Oxidation of Aryl Trityl Sulfides with Hydrogen Peroxide

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Recent attempts to characterize aryl trityl sulfides by preparation of sulfoxides and sulfones by means of oxidations in acidic media have been unsuccessful.[1,2] Apparently the sulfides were cleaved in the acidic media because partial oxidations produced significant amounts of the diaryl disulfides and triphenylcarbinol. Complete oxidations produced the arylsulfonic acids, or derivatives of these, and triphenylcarbinol.

Knoll[3] observed no reaction during an unsuccessful attempt to prepare phenyl trityl sulfone by oxidation of phenyl trityl sulfide with hydrogen peroxide in glacial acetic acid at room temperature for 12 hours.

During the present work, phenyl trityl sulfide (I) in glacial acetic acid was kept at 21–22° for 12 hours with the same mole ratio of hydrogen peroxide as was used by Knoll. There was isolated a 44% yield of benzophenone (II), and small amounts of phenol (III), diphenyl disulfide and trityl peroxide. The rate of oxidation of I was markedly increased by the addition of an equimolar quantity of sulfuric acid, and after ten minutes at 26–28° a 65% yield of II was obtained.

o-Tolyl trityl sulfide in acetone was oxidized very slightly, if at all, by an excess of hydrogen peroxide during six hours at room temperature. In the presence of mercuric chloride and much less peroxide, a 41% yield of II was obtained in ten minutes.

By using four moles of hydrogen peroxide per mole of I in acetic acid at an initial temperature of 80°, oxidation was complete within ten minutes. Good yields of II, III and benzenesulfonic acid (as its sodium salt) were obtained. At an initial temperature of 60° and the same reaction period, an 81% yield of II was obtained, and at 40°, not over 50% of I had reacted.

The experimental evidence appeared to indicate that the main reactions during the oxidation of an aryl trityl sulfide by hydrogen peroxide in acidic media were, (a) the oxidation of either free or incipient aryl thiol through the disulfide stage to arylsulfonic acid, and (b) the oxidation of either free or incipient trityl cation to II and III.

Acknowledgment.—This work was supported by a Frederick Gardner Cottrell grant from the Research Corporation, New York, N. Y.

Experimental[4]

Preparation of Aryl Trityl Sulfides.—The sulfides were prepared by using the procedures previously reported.[5]

(1) D. C. Gregg and C. A. Blood, Jr., J. Org. Chem., 16, 1255 (1951).

(2) D. C. Gregg, K. Hazleton and T. F. McKeon, Jr., ibid., 18, 36 (1953).

(3) R. Knoll, J. prakt. Chem., 113, 40 (1926).

(4) The Superoxol was Merck's 30% hydrogen peroxide. The identity of each oxidation product and each derivative was established, where possible, by mixed melting points with an authentic sample. The sodium arylsulfonates were characterized by preparing the corresponding arylsulfonamides and S-benzylthiuronium salts. All yields are based on complete cleavage of the sulfides. Temperatures are uncorrected.

(5) D. C. Gregg, H. A. Iddles and P. W. Stearns, Jr., J. Org. Chem., 16, 246 (1951).

Oxidation of I at Room Temperature.—To 200 ml. of glacial acetic acid were added 4.2 g. (0.012 mole) of I and 0.024 mole of hydrogen peroxide, as Superoxol. The reaction mixture was kept at 21–22° for 12 hours and then poured into water. This mixture was extracted with ether, and the ethereal solution then extracted with 20% sodium hydroxide. A small amount of III was obtained from the alkaline extract. From the ethereal solution was obtained 0.15 g. (5%) of trityl peroxide, a 44% yield of II (1.9 g. of its 2,4-dinitrophenylhydrazone), and 0.1 g. (8%) of diphenyl disulfide.

Oxidation of I in Presence of Sulfuric Acid.—To 200 ml. of glacial acetic acid were added 9.6 g. (0.027 mole) of I and 1.52 ml. (0.027 mole) of concentrated sulfuric acid. To this solution was added 0.054 mole of hydrogen peroxide. By cooling, the solution was kept at 26–28° for ten minutes. The yields were: II (65%, 6.4 g. of the 2,4-dinitrophenylhydrazone); III, 0.9 g. (35%); 0.3 g. (4.5%) of trityl peroxide; and 0.6 g. (30%) of diphenyl disulfide.

Oxidation of o-Tolyl Trityl Sulfide in Presence of Mercuric Chloride.—To 100 ml. of acetone at 28° were added 5.15 g. (0.014 mole) of o-tolyl trityl sulfide and 0.028 mole of hydrogen peroxide. A solution containing 4.5 g. (0.016 mole) of mercuric chloride in 35 ml. of acetone was added dropwise for 12 minutes. After two minutes the mixture was cooled, and 0.8 g. of o-tolylmercaptomercuric chloride was obtained by filtration. After evaporation of the filtrate, the residue was found to contain 0.3 g. of the mercaptomercuric chloride, 14% of III, 41% of II and 10% of o-tolyl disulfide.

