[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE, REHOVOTH, ISRAEL]

Reactions of Active Methylene Compounds in Pyridine Solution. V. α-Hydroperoxyesters[1]

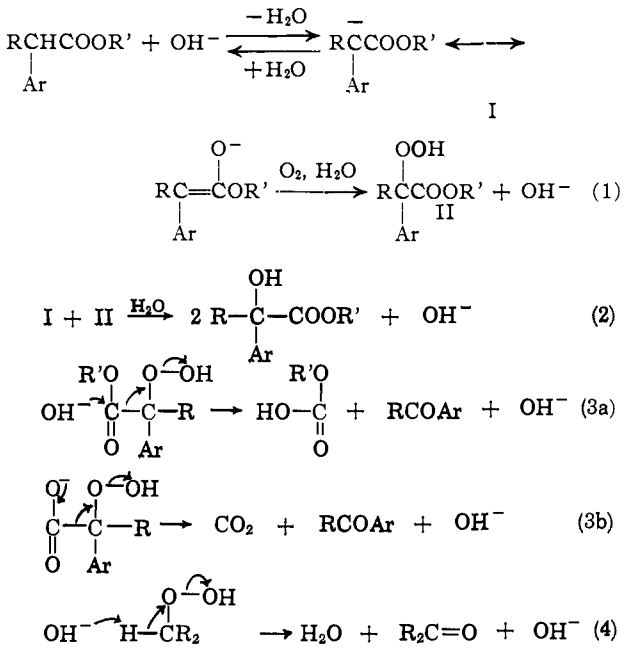
BY M. AVRAMOFF AND Y. SPRINZAK

RECEIVED DECEMBER 17, 1962

Base-catalyzed autoxidation of esters of diarylacetic acids and 2,3-diarylpropionic acids affords α-hydroperoxyesters, a novel type of hydroperoxides, along with α-hydroxyesters and ketones. The formation of the latter two types of compounds is explained in terms of reduction and decomposition of the hydroperoxyesters.

The high reactivity of compounds of the cyclopentadiene series in pyridine solution under alkaline conditions, as shown in autoxidation and condensation reactions,[2] has led us to study the behavior of other active methylene compounds, including nitriles and esters. In the present paper we report on the autoxidation of esters of diarylacetic acids and 2,3-diarylpropionic acids.

Pyridine solutions of these esters turn yellow on treatment with benzyltrimethylammonium hydroxide (Triton B), the color presumably being due to the presence of ambident ester anions (eq. 1). The alkaline solutions absorb oxygen readily, giving three types of oxidation products, namely, α-hydroperoxyesters,[3] α-hydroxyesters (extensively hydrolyzed to the corresponding acids) and ketones.



The formation of the first two types (eq. 1 and 2) is similar to that of hydroperoxides and carbinols from 9-alkylfluorenes under identical conditions.[2a] The occurrence of reaction 2 was confirmed by an experiment in which equivalent quantities of methyl diphenylacetate and methyl diphenylhydroperoxyacetate (Ar = R = C_6H_5; R′ = CH_3) were treated with Triton B in pyridine in the absence of oxygen. Ketone formation (eq. 3) was established by the isolation of benzophenone from autoxidations of methyl diphenylacetate (Ar = R = C_6H_5, R′ = CH_3) and was most readily demonstrated by an experiment in which the hydroperoxyester alone was submitted to the action of the base. The presence of carbonate as a reaction product was also established. A similar decomposition experiment with methyl 2-hydroperoxy-2,3-diphenylpropionate (Ar = C_6H_5, R = $C_6H_5CH_2$, R′ = CH_3) afforded desoxybenzoin, along with a considerable quantity of 2,3-diphenyllactic acid and benzoic acid. The lactic acid must have arisen, in a secondary reaction, from reduction of the hydroperoxide by part of the ketone, which in turn is converted to benzoic acid. The easy formation of benzoic acid from desoxybenzoin in alkaline pyridine solution, shown by independent experiments in which the ketone was oxidized by oxygen[4] or by a hydroperoxide, also accounts for the failure to isolate this ketone in the autoxidation of methyl 2,3-diphenylpropionate.

