(b) With $P_2O_5-H_3PO_4$.—Cytidine (199 mg.) was converted to its isopropylidene derivative (Table I) except that 50% less acetone (4 ml.) was used. Paper chromatographic analysis showed that conversion of the cytidine was complete after 3.5 hr. The solution was evaporated under reduced pressure; considerable frothing occurred in the final stages and prevented exhaustive removal of the volatile components. To the residual orange, gummy froth was added 2 ml. of $P_2O_5-85\%$ H_3PO_4 (1:1.3, w./w.). The mixture was stirred magnetically for 2 hr. in a bath at 60–62°, with exclusion of moisture. The gum became dark brown and much of it did not dissolve. Water (8 ml.) was added, and the mixture was heated for 30 minutes on a steam-bath, cooled and filtered from dark gummy solid. Inorganic phosphate was removed as lithium phosphate at pH 9 as described by Chambers, et al.[7] A portion (50 μl.) of the supernate (6.55 ml.) was subjected to paper electrophoresis in 0.05 M sodium tetraborate (pH 9.1) for 4 hr. at 18 volts/cm. together with appropriate reference compounds. Bands corresponding to cytidine 5'-phosphate, mixed cytidine 2'(3')-phosphates, p-nitrophenol and di-p-nitrophenyl phosphate migrated 30.8, 25.2, 22.9 and 16.0 cm., respectively, from the origin. Cytidine had the same

mobility as di-p-nitrophenyl phosphate and, if present, was not detectable. The band corresponding to cytidine 5'-phosphate was eluted with water (25 ml.); the solution showed an absorption maximum at 271 mμ (A = 0.96), minimum at 249–250 mμ, A_{250}/A_{260} 0.87, A_{280}/A_{260} 0.98; at pH 1, maximum at 280 mμ, minimum at 241 mμ, A_{250}/A_{260} 0.49, A_{280}/A_{260} 1.99. These values are closely similar to those recorded for this nucleotide.[32] The yield of cytidine 5'-phosphate was 45% (using $E_{max.}$ = 9.0 × 10³ at 271 mμ and pH 7). The electrophoretic band corresponding to the mixed 2' and 3'-isomers had similar spectral characteristics and the absorbancy corresponded to a yield of 8.1%.

(32) Pabst Laboratories, Pabst Brewing Co., Wisconsin, Circular OR-10, "Ultraviolet Absorption Spectra of 5'-Ribonucleotides" (1956); Ref. 18a, p. 531.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA, MINNEAPOLIS, MINN.]

The Autoöxidation of 2,3-Diethylindole to 2-Acetyl-3-ethylindole[1]

By Edward Leete

Exposure of 2,3-diethylindole to air yielded 2-acetyl-3-ethylindole. This oxidation apparently proceeds via 2,3-diethyl-3-hydroperoxyindolenine since this compound is converted to 2-acetyl-3-ethylindole under various reaction conditions. A plausible mechanism for this remarkable transformation is suggested.

When 2,3-diethylindole, which is a colorless crystalline solid melting at 29–30°,[2] was exposed to air and light for several days, it changed to a brownish-yellow viscous liquid. The infrared spectrum of this material had strong absorptions in the 1600 to 1700 cm.$^{-1}$ region indicating the presence of carbonyl groups. Chromatography of this material yielded a colorless crystalline solid melting at 117–118°, having strong absorptions in the infrared at 3330 and 1632 cm.$^{-1}$. The ultraviolet spectrum of this compound in ethanol was very similar to that of 2-acetyl-3-methylindole[3] having maxima at 212, 238 and 314 mμ. It thus seemed probable that this oxidation product of 2,3-diethylindole was 2-acetyl-3-ethylindole and this was confirmed by independent synthesis. The synthesis is analogous to that used by Oddo[4] for the preparation of 2-acetyl-3-methylindole. 3-Ethylindole was added to an ethereal solution of methylmagnesium iodide and the resultant 3-ethylindolylmagnesium iodide treated with acetyl chloride to yield a mixture of 1- and 2-acetyl-3-ethylindole which was readily separated by chromatography.