Oxidation of Sulfides at 80°.—To 120 ml. of glacial acetic acid was added 9.6 g. (0.027 mole) of I. The solution was heated to 80°, and 0.108 mole of hydrogen peroxide added dropwise within three minutes. The reaction was strongly exothermic, and after a total of ten minutes the solution was poured into 300 ml. of cold water. The aqueous suspension was extracted with ether, and 1.3 g. (50%) of III was obtained from the ethereal solution by alkaline extraction. From the ethereal solution was obtained 4.5 g. (91%) of II. The aqueous acetic acid was evaporated to dryness, and after addition of sodium hydroxide 3.3 g. (62%) of sodium benzenesulfonate was obtained. By using identical conditions, 10 g. of p-tolyl trityl sulfide was oxidized. The yields were: II, 4.5 g. (91%); III, 1.7 g. (68%); sodium p-toluenesulfonate, 2.6 g. (45%). A similar oxidation of o-tolyl trityl sulfide produced II (79%) and III (45%). An oxidation of m-tolyl trityl sulfide produced II (80%) and III (50%).

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Existence of Two Solid Forms of 2-Methylfuran

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In the course of continuation of earlier work[1] on the f.p.–composition behavior of the system, 2-methylfuran–methanol, it was found that 2-methylfuran upon cooling gives two distinct halts in the time–temperature curve, presumably corresponding to two different solid modifications. The higher-melting solid (I), f.p. −90.19°, obtained by rapid cooling, is evidently the one concerned in the f.p. data previously reported.[1,2] The lower-melting solid (II), f.p. −101.92°, can be obtained by slower cooling, ordinarily resulting in inception of freezing from a less highly supercooled liquid. (The f.p. values stated represent results reproduced three or more times within ±0.01°; however, if the shortness of equilibrium time, and the extent of extrapolation of the equilibrium curve involved are

(1) J. B. Hickman and J. L. Hall, Proc. W. Va. Acad. Sci., 22, 72 (1950).

(2) E. I. du Pont de Nemours Corp., "New Products Bulletin," No. 24, May 4, 1948.

considered, ±0.1° should be regarded as the uncertainty of the absolute value of the f.p. data).

Although the time–resistance cooling curve for solid II shows the usual portions representing recovery from supercooling, equilibrium, and cooling of the solid, it has been found impossible to freeze the entire contents of the f.p. tube to solid II, since at a temperature 2–7° below the f.p., a sudden rise in temperature occurs, and the tube is shattered. Since the form of the curve strongly indicates complete solidification to solid II in the immediate vicinity of the temperature-sensitive portion of the resistance thermometer, the temperature rise presumably is occasioned by the freezing to solid I of pockets of liquid contained in portions of the tube not adjacent to the temperature-sensitive element.

If a glass or metal rod cooled in liquid nitrogen is touched to the surface of the liquid from which solid II is separating, solid I at once begins to form, and the temperature rises correspondingly. If only a small amount of solid II has separated when this change is caused to take place, the f.p. tube remains intact. In Fig. 1, the time marked A corresponds to initial separation of solid II, induced by causing the mechanical stirrer to scratch the wall of the f.p. tube, while the time marked B corresponds to touching the surface with the cooled rod.
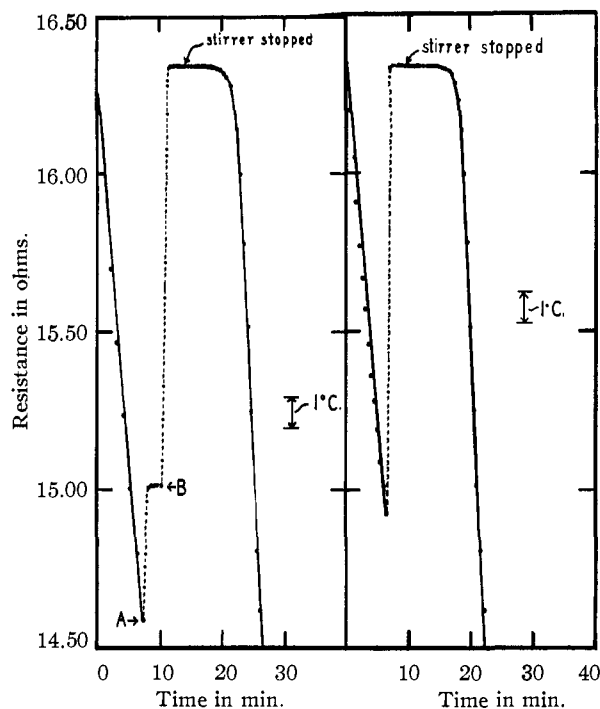

Fig. 1.—Time–resistance
cooling curve, 2-methylfuran.

Fig. 2.—Time–resistance
cooling curve, solid I.