Reaction 3 bears some resemblance to the well known base-catalyzed dehydration of primary and secondary hydroperoxides[5] (eq. 4). Whether the reaction involves directly the ester (eq. 3a) or an intermediate acid produced by its hydrolysis (eq. 3b) cannot be decided on the basis of available data. In the former case, the reaction may be visualized as an elimination of alkyl hydrogen carbonate induced by hydroxide ions, while in the latter it may be described as an eliminative decarboxylation. The mechanism of reaction 3a may also operate in the decomposition of the hydroperoxyketones postulated as intermediates in the autoxidation of certain ketones in the presence of potassium *t*-butoxide.[4]

Most autoxidation experiments (Table I) were performed at lower temperatures with a view to obtaining hydroperoxyesters, which are readily isolated by crystallization.[6] The reaction was stopped after several hours when oxygen absorption became slow, the total quantity absorbed ordinarily amounting to 0.7 mole per mole of ester. Triton B was continuously added to the stirred mixture, to replenish the amount consumed by hydrolysis of part of the esters and by the carbonic acid formed by decomposition of part of the hydroperoxyester.

At room temperature, methyl diphenylacetate was converted to benzilic acid and its ester, with benzophenone as a by-product. Similarly, methyl 2,3-diphenylpropionate afforded 2,3-diphenyllactic acid and its ester, along with benzoic acid. No hydroperoxyesters could be detected in the reaction mixtures.

The presence of an α-aryl group appears to be a prerequisite for the formation of hydroperoxyesters. Thus ethyl isobutyrate failed to react under the conditions of the present autoxidation. While the propionic esters used invariably contained a β-aryl group, an oxidation performed with methyl 2-phenylbutyrate indicated that its presence is not necessary, although the hydroperoxyester could not be isolated in the pure state.

(1) For part IV, see M. Avramoff and Y. Sprinzak, *J. Org. Chem.*, **26**, 1284 (1961). For a preliminary account of the present work, see M. Avramoff and Y. Sprinzak, *Proc. Chem. Soc.*, 150 (1962).

(2) (a) Y. Sprinzak, *J. Am. Chem. Soc.*, **80**, 5449 (1958); (b) E. Ghera and Y. Sprinzak, *ibid.*, **82**, 4945 (1960).

(3) A recent publication reports the preparation of α-hydroperoxyesters and α-hydroperoxyketones by autoxidation of esters and ketones in the presence of potassium *t*-butoxide suspended in an aprotic solvent. Remarkably a secondary hydroperoxide could be isolated from the autoxidation of *t*-butyl phenylacetate at −75° [H. R. Gersmann, H. J. W. Nieuwenhuis and A. F. Bickel, *Proc. Chem. Soc.*, 279 (1962)].

(4) *Cf.* W. von E. Doering and R. M. Haines, *J. Am. Chem. Soc.*, **76**, 482 (1954).

(5) M. Kornblum and H. E. De La Mare, *ibid.*, **73**, 880 (1951); A. G. Davies, "Organic Peroxides," Butterworths, London, 1961, pp. 183–186.

(6) Attempts to isolate the hydroperoxyesters as their sodium salts [J. D'Ans and H. Gould, *Chem. Ber.*, **92**, 2559 (1959)] or as the 1-methyl-6,8-dinitro-2-ethoxy-1,2-dihydroquinoline complex [A. Rieche, E. Schmitz, and P. Dietrich, *ibid.*, **92**, 2239 (1959)] were unsuccessful.

