

## Reactions of Organic Peroxides. Part XIX.<sup>1</sup> Hydroperoxides from Alkylpyridines

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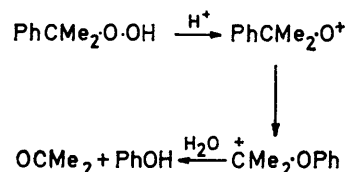
The hydroperoxides obtained by autoxidation of 5-ethyl-2-methyl-, and 2-, 3-, and 4-isopropylpyridine were converted into the corresponding alcohols or acetylpyridines on reaction with bases or on pyrolysis. Acetylpyridines were also the major products from the slow reaction of these hydroperoxides with strong sulphuric acid.

LITTLE information is available concerning the formation and reactions of the hydroperoxides of alkylpyridines. 5-(1-Hydroperoxyethyl)-2-methylpyridine, isolated from the products of autoxidation of 5-ethyl-2-methylpyridine, provided mainly 5-acetyl-2-methylpyridine on treatment with iron(II) sulphate, sodium hydrogen sulphite, or mineral acid,<sup>2</sup> and the hydroperoxide from 4-isopropylpyridine<sup>3,4</sup> is reported to give the corresponding alcohol and some 4-acetylpyridine on thermal decomposition.

In the present work, isolation of the secondary hydroperoxide, obtained by autoxidation of 5-ethyl-2-methylpyridine, by alkaline extraction<sup>2</sup> led to considerable loss through decomposition, whereas high recovery was achieved by removal of the unchanged alkylpyridine under vacuum and crystallisation of the residue from ether. This hydroperoxide yielded mainly 5-acetyl-2-methylpyridine on treatment with sodium methoxide, lithium chloride in methanol, or formic acid, and on pyrolysis.

Crystalline hydroperoxides were similarly isolated from the products of autoxidation of 2-, 3-, and 4-isopropylpyridine. These tertiary hydroperoxides were converted into the corresponding alcohols when heated with sodium methoxide or sodium hydroxide, and, surprisingly, on treatment with formic acid (*i.e.* reduction predominated over acid-catalysed rearrangement). Pyrolysis of the hydroperoxides led to the corresponding acetyl compounds by homolysis, although the crude products derived from the 3- and 4-isopropyl compounds contained the corresponding tertiary alcohol; that a radical reaction occurred was shown by the production of biphenyl during pyrolysis in benzene.

At first sight, the most unexpected result was the slow conversion of these tertiary hydroperoxides mainly into the corresponding acetyl derivatives by strong sulphuric acid. Aralkyl hydroperoxides are converted into phenols and carbonyl compounds by a heterolytic route involving migration of the aryl group under relatively mild conditions with catalytic amounts of acid:



However, the present hydroperoxides, with a hetero-aromatic group, needed prolonged heating with concentrated (50–60%) sulphuric acid to bring about decomposition, and hydroxypyridines were not isolated from the products. Such behaviour is similar to that of tertiary alkyl and cycloalkyl hydroperoxides, where 50–98% sulphuric acid brings about rearrangement of an alkyl group with formation of a ketone and alkyl hydrogen sulphate,<sup>5,6</sup> dialkyl peroxide, and hydrogen peroxide,<sup>7,8</sup> or, in the presence of alcohols, ethers,<sup>7</sup> and reflects the fact that intramolecular electrophilic attack of the oxonium ion (I) on the group R is promoted when R is aryl and inhibited when R is pyridyl, increasingly so on protonation of the nitrogen atom (*i.e.* under acidic conditions) to give species (II).<sup>9</sup> The same argument is applicable to the formation of an intermediate species of type (III). Hence, a methyl

<sup>5</sup> N. C. Deno, W. E. Billups, K. E. Kramer, and R. R. Lastomirsky, *J. Org. Chem.*, 1970, **35**, 3080.

<sup>6</sup> R. D. Bushick, *Tetrahedron Letters*, 1971, 579.

<sup>7</sup> J. O. Turner, *Tetrahedron Letters*, 1971, 887.

<sup>8</sup> Sun Oil, Ger. Offen, 2,100,784.

<sup>9</sup> P. Sykes, 'A Guidebook to Mechanism in Organic Chemistry,' Longmans, London, 1970, p. 147.

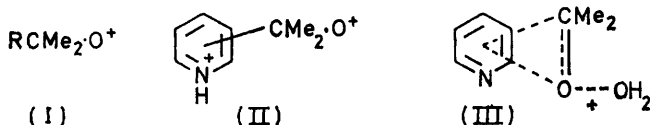
<sup>1</sup> Part XVIII, E. G. E. Hawkins, *J.C.S. Perkin I*, 1972, 13.