The formation of 2-acetyl-3-ethylindole from 2,3-diethylindole by atmospheric oxidation is unusual. The only other example of an analogous reaction which has been found in the literature is the autoöxidation of heptahydrocyclooct[b]indole (I) to the ketone II.[5] This was also a very facile

oxidation, occurring in a variety of solvents and in the solid state. However, the normal initial prod-

I   II
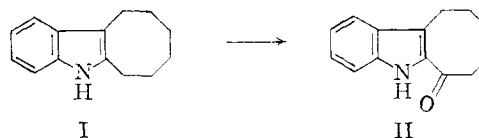
uct of atmospheric oxidation of a 2,3-disubstituted indole is a 3-hydroperoxyindolenine.[5–8] In general these oxidations have been carried out in petroleum ether or ethyl acetate. A solution of 2,3-diethylindole in petroleum ether was thus exposed to air and after 24 hours an almost quantitative yield of 2,3-diethyl-3-hydroperoxyindolenine (III) had separated from the solution. The structure of this product was deduced from its properties, which were analogous to those of 2,3-dimethyl-3-hydroperoxyindolenine.[7] The two compounds had very similar ultraviolet spectra and on reduction the indolenine III yielded 2,3-diethyl-3-hydroxyindolenine (IV). On boiling the indolenine III with water it rearranged to o-propionaminopropiophenone (VII). Under similar conditions 2,3-dimethyl-3-hydroperoxyindolenine yields o-acetaminoacetophenone.[7] The propiophenone derivative VII was also obtained in very small yield when a solution of the indolenine III in ethyl acetate was

(1) The investigation was supported by a research grant CY-5336 from the National Institutes of Health, Public Health Service.

(2) E. Leete, Tetrahedron, in press.

(3) J. A. Ballantine, C. B. Barrett, R. J. S. Beer, B. G. Boggiano, S. Eardley, B. E. Jennings and A. Robertson, J. Chem. Soc., 2227 (1957).

(4) B. Oddo, Gass. chim. ital., 43, II, 190 (1913).

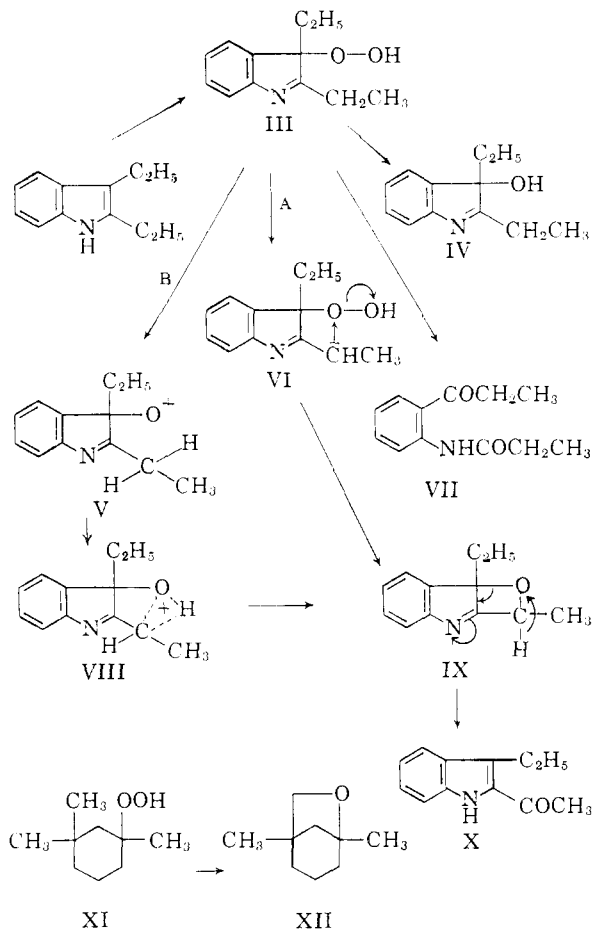(5) B. Witkop, J. B. Patrick and M. Rosenblum, J. Am. Chem. Soc., 73, 2641 (1951).

(6) R. J. S. Beer, L. McGrath and A. Robertson, J. Chem Soc., 2118, 3283 (1950).

(7) R. J. S. Beer, T. Donoavanik and A. Robertson, ibid., 4139 (1954).