TABLE I

OXIDATION OF ESTERS TO α-HYDROPEROXYESTERS[a]

Expt. No.	Ester	O_2 absorbed		Hydroperoxyester			Oxygen, %[c]		Hydroxyester[b]			Carbon, %		Hydrogen, %	
		mmoles	Time, hr.	mmoles	Yield, %	M.p., °C.[d]	Formula	Calcd.	Found	M.p., °C.[d,e]	Formula	Calcd.	Found	Calcd.	Found
I	$(C_6H_5)_2CHCO_2CH_3$	10	3	6.7	31	69.5–70.5	$C_{15}H_{14}O_4$	6.2	6.1	72–73[f]	$C_{15}H_{14}O_3$	74.36	74.15	5.83	5.70
II	$(p\text{-}CH_3C_6H_4)_2CHCO_2C_2H_5$[g]	3	1.5	2.2	41	69–71[h]	$C_{18}H_{20}O_4$	5.3	5.5	66–67[i]	$C_{18}H_{20}O_3$	76.03	75.93	7.09	6.86
III	$C_6H_5CH_2CH(C_6H_5)CO_2CH_3$[j]	10	1	7.1	24	108.5–109.5[k]	$C_{16}H_{16}O_4$	5.9	5.7	88–89	$C_{16}H_{16}O_3$	74.98	75.06	6.29	6.09
IV	$p\text{-}ClC_6H_4CH_2CH(C_6H_5)CO_2CH_3$[l]	10	4	7.1	46	94–96	$C_{16}H_{15}ClO_4$	5.2	4.8	70–72	$C_{16}H_{15}ClO_3$	66.26	66.52	5.21	5.31
V	$p\text{-}CH_3OC_6H_4CH_2CH(C_6H_5)CO_2CH_3$[m]	5	5	4.5	45	90–91[n]	$C_{17}H_{18}O_5$	5.3	5.2	83.5	$C_{17}H_{18}O_4$	71.31	71.40	6.34	6.38
VI	$p\text{-}CH_3OC_6H_4CH_2CH(C_6H_5)CO_2C_2H_5$[o]	5	6	4.4	40	73.5–75	$C_{18}H_{20}O_5$	5.1	5.1	62–64	$C_{18}H_{20}O_4$	71.98	72.20	6.71	6.54

[a] Five ml. of pyridine was used per mmole of ester; all oxidations were performed at −18°, except expt. III, which was performed at 0°. [b] Obtained by reduction of the hydroperoxyesters with potassium iodide in acetic acid. [c] Reference 10. [d] Corr. [e] Recrystallized from petroleum ether. [f] Reported m.p. 73° [S. F. Acree, *Ber.*, **37**, 2764 (1904)]. [g] W. Voegtli and P. Länger, *Helv. Chim. Acta*, **38**, 46 (1955). [h] In one experiment the melting point was 113°; the lower melting form could be transformed into the higher melting one by seeding. [i] Previously described as an oil (ref. *g*). [j] A. Meyer, *Ber.*, **21**, 1313 (1888). [k] Infrared absorption (KBr pellet) at 2.8 and 11.75 μ (*cf.* L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Second Ed., J. Wiley and Sons, Inc., New York, N. Y., 1958, pp. 120, 122). [l] M.p. 58–59° (from alcohol). *Anal.* Calcd. for $C_{16}H_{15}ClO_2$: C, 69.82; H, 5.50. Found: C, 70.13; H, 5.46. [m] M.p. 61–63°; reported 59–60° [F. Faltis, S. Wrann and E. Kiihas, *Ann.*, **497**, 69 (1962)]. [n] From benzene–heptane (1:3). [o] B. H. Alexander and W. F. Barthel, *J. Org. Chem.*, **23**, 389 (1958).

Experimental[7]

Materials.—Pyridine was dried and a 40% solution of Triton B was prepared as described previously.[2a] All the substituted propionic acids were prepared from the appropriate acrylonitriles.[8]

Apparatus and Procedure.—The autoxidation experiments were carried out as described previously.[2a] Triton B was continuously added to the reaction mixture to maintain oxygen absorption, the total amount required varying between one-half to one mole per mole of ester. The reaction product was poured into an excess of ice–hydrochloric acid mixture and extracted with ether. The ethereal extract was washed with water, extracted with a 10% sodium carbonate solution, dried over sodium sulfate and evaporated at room temperature. The hydroperoxides were isolated by crystallizing the residue from petroleum ether. In one instance, a duplicate of expt. I, the residue (1.98 g.), containing 43% of hydroperoxyester as determined by titration, was chromatographed on deactivated silica[9] to give 0.47 g. of starting material (eluted with a 1:3 benzene–petroleum ether mixture), 0.72 g. of hydroperoxyester (1:1 benzene–petroleum ether) and 0.24 g. of methyl benzilate (eluted with benzene).

