C}<$ (11).

The marked hypsochromic shift in the ultraviolet (294 → 264 mμ) observed on salt formation (Fig. 2) is good evidence for the interaction of the azomethine element with the hydroperoxy group. Model considerations showing that the two groups are within convenient intramolecular bonding distance make less likely the alternative possibility of *inter*molecular interaction.

EXPERIMENTAL[1]

2-Phenyl-4-methyl-1,3,4a-benzoxazine (Va). *o*-Benzamidophenylmethylcarbinol (3 g.) (IVa) (5) was suspended in 8 cc. of concentrated sulfuric acid and heated on the steam-bath for eight minutes (3). The red solution was poured onto crushed ice and the ice-cold solution was made basic with strong potassium hydroxide solution while ice was being added as necessary to keep the mixture at 0–5°. The basic solution was extracted with ether, and the extract was washed with saturated salt solution, dried over magnesium sulfate, and evaporated. The residual yellow oil weighed 3.17 g. (97.8% of theory). In similar runs the yields obtained were 88–92%. Vacuum distillation yielded a clear, slightly yellow-green, highly refractive mobile liquid, b.p. 128–135°/0.15–0.7 mm.; n_D^{20} 1.6390. After standing for several weeks the liquid crystallized in needles which were washed with petroleum ether; melting point 37°.

Anal. Calc'd for $C_{15}H_{13}NO$: C, 80.55; H, 5.86; N, 6.26.
Found: C, 80.49, 80.25; H, 5.51, 5.62; N, 6.54.

Infrared spectrum (chloroform): no bands in OH or NH region; 6.15^{s}; 6.23^{s}; 6.34^{s}; 6.73^{s}; 6.89^{s}; 7.30^{sh}; 7.43^{s}; 7.62^{m}; 7.92^{s}; 8.54^{m}; 9.27^{s}; 9.35^{s}; 9.76^{m}; 10.04^{m}; 10.65^{w}; 11.34^{m}; 11.78^{w}.

Attempted autoxidation. Solutions of the oxazine in technical ligroin or diethyl or diisopropyl ether under oxygen for several days or even weeks on exposure to ultraviolet and sunlight gave back mainly starting material. When the solutions were refluxed on irradiation, the small neutral fractions obtainable from such runs showed the typical infrared bands (5.95; 6.02) of *o*-benzamidoacetophenone.

Picrate. The addition of ethereal picric acid to an ether solution of the oxazine precipitated the *picrate*, crystallizing in light-yellow, birefringent microcrystals, m.p. 134–138° (clear yellow melt).

Anal. Calc'd for $C_{21}H_{16}N_4O_8$: C, 55.75; H, 3.57; N, 12.39.
Found: C, 55.83; H, 3.47; N, 12.50.

Hydrochloride. The addition of ethereal hydrogen chloride to an ether solution of the

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[1] All melting points are corrected, all boiling points are uncorrected. The analyses were performed by Dr. W. C. Alford and his associates, Microanalytical Service Laboratory of the National Institutes of Health.

oxazine precipitated the hydrochloride as colorless needles, m.p. 125–140°. The substance was readily soluble in chloroform and crystallized from such solutions by the addition of ligroin. It was insoluble in ethyl acetate, but crystallized from acetone or methyl ethyl ketone. After recrystallization from methyl ethyl ketone the hydrochloride was obtained as colorless birefringent prisms, m.p. 117–129.5° (sublimation in prisms at 110°; clear colorless melt).

Anal. Calc'd for $C_{15}H_{13}NO \cdot HCl$: C, 69.36; H, 5.43; N, 5.39.

Found: C, 69.24; H, 5.43; N, 5.44.

2-Phenyl-3-methyl-6-methoxyindole (Ib). 3-Methoxyphenylhydrazine (2.70 g.) and propiophenone (2.70 g.) were mixed with a quantity of polyphosphoric acid (2) equal to their combined volume and stirred with a thermometer. The temperature of the mixture rose to 50°, then fell. By heating the mixture on the steam-bath the temperature rose again rapidly to 120°, whereupon the reaction was stopped by external ice-cooling. The mixture was decomposed with water, extracted with ether, and the red ether layer was washed successively with 2 *N* potassium hydroxide solution, water, and saturated sodium chloride solution. The extract was dried over magnesium sulfate, filtered, and evaporated. The crude product yielded 3.71 g. (80%). After two recrystallizations from benzene the analytical sample formed colorless birefringent plates, m.p. 164–167° (sublimation in birefringent plates at 143°; clear colorless melt). For analysis the substance was dried at 100° *in vacuo.*

Anal. Calc'd for $C_{16}H_{15}NO$: C, 80.99; H, 6.37; N, 5.90.