(8) B. Witkop and J. B. Patrick, J. Am. Chem. Soc., 73, 2188 (1951); 74, 3855 (1952).

evaporated on a steam-bath and the residue heated at 100° for 30 minutes. The main product from this reaction was 2-acetyl-3-ethylindole (52% yield). It therefore seems reasonable to assume that the formation of this ketone by the autoöxidation of 2,3-diethylindole proceeds via the indolenine III.

Plausible mechanisms for the formation of 2-acetyl-3-ethylindole from the hydroperoxide III are illustrated in Fig. 1. Loss of a proton from the methylene group alpha to the imine yields the resonance-stabilized carbanion VI (mechanism A), which attacks the neighboring hydroperoxy group, eliminating hydroxide and yielding the intermediate IX. This intermediate then undergoes a plausible prototropic shift, as illustrated, affording 2-acetyl-3-ethylindole (X). Alternatively heterolytic fission of the hydroperoxy group of III yields compound V containing cationic oxygen which attacks a C–H bond of the ethyl group at the 2-position leading to the non-classical ion VIII. Expulsion of a proton from this ion then yields the intermediate IX. This second route (mechanism B) to IX is

liquid ammonia containing sodamide, the starting material being recovered unchanged. The main product obtained when a solution of the indolenine in pyridine was treated with a small amount of methanolic potassium hydroxide was o-propionaminopropiophenone. No identifiable compounds were isolated when the indolenine was added to a solution of potassium hydroxide in ethanol. On the other hand, acidic solvents led to the formation of 2-acetyl-3-ethylindole, thus favoring mechanism B. A 44% yield of this ketone was obtained when a solution of the hydroperoxide in glacial acetic was kept at 20° for 16 hours. The best yield (60%) of the ketone was obtained when the hydroperoxide was dissolved in ethyl acetate which contained 10% acetic acid and the mixture maintained at room temperature for 16 hours.

The scope of this unusual rearrangement of a 3-hydroperoxyindolenine is being examined. The ketone II may be also formed from the indole I via the corresponding 3-hydroperoxyindolenine. It is also tempting to speculate that tabernaemontanine,[10] dregamine,[10] vocacafrine[11] and vobasine,[12] which are 2-acylindole alkaloids, are produced by an analogous in vivo oxidation of 2,3-disubstituted indoles. Exposure of 2,3-dimethyl-3-hydroperoxyindolenine to the same experimental conditions which afforded 2-acetyl-3-ethylindole from III has so far failed to yield any 3-methylindole-2-aldehyde. The only crystalline product obtained was o-acetaminoacetophenone.

similar to one which Corey[9] suggested for the formation of the cyclic ether XII from the hydroperoxide XI. If the rearrangement proceeded according to mechanism A, one would expect the reaction to be based catalyzed. However no reaction occurred when the indolenine III was dissolved in

(9) E. J. Corey and R. W. White, J. Am. Chem. Soc., 80, 6686 (1958).

Experimental[13]

2,3-Diethyl-3-hydroperoxyindolenine (III).—2,3-Diethylindole[2] (1.0 g.) was dissolved in petroleum ether (b.p. 60–70°, 100 ml.) and the solution exposed to air in a 250-ml. beaker for 24 hr. The crude product which separated (1.09 g.) was crystallized from a mixture of ethyl acetate and petroleum ether to yield colorless prisms of 2,3-diethyl-3-hydroperoxyindolenine (0.82 g.), m.p. 127–128° with only slight darkening; $\lambda_{max}^{95\% \ EtOH}$ 220 (log ε 4.29), 260 (log ε 3.57) with inflections at 215 and 225 mμ.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.84; H, 7.44; N, 6.69.

2,3-Dimethyl-3-hydroperoxyindolenine prepared as previously described[7] had $\lambda_{max}^{95\% \ EtOH}$ 213 (log ε 4.26), 218 (log ε 4.29), 249 (log ε 3.56) with an inflection at 224 mμ.