Active oxygen was determined iodometrically by the procedure of Wibaut, van Leeuwen and van der Wal,[10] using a 0.1 *N* solution of sodium thiosulfate.

Room Temperature Oxidation. (a) **Methyl Diphenylacetate.**—A solution of the ester (10 mmoles) in pyridine (50 ml.) absorbed 7.1 mmoles of oxygen in 1 hr., the Triton B added during the reaction amounting to 12 mmoles. Acidification of the carbonate extract, obtained according to the general procedure, precipitated 0.95 g. (42%) of benzilic acid. Chromatography of the neutral fraction afforded 0.47 g. (26%) of benzophenone (1:3 benzene–petroleum ether) and 0.13 g. (5%) of methyl benzilate (benzene).

(b) **Methyl 2,3-Diphenylpropionate.**—A solution of the ester (10 mmoles) in pyridine (50 ml.) absorbed 7.5 mmoles of oxygen during 3 hr., the Triton B required amounting to 13 mmoles. Acidification of the carbonate extract precipitated 0.95 g. (39%) of 2,3-diphenyllactic acid.[11] Extraction of the mother liquor with ether gave, after recrystallization from water, 0.22 g. of benzoic acid (corresponding to 1.0 mmole of desoxybenzoin). The neutral fraction, crystallized from petroleum ether, afforded 0.32 g. (13%) of methyl 2,3-diphenyllactate. Chromatography of the concentrated mother liquor afforded 0.81 g. (34%) of starting material.

Decomposition of Hydroperoxyesters. (a) **Methyl Diphenylhydroperoxyacetate.**—A solution of the hydroperoxyester (2.58 g., 10 mmoles) in pyridine (20 ml.) was treated at 0° with an excess (15 mmoles) of Triton B, left at room temperature until complete disappearance of peroxide reaction (24 hrs.), cooled again and acidified with 15 ml. of 50% acetic acid. The gases liberated were swept by nitrogen into a mixture of 5 ml. of 10% sodium hydroxide, 30 ml. of 10% barium chloride and 100 ml. of water containing phenolphthalein. A fine crystalline precipitate of barium carbonate formed immediately. The carbon dioxide absorbed, determined volumetrically,[12] amounted to 5.6 mmoles. Acidification of the carbonate extract, obtained by the general procedure, afforded 0.29 g. (13%) of benzilic acid,[13] while chromatography of the neutral fraction gave 1.28 g. (71%) of benzophenone and 0.05 g. (2%) of methyl benzilate.

(b) **Methyl 2-Hydroperoxy-2,3-diphenylpropionate.**—A solution of the hydroperoxyester (1.09 g., 4.0 mmoles) in pyridine was treated at 0° under nitrogen with an excess of Triton B (6 mmoles) and left at room temperature for 2 hr. to complete destruction of the peroxide. From the neutral fraction desoxybenzoin was isolated as its 2,4-dinitrophenylhydrazone (0.19 g., 13%). Acidification of the carbonate extract precipitated

(7) Melting points are corrected. Chromatographies were carried out with Merck "acid-washed" alumina. Carbon and hydrogen determinations were carried out in our microanalytical department. The identity of all known compounds isolated was checked by mixture melting point determinations.

(8) M. Avramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, **80**, 493 (1958).

(9) C. Djerassi and J. Staunton, *ibid.*, **83**, 736 (1961), footnote 33.

(10) J. P. Wibaut, H. B. van Leeuwen and B. van der Wal, *Rec. trav. chim.*, **73**, 1033 (1954).

(11) O. Widman, *Ber.*, **49**, 477 (1916). Prepared by the general method of E. Rohrmann, R. G. Jones and H. A. Schonle, *J. Am. Chem. Soc.*, **66**, 1856 (1944).