<sup>2</sup> Distillers Co. Ltd., B.P. 867,488—867,490.

<sup>3</sup> J. Drillat, L. Torres, and E. Bordier, *Compt. rend.*, 1968, **266**, 1381.

<sup>4</sup> E. Bordier, *Bull. Soc. chim. France*, 1972, 1147.

group migrates in preference to the pyridyl group to provide an acetylpyridine and (presumably) methyl hydrogen sulphate. The small quantities of tertiary



alcohols isolated from the reaction products were probably derived from thermal decomposition.

#### EXPERIMENTAL

**Autoxidation of 5-Ethyl-2-methylpyridine.**—The alkylpyridine (800 g) was refluxed over solid sodium hydroxide (100 g) for 4 h and redistilled before use. The distillate was oxygenated, in a recycle stirred system, at 100° for 14 h; 9.3 l of oxygen were absorbed and the oxidate contained 0.364 mol of peroxide. The unchanged material was removed at 0.1 mmHg, and the residue (36 g), peroxide equiv. 220, crystallised from ether, provided 5-(1-hydroperoxyethyl)-2-methylpyridine, m.p. 91–92° (Found: C, 62.45; H, 7.45; N, 9.05%; peroxide equiv., 155. Calc. for  $\text{C}_8\text{H}_{11}\text{NO}_2$ : C, 62.75; H, 7.2; N, 9.15%; peroxide equiv., 153).

**Reactions of the Hydroperoxide.**—(a) *With sodium methoxide.* The hydroperoxide (10 g) was added to a solution of sodium (2 g) in methanol (40 cm<sup>3</sup>); after 0.5 h at 40–50° the peroxide had reacted. The solution was diluted with water and extracted with chloroform; distillation of the extract provided material (6.9 g), b.p. 110–120° at 10 mmHg [2,4-dinitrophenylhydrazone, m.p. 224–225° (Found: C, 53.0; H, 4.15; N, 22.0.  $\text{C}_{14}\text{H}_{13}\text{N}_5\text{O}_4$  requires C, 53.35; H, 4.1; N, 22.2%) identified as 5-acetyl-2-methylpyridine by its i.r. spectrum.

(b) *With lithium chloride in methanol.* The hydroperoxide (10 g) was heated on a water-bath with a solution of lithium chloride (10 g) in methanol (40 cm<sup>3</sup>) for 7 h. The product, on work-up as above, gave 5-acetyl-2-methylpyridine (7.3 g) as before.

(c) *With formic acid.* Slight warming of a solution of the hydroperoxide (8 g) in formic acid (20 cm<sup>3</sup>) led to an exothermic reaction; after 5 min no active oxygen remained. Distillation of the product provided slightly impure 5-acetyl-2-methylpyridine (7.7 g), which contained unidentified formates.

(d) *Pyrolysis.* The hydroperoxide (10 g) in benzene (15 cm<sup>3</sup>) was dropped (during 20 min) into a heated (300°) glass bead packed tube at 200 mmHg under nitrogen. From the product was isolated 5-acetyl-2-methylpyridine (8.3 g).

**Autoxidation of 2-Isopropylpyridine.**—The purified alkylpyridine (67.8 g) was autoxidised as before; after 21.5 h at 110°, 3.8 l of oxygen had been absorbed and the oxidate contained 0.14 mol of peroxide. Normal work-up provided 2-(1-hydroperoxy-1-methylethyl)pyridine (21 g), m.p. 69–71.5° (from benzene) (Found: C, 62.65; H, 7.2; N, 9.05%; peroxide equiv., 154.4.  $\text{C}_8\text{H}_{11}\text{NO}_2$  requires C, 62.7; H, 7.25; N, 9.15%; peroxide equiv., 153);  $m/e$  137 ( $M - O$ ) and 122 ( $M - O - \text{CH}_3$ );  $\tau$  8.41 (Me), 2.53 (H-6), 2.0–3.1 (H-3, -4, and -5), and -2.27 (O·OH).