2,3-Diethyl-3-hydroxyindolenine (IV).—The indolenine III (0.4 g.) was shaken with 10% sodium hydroxide solution (10 ml.) containing sodium hydrosulfite (1.0 g.) and ether (20 ml.) for 1 hr. Evaporation of the dried ether layer yielded a pale yellow solid (0.3 g.). Crystallization from a mixture of ethyl acetate and petroleum ether yielded colorless needles of 2,3-diethyl-3-hydroxyindolenine, m.p. 112–113°; $\lambda_{max}^{95\% \ EtOH}$ 215 (log ε 4.22), 220 (log ε 4.27), 258 (log ε 3.49) with an inflection at 225 mμ.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.90; H, 8.16; N, 7.46.

o-Propionaminopropiophenone (VII).—The indolenine III (0.3 g.) was refluxed with water (50 ml.) for 20 min. The cooled solution was extracted with ether and the dried ether extract evaporated. The brownish-yellow residue was chromatographed on alumina, eluting with benzene. Evaporation of the first fractions yielded a low melting solid which was distilled in vacuo (160° (0.01 mm.)). The solidified

(10) M. Gorman, N. Neuss, N. J. Cone and J. A. Deyrup, ibid., 82, 1142 (1960).

(11) K. V. Rao, J. Org. Chem., 23, 1455 (1958).

(12) U. Renner, Experientia, 15, 185 (1959).

(13) Melting points are corrected. Microanalyses were performed by Mrs. Olga Hamerston and her assistants at the University of Minnesota. All chromatography was carried out on neutral Woelm alumina, activity III.

distillate was crystallized from petroleum ether to yield pale yellow needles of o-propionaminopropiophenone, m.p. 44–45°; $\lambda_{max}^{95\% EtOH}$ 230 (log ε 4.37), 234 (log ε 4.37), 259 (log ε 4.02), 266 (log ε 3.94) and 324 mμ (log ε 3.61). The infrared spectrum in a KBr pellet had an NH absorption at 3120 cm.$^{-1}$ and carbonyl absorptions at 1682 (ketone) and 1650 cm.$^{-1}$ (amide).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.43; H, 7.40; N, 6.74.

2-Acetyl-3-ethylindole. (a) From 2,3-Diethyl-3-hydroperoxyindolenine.—(1) The indolenine III (0.5 g.) was dissolved in ethyl acetate (20 ml.) and evaporated to dryness on a steam-bath. The yellow residue was heated on the steam-bath for a further 30 min. The light brown viscous residue, which showed strong absorptions in the 1600–1700 cm.$^{-1}$ region of the infrared spectrum, was dissolved in benzene and chromatographed on alumina, eluting with benzene. A small amount of crystalline material (15 mg.) was obtained from the first fractions and was identical with o-propionaminopropiophenone (infrared and ultraviolet spectra). Later fractions yielded 2-acetyl-3-ethylindole (0.24 g.) which was obtained as colorless needles from petroleum ether, m.p. 117–118°; $\lambda_{max}^{95\% EtOH}$ 212 (log ε 4.26), 238 (log ε 4.20), 314 (log ε 4.30). The infrared spectrum in a KBr pellet had an NH absorption at 3330 cm.$^{-1}$ and a carbonyl absorption at 1632 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48. Found: C, 77.17; H, 7.17; N, 7.41.

Continued elution of the column with benzene containing 1% methanol yielded viscous oils of unknown composition.

(2) The indolenine III (410 mg.) was dissolved in ethyl acetate (20 ml.), acetic acid (2 ml.) added, and the mixture allowed to stand at room temperature for 16 hr. During this time the solution became light brown. The solution was then evaporated *in vacuo* and the residue dissolved in benzene and chromatographed on alumina yielding 2-acetyl-3-ethylindole (0.22 g.). When the indolenine III was dissolved in acetic acid a pale yellow solution was obtained which became dark brown after 16 hr. Chromatography of the residue obtained after evaporation afforded a 44% yield of the ketone X.

(b) From 2,3-Diethylindole.—2,3-Diethylindole (1.0 g.) was exposed to air for several days. The brownish-yellow resinous mass was dissolved in benzene and chromatographed on alumina, eluting with benzene. The first fractions yielded

unchanged 2,3-diethylindole. Later fractions yielded crystalline 2-acetyl-3-ethylindole (yield varied from 0.1 to 0.3 g. in different experiments). In another experiment a freshly distilled, chromatographically pure sample of 2,3-diethylindole (1.0 g.) was exposed to the ultraviolet and visible light generated by a 125 watt Hanovia UV lamp. After 3 hr. the infrared spectrum of the reaction mixture indicated the presence of carbonyl compounds. After 6 hr. the yellow resinous material was chromatographed on alumina as before, yielding unchanged 2,3-diethylindole (0.17 g.) and 2-acetyl-3-ethylindole (0.22 g.).