(12) C. L. Wilson and D. W. Wilson, "Comprehensive Analytical Chemistry," Vol. 1c, Elsevier Publishing Co., Amsterdam, 1962, p. 147.

(13) The formation of benzilic acid in this experiment was unexpected. A possible reduction of the hydroperoxyester by the solvent to form pyridine 1-oxide was considered, but was ruled out by our inability to detect the oxide in the reaction mixture. It was also checked that added pyridine 1-oxide is not destroyed under the reaction conditions. Moreover, since it was ascertained that oxygen was not liberated in the reaction, this known mode of decomposition of tertiary hydroperoxides [M. S. Kharasch, A. Fono, W. Nudenberg and B. Bischof, *J. Org. Chem.*, **17**, 207 (1952)] was also eliminated.

0.62 g. (64%) of 2,3-diphenyllactic acid, while 0.12 g. of benzoic acid [1 mmole, corresponding to 0.5 mmole (12%) of desoxybenzoin] was obtained by ether extraction of the mother liquor.

Oxidation of Methyl Diphenylacetate by its Hydroperoxide.—A mixture of methyl diphenylacetate and methyl diphenylhydroperoxyacetate (5 mmoles of each) in pyridine (50 ml.) was treated with Triton B (10 mmoles) under nitrogen and left at room temperature for 2 hr. The peroxide-free mixture was worked up according to the general procedure. From the neutral fraction benzophenone (0.43 g., 2.4 mmoles) was isolated by means of Girard reagent. The non-ketonic residue was chromatographed to give methyl diphenylacetate (0.60 g., 2.7 mmoles; eluted with petroleum ether) and methyl benzilate (0.31 g., 1.3 mmoles; eluted with a 1:1 benzene–petroleum ether mixture). The carbonate fraction afforded upon acidification benzilic acid (0.75 g., 3.3 mmoles).

Oxidation of Methyl α-Phenylbutyrate.[14]—The ester (10 mmoles), autoxidized at −18°, absorbed 4.2 mmoles of oxygen during 3.5 hr. The neutral fraction contained 26% of the hydroperoxyester, as determined by titration. Oxidation at 0° afforded phenylethylglycolic acid, isolated from the carbonate extract in 15% yield, m.p. 130–131.5°; recorded[15] 131.5°. The neutral fraction contained 13% of hydroperoxyester.

Oxidation of Desoxybenzoin. (a) **By Oxygen.**—A solution of desoxybenzoin (1.96 g., 10 mmoles) in pyridine (20 ml.) absorbed at room temperature 14.2 mmoles of oxygen in 2 hr., the Triton added amounting to 22 mmoles. A 67% yield of benzoic acid was obtained.

(b) **By 9-Hydroperoxy-9-phenylfluorene.**[2a]—A solution of desoxybenzoin (0.65 g., 3.3 mmoles) in pyridine (5 ml.), kept under nitrogen at 0°, was treated with Triton B (10 mmoles), and a solution of the hydroperoxide (10 mmoles) in pyridine (15 ml.) was added to the mixture during 5 min. After standing at room temperature for 4 hr., the peroxide-free mixture was worked up according to the general procedure. Extraction with ether of the acidified carbonate fraction afforded 0.71 g. of recrystallized benzoic acid [5.8 mmoles, corresponding to 2.9 mmoles of desoxybenzoin (88%)]. The neutral fraction gave upon recrystallization from benzene–heptane 2.39 g. (94%) of 9-phenylfluorenol.[2a]

Acknowledgment.—The authors are indebted to Mr. Abraham Deshe for his capable assistance in carrying out the oxidation experiments.

(14) K. Neuve, *Ann.*, **250**, 140 (1889).
(15) L. Smith, *J. prakt. Chem.*, [2] **84**, 744 (1911).

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, HARVARD MEDICAL SCHOOL, BOSTON 15, MASS.]