**Reactions of the Hydroperoxide.**—(a) *With sodium methoxide.* The hydroperoxide (6 g) was added to a solution of sodium (1.5 g) in methanol and the mixture refluxed for 6.75 h. Work-up as before gave 2-(1-hydroxy-1-methylethyl)pyridine (4.5 g), b.p. 88–91° at 15 mmHg, m.p. 50–52° (lit.,<sup>10</sup> 50–51°) (from benzene) (Found: C, 69.9; H, 8.05; N, 9.95. Calc. for  $\text{C}_8\text{H}_{11}\text{NO}$ : C, 70.05; H, 8.05; N, 10.2%), identified spectroscopically [ $m/e$  137 ( $M$ ), 136 ( $M - H$ ), 122 ( $M - \text{CH}_3$ ), 104 ( $M - \text{CH}_3 - \text{H}_2\text{O}$ ), 80, 79, and 52;  $\tau$  8.53 (Me), 1.57 (H-6), 2.10–3.20 (H-3, -4, and -5), and 5.32 (OH)]. The slower reaction (10 h) with aqueous 10% sodium hydroxide gave the same product.

(b) *With formic acid.* The hydroperoxide (6 g) and formic acid (22 cm<sup>3</sup>) were heated for 1 h on a water-bath; distillation gave fractions (6.7 g), b.p. 72–92° at 15 mmHg, shown to consist of a mixture of the tertiary alcohol and its formate.

(c) *Pyrolysis.* A solution of the hydroperoxide (6 g) in benzene (40 cm<sup>3</sup>) was pyrolysed by passing through a column at 400°. Distillation of the product at 15 mmHg gave three fractions: (i) (3.3 g), b.p. 74–80°; (ii) (1.2 g), b.p. 80–150°; and (iii) (0.3 g), b.p. 150–190°; and a residue (0.5 g). Fraction (i) apparently (i.r. spectrum) consisted largely of 2-acetylpyridine [oxime, m.p. 119–121° (from ethanol) (lit.,<sup>11</sup> 120°) (Found: C, 62.0; H, 6.05; N, 20.55. Calc. for  $\text{C}_7\text{H}_8\text{N}_2\text{O}$ : C, 61.75; H, 5.9; N, 20.6%), and 2,4-dinitrophenylhydrazone, m.p. 231–232° (from nitrobenzene–benzene) (lit.,<sup>12</sup> 224–228°) (Found: C, 51.7; H, 3.85; N, 23.2. Calc. for  $\text{C}_{13}\text{H}_{11}\text{N}_5\text{O}_4$ : C, 51.8; H, 3.65; N, 23.25%)]. From fraction (ii), which contained 2-acetylpyridine and biphenyl, was isolated biphenyl (0.25 g) (m.p. and mixed m.p. 64–68°); and fraction (iii) was shown spectroscopically to contain biphenyl and an amide or imine.

(d) *With sulphuric acid.* The hydroperoxide (6 g) was heated at reflux with 10% sulphuric acid (30 cm<sup>3</sup>) for 5 h, but only a slight fall in peroxide content occurred. Further additions of concentrated sulphuric acid (4 cm<sup>3</sup> with 4.5 h heating, 5 cm<sup>3</sup> with 33.25 h heating, and 6 cm<sup>3</sup> with 12 h heating) were needed for total decomposition. The solution was cooled, neutralised with ammonia, and extracted with chloroform; distillation of the extract gave 2-acetylpyridine (3.4 g), b.p. 84–90° at 15 mmHg, identified as before.

**Autoxidation of 3-Isopropylpyridine.**—The 3-isopropylpyridine was synthesised by a reported route<sup>13</sup> from ethyl nicotinate except that the catalytic hydrogenation of the 3-isopropenylpyridine was carried out at atmospheric pressure. Autoxidation at 120–130° for 13.5 h led to absorption of 3.12 l of oxygen and formation of 0.11 mol of peroxide. Addition of ether led to the separation of 3-(1-hydroperoxy-1-methylethyl)pyridine (9.4 g), m.p. 99–102° (from ethyl acetate) (Found: C, 62.75; H, 7.1; N, 9.35%; peroxide equiv., 153.5);  $m/e$  153 ( $M$ ), 137 ( $M - O$ ), and 122 ( $M - O - \text{CH}_3$ );  $\tau$  8.40 (Me), 1.42 (H-2), 2.22 (H-3), 2.80 (H-5), 1.62 (H-6), and -2.19 (O·OH). Removal of the unchanged alkylpyridine from the filtrate provided a residue (13.0 g), from which further hydroperoxide (6.4 g) was isolated.

**Reactions of the Hydroperoxide.**—(a) *With sodium methoxide.* The hydroperoxide (5 g), treated essentially as

<sup>12</sup> U. Haug and H. Fürst, *Chem. Ber.*, 1960, **93**, 593.