(c) From 3-Ethylindole.—3-Ethylindole[14] (4.0 g.) dissolved in ether (10 ml.) was added with stirring to a cooled solution of methylmagnesium iodide (prepared from methyl iodide (2 ml.) and magnesium (0.67 g.)) in ether (40 ml.). After 10 min. freshly distilled acetyl chloride (2 ml.) in ether (10 ml.) was added to this solution which was cooled to 0°. The yellow mixture was stirred for 2 hr. at room temperature and then water was added and the ether layer separated. The dried ether layer was evaporated and the residue chromatographed on alumina, eluting with a 1:1 mixture of benzene and petroleum ether. The first fractions were unchanged 3-ethylindole, then a series of liquid fractions which were apparently impure 1-acetyl-3-ethylindole. Final fractions yielded 2-acetyl-3-ethylindole (1.2 g.) identical (mixed m.p., infrared and ultraviolet spectra) with material obtained by the autoöxidation of 2,3-diethylindole and by the action of heat on 2,3-diethyl-3-hydroperoxindolenine.

Action of Heat on 2,3-Dimethyl-3-hydroperoxyindolenine.—2,3-Dimethyl-3-hydroperoxyindolenine[7] (0.44 g.) was dissolved in ethyl acetate (20 ml.) and heated on the steam-bath for 15 min. The yellow residue was chromatographed on alumina yielding o-acetaminoacetophenone (0.17 g.) as fine pale yellow needles (from petroleum ether), m.p. 76–77° (lit.[7] 77–78°); $\lambda_{max}^{95\% EtOH}$ 230 (log ε 4.42), 235 (log ε 4.42), 258 (log ε 4.04), 265 (log ε 3.97) and 324 mμ (log 3.64).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.85; H, 6.48; N, 7.77.

No identifiable materials were obtained when the hydroperoxide was dissolved in acetic acid and maintained at room temperature for 24 hr. except o-acetaminoacetophenone. A similar result was observed when the hydroperoxide was added to a mixture of ethyl acetate and acetic acid.

(14) E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953).

Kinetic Study of the Pyrolysis of 1,2-Diarylethyl Acetates. IV[1,2]

BY GRANT GILL SMITH, FRANK D. BAGLEY[3a] AND ROGER TAYLOR[3b]

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A kinetic study of the thermal decomposition of eleven *meta* and *para* substituted 1,2-diphenylethyl acetates has been made; the energies and entropies of activation range from 40.6 to 43.8 kcal./mole and −0.215 to −2.54 e.u., respectively. The esters (both solids and liquids) were each pyrolyzed over a temperature range of 50° in a static system at reactant pressure of 15 to 150 mm. by use of a specially designed apparatus. The importance of the breaking of the carbon–hydrogen and carbon–oxygen single bonds and the formation of olefinic bond to the stability of the ester has been evaluated. Esters with strongly electron-releasing groups (*e.g.*, 4-OCH₃) in the 1-phenyl ring were very sensitive to surface reactions and could only be studied satisfactorily in the presence of an inhibitor.

Although much has been published recently about the pyrolysis of esters, no previous kinetic study

has been reported of the effect of substituents on the absolute reaction rate of pyrolysis of esters except for a study of the deuterium isotope effect.[4] The thermal decomposition of esters with β-hydrogens lends itself to kinetic studies, since the reaction follows definite stoichiometry and side reactions are few. Rate studies have shown the reaction to follow first-order kinetics; it is unimolecular, homogeneous and generally has a negative entropy of activation.[5] In comparative rate studies the sta-

(4) D. Y. Curtin and D. B. Kellom, *J. Am. Chem. Soc.*, **75**, 6011 (1953).

(5) (a) G. L. O'Conner and H. R. Nace, *ibid.*, **75**, 2118 (1953); (b)