Proton Magnetic Resonance Studies of Purine and Pyrimidine Derivatives. IX. The Protonation of Pyrimidines in Acid Solution

BY OLEG JARDETZKY, PETER PAPPAS AND NORMA G. WADE

RECEIVED SEPTEMBER 25, 1962

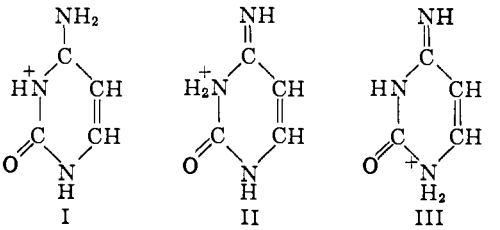
Proton magnetic spectra of the nitrogen-bound protons of a series of pyrimidines in acid solution have been observed. The area under the peak assigned to the amino group corresponds to two protons even in the most acid solutions, and separate peaks are found for protons attached to ring nitrogens. The observations support the view that the order of basicity in pyrimidines is N ring > N amino > oxygen.

Introduction

In an earlier communication[1] the suggestion has been made that the protons added to aminopurines and aminopyrimidines in acid solutions are attached to ring nitrogens, rather than to the amino groups. This inference was drawn from the relative magnitude of the chemical shifts in the nuclear magnetic resonance (n.m.r.) spectra of the pyrimidine and imidazole protons on carbon atoms adjacent to the ring nitrogens. It was therefore subject to some uncertainty, despite the fact that it was consistent with similar suggestions based on other evidence.[2-5] Less equivocal evidence for the site of protonation is provided by the n.m.r. spectra of the nitrogen-bound protons. Such spectra are not observable in aqueous solutions because of the rapid exchange of the protons with the solvent. However, in nearly anhydrous trifluoroacetic acid (TFA) the exchange can be slowed down sufficiently to allow the observation of some of the peaks. The data obtained support the view that the order of basicity in these compounds is N ring > N amino > oxygen.

Results and Discussion

A typical pyrimidine spectrum, that of cytosine in TFA, is shown in Fig. 1. In addition to the two doublets arising from the C_5- and C_4-protons at +0.45 and −0.72 p.p.m. with respect to benzene (as an external reference standard), there are three peaks at approximately −1.1, −2.9 and −3.4 p.p.m., respectively, with the solvent peak appearing at −3.9 p.p.m. The relative areas of the five peaks are approximately 1:1:2:1:1 (the width of the peaks at low fields precludes a very accurate integration, but differences in area equivalent to a single hydrogen would nevertheless have been detected). The spectrum is thus clearly inconsistent with tautomeric structures: 1, containing a tetrahedral ammonium group and a single proton in one of the other three possible positions (1, 2 or 3) (expected spectrum: two peaks, with a ratio of areas 3:1); 2, containing one proton in each of the positions 1, 2, 3 and 6 (expected spectrum: four peaks, ratio of areas 1:1:1:1), or 3, containing an amino group and two protons in one of the positions (1, 2 or 3) (expected spectrum: two peaks, ratio of areas 1:1). The broadening and the selective shift of the C_4-proton strongly suggests the protonation of N_3. If the added proton were located on the oxygen, its exchange would not affect the line width of the C_4-proton from which it is separated by five bonds, just as the exchange of the amino hydrogens does not affect the line width of the C_5-proton. The fact that three separate absorption lines can be observed also makes extremely unlikely (although does not rigorously rule out) the possibility that one or more of the protons are predominantly located on the oxygen atom: a separate resonance attributable to a hydroxyl proton is generally not observed in acid solution. Thus, the spectrum is consistent with one of the following three among the sixteen possible tautomeric structures (neglecting dipolar and nitrile forms)



I II III

The magnitude of the observed shifts allows us to favor structure I for the following reason: Taken by itself

(1) C. D. Jardetzky and O. Jardetzky, *J. Am. Chem. Soc.*, **82**, 222 (1960).
(2) T. Nakajima and B. Pullman, *Bull. soc. chim. France*, **25**, 1502 (1958).
(3) T. Nakajima and B. Pullman, *J. Am. Chem. Soc.*, **81**, 3876 (1959).
(4) G. Zubay, *Biochim. Biophys. Acta*, **28**, 644 (1958).
(5) H. T. Miles, *Proc. Natl. Acad. Sci. U.S.*, **47**, 791 (1961).