Found: C, 80.81; H, 6.29; N, 5.83.

2-Phenyl-4-methyl-4-hydroperoxy-7-methoxy-3,1,4a-benzoxazine (IIb). A solution of one gram (4.22 millimoles) of 2-phenyl-3-methyl-6-methoxyindole (Ib) in 100 cc. of ethyl acetate was treated with a stream of ozonized oxygen (0.226 millimole per minute) for 20 minutes. The yellowish solution was evaporated *in vacuo* at 22°, leaving a yellow solid residue, which was washed with alcohol. The residual white crystalline material showed a positive starch-iodide test and yielded a yellowish hydrochloride on treatment with ethereal hydrogen chloride. Two recrystallizations of the free base from ethanol produced long colorless needles (395 mg.), m.p. 115.5–116°.

Anal. Calc'd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91.

Found: C, 67.58; H, 5.33; N, 4.63.

Infrared spectrum (in chloroform): 2.83^m (—OOH); 3.07 [broad shallow band possibly due to protonated ammonium cation of zwitterionic contribution (3)]; 4.15^w (zwitterionic ammonium); 6–8μ see Fig. 1; 8.58^w; 8.72^w; 8.96^w; 9.08^w; 9.24^s; 9.45^s; 9.77^s; 10.50^m; 10.97^m; 11.73^m. The *hydrochloride* (in Nujol) shows the following changes outside the 6–8μ region: no bands in the OH, NH region; 3.87 (saturated ammonium cation); no immonium bands; 8.34^m; 8.78^w; 8.93^w; 11.25^m; 11.58^m; 12.38^m; 12.69^m; 13.16^m.

o-Benzamido-5-methoxyphenylmethylcarbinol (IVb). A solution of 300 mg. of the hydroperoxide (IIb) in 20 cc. of methanol was treated with 100 mg. of solid sodium borohydride. After the initial effervescence had subsided the solution was refluxed for an hour and then evaporated at 100° *in vacuo.* The residue was suspended in 2 cc. of 2 *N* hydrochloric acid, diluted to 6 cc. with water, and extracted with ether. After drying over magnesium sulfate the ether extract, on evaporation, left 275 mg. (91%) of a yellow oil which crystallized on trituration with ether. Ether washing left 185 mg. of crystalline residue which was crystallized once from benzene, once from benzene-ligroin, and once from ether to leave 63 mg. of colorless needles, m.p. 96.3–106° (clear colorless melt).

Anal. Calc'd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16.

Found: C, 70.69; H, 6.33; N, 5.23.

2-Phenyl-4-methyl-7-methoxy-3,1,4a-benzoxazine (Vb). The carbinol (IVb) (500 mg.) in 1 cc. of concentrated sulfuric acid was heated on the steam-bath for five minutes, then poured onto ice and made basic with concentrated potassium hydroxide solution, keeping the temperature around zero. The mixture was extracted with ether; the extract was dried over magnesium sulfate, filtered, and evaporated to leave 330 mg. (71%) of an oil which resisted crystallization. The hydrochloride, made in ether, did not crystallize well from organic solvents. On recrystallization from concentrated hydrochloric acid it melted at 103–122° (clear yellow melt).

Anal. Calc'd for $C_{16}H_{15}NO_2 \cdot HCl$: C, 66.32; H, 5.57; N, 4.84.

Found: C, 66.13; H, 5.48; N, 4.75.

Infrared spectrum (chloroform): no band in the OH, NH region; bands 6–8μ see Fig. 1; 8.40^w; 8.61^s; 8.86^w; 8.98^w; 9.36^s; 9.76^m; 10.05^w; 10.56^w; 11.50^w; 11.70^m. The *hydrochloride* shows the following new bands: small dip near 3μ (proton of azomethine salt); 4.10^w (ammonium cation); 5.39^w (immonium cation); 6–8μ see Fig. 1; 9.11^s; 10.11^w; 11.18^w.

SUMMARY

The benzoxazine hydroperoxides (IIa, IIb) resulting from ozonolysis of the respective phenylskatoles (Ia, Ib) have been converted to the parent benzoxazines (Va, Vb) by dehydration of their sodium borohydride reduction products (IVa, IVb). The autoxidizability of the two oxazines has been tested.

BETHESDA 14, MD.

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