<sup>13</sup> H. C. Brown and W. A. Murphey, *J. Amer. Chem. Soc.*, 1951, **73**, 3308.

<sup>10</sup> W. Sobiecki, *Ber.*, 1908, **41**, 4103.

<sup>11</sup> C. Engler and P. Rosumov, *Ber.*, 1891, **24**, 2527.

the 2-isomer, gave 3-(1-hydroxy-1-methylethyl)pyridine (3.5 g), m.p. and mixed m.p. 54—57° (from ethyl acetate-petroleum) (authentic material produced during the synthesis of 3-isopropylpyridine).

(b) *With formic acid.* From the hydroperoxide (5 g) and formic acid (20 cm<sup>3</sup>) was obtained a product (4.15 g) consisting of the foregoing alcohol with some of its formate.

(c) *Pyrolysis.* From pyrolysis of the hydroperoxide (5 g) in ethanol (40 cm<sup>3</sup>) in a column at 400° was obtained a distillate (3.5 g), b.p. 98—144° at 15 mmHg, shown (i.r.) to contain 3-acetylpyridine (mainly) and the tertiary alcohol. It provided a semicarbazone, m.p. 202—204° (lit.,<sup>14</sup> 201°) (Found: C, 54.15; H, 5.8; N, 31.45. Calc. for C<sub>8</sub>H<sub>10</sub>N<sub>4</sub>O: C, 53.95; H, 5.65; N, 31.45%).

(d) *With sulphuric acid.* No reaction occurred on heating together the hydroperoxide (5 g) and 20% sulphuric acid (30 cm<sup>3</sup>); further additions of concentrated sulphuric acid (3 × 5 cm<sup>3</sup>) and heating (total 13.5 h) brought about complete decomposition of the peroxide. Normal work-up gave a product (2.8 g), shown (i.r.) to contain 3-acetylpyridine (mainly) and the tertiary alcohol.

*Autoxidation of 4-Isopropylpyridine.*—Autoxidation of the alkylpyridine (98.9 g) at 105—110° afforded 4-(1-hydroperoxy-1-methylethyl)pyridine (24.0 g), m.p. 145—148° (lit.,<sup>3</sup> 145—146°) (Found: C, 62.6; H, 7.0; N, 9.05%; peroxide equiv., 152.5) [*m/e* 153 (*M*), 137 (*M* - O), and 122 (*M* - O - CH<sub>3</sub>); τ 8.40 (Me), 1.46 (H-2 and -6), 2.58 (H-3 and -5), and -0.4 (O-OH)] and a solid (2.8 g), m.p. 110—115°, peroxide equiv., 249, found to be a mixture of the hydroperoxide and the corresponding alcohol.

<sup>14</sup> A. G. Pozdeeva and E. G. Novikov, *Zhur. priklad. Khim.*, 1966, **39**, 2669.

*Reactions of the Hydroperoxide.*—(a) *With sodium methoxide.* When treated in the same way as the isomeric compounds the hydroperoxide (6 g) provided 4-(1-hydroxy-1-methylethyl)pyridine (4.4 g), m.p. 137—140° (from benzene) (lit.,<sup>15</sup> 135.2—135.4°) (Found: C, 70.0; H, 8.15; N, 10.1%); τ 8.35 (Me), 1.54 (H-2 and -6), 2.60 (H-3 and -5), and 5.93 (OH).

(b) *With formic acid.* The hydroperoxide (6 g) afforded the corresponding alcohol (5.0 g).

(c) *Pyrolysis.* The hydroperoxide (6 g) in ethanol (50 cm<sup>3</sup>) pyrolysed at 400° gave a mixture of the corresponding tertiary alcohol and 4-acetylpyridine (mainly), and provided a semicarbazone, m.p. 216—218° (from aqueous ethanol) (lit.,<sup>16</sup> 218—219°) (Found: C, 53.85; H, 5.7; N, 31.65%) and a 2,4-dinitrophenylhydrazone, m.p. 262—264° (lit.,<sup>12</sup> 261—263°) (Found: C, 51.55; H, 3.65; N, 22.7%).

(d) *With sulphuric acid.* Prolonged heating with sulphuric acid (as before) gave a product found to contain both the tertiary alcohol and 4-acetylpyridine.

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<sup>15</sup> J. P. Wibaut and L. G. Heeringa, *Rec. Trav. chim.*, 1955, **74**, 1003.

<sup>16</sup> B. Emmert and A. Wolpert, *Ber.*, 1941, **74**, B, 1015.