Figure 2 represents data obtained by measurements on a sample from which no solid II separated, while Fig. 3 represents similar data for a sample allowed to solidify as solid II. Two minutes after the time corresponding to the last point in Fig. 3, the temperature sharply increased, and the f.p. tube was shattered.

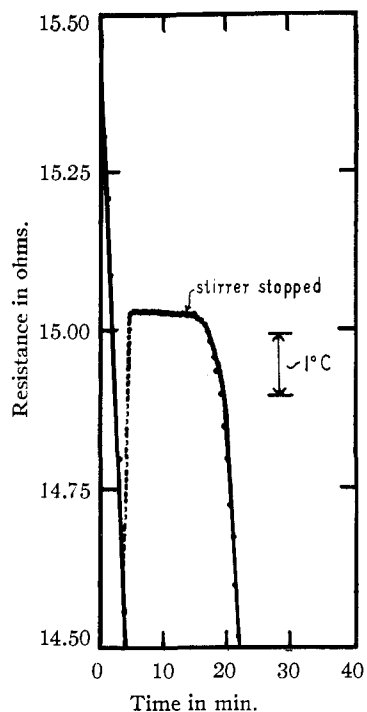In all experiments here reported, liquid nitrogen was used as a coolant.

Fig. 3.—Time–resistance cooling curve, solid II.

Large-scale plots of the data of Figs. 2 and 3 were analyzed by the methods of Rossini and co-workers[3–5] to obtain f.p. and estimated purity values. In applying these methods, a much shorter equilibrium time than recommended had to be used, with corresponding decrease in certainty of results.

Purity in excess of 99.5% for the liquid regardless of which solid was separating was estimated, eliminating the possibility that the phenomenon here dealt with is the separation of two different materials from a highly impure solution.

Experimental

2-Methylfuran.—Du Pont Electrochemicals 2-methylfuran was washed with an acidified saturated solution of iron(II) sulfate to remove peroxides, separated, dried over calcium chloride and distilled through a six-plate column. The 2-methylfuran was diluted before distillation with about one third its own volume of heavy mineral oil to reduce the possibility of spontaneous polymerization. A typical 100 ml. sample taken for use distilled in the range 62.7–62.8° (cor.) at a pressure (cor.) of 730.9 mm. Sealed bottles of 2-methylfuran became slightly yellow within a few hours. This was found to have no measurable effect on the f.p. or on the conditions concerned with formation of the two solids; nevertheless, only freshly distilled material was used.

Determination of Cooling Curves.—Time–resistance cooling curves were determined for 20-ml. samples, using conventional f.p. tube, mechanical reciprocating stirring, and liquid nitrogen as a coolant. Temperatures were measured by means of a platinum resistance thermometer calibrated by the U. S. National Bureau of Standards, the resistance values being determined by means of a calibrated Leeds and Northrup type G-2 Mueller Bridge. Curves of resistance vs. time were plotted and analyzed. Only the resistance values corresponding to the f.p. were converted to temperature by means of the Callendar equation.

In carrying out a determination, the sample was placed in the f.p. tube, the stirrer started and the temperature

(3) W. J. Taylor and F. D. Rossini, *J. Research Natl. Bur. Standards*, **32**, 197 (1944).

(4) B. J. Mair, A. R. Glasgow, Jr., and F. D. Rossini, *ibid.*, **26**, 591 (1941).

(5) A. R. Glasgow, Jr., A. J. Streiff and F. D. Rossini, *ibid.*, **35**, 355 (1945).

allowed to fall to $-80°$ with the jacket at atmospheric pressure. At this temperature, evacuation of the jacket space to 0.1 mm. gave slow cooling, with probable formation of solid II, while evacuation to 100 mm. gave faster cooling, usually resulting in separation of solid I without detectable formation of solid II. If the sample was allowed to supercool more than about 15°, the halt corresponding to solid II was very brief, with a spontaneous rise in temperature and separation of solid I after a period of one-half to 3 minutes. Such supercooling could be prevented by momentarily tilting the f.p. tube, causing the stirrer to rub against the side of the tube inducing initial formation of solid II crystals.

From the available evidence, the change involved appears to be monotropic, solid II being the metastable form. The fact that no conclusive evidence for complete solidification of the sample to solid II has been obtained, and that no definite temperature is associated with the inception of change from solid II to solid I seems to indicate that solid II is continuously changing to solid I at a finite rate. It is not to be inferred that the rather sudden increase in temperature 2–7° below the f.p. of solid II necessarily corresponds to conversion of the solid II to solid I, but more probably that liquid remaining unfrozen in the necessarily unstirred sample is in contact with sufficient solid I to freeze directly to this form.

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N-Fluoroacetyl Derivatives of Carcinogenic Amines[1]

BY EUGENE SAWICKI AND F. E. RAY

In a previous paper[2] trifluoroacetyl derivatives of carcinogenic amines were described. The fluoroacetyl analogs were prepared for a comparative study of their carcinogenic and cancer therapeutic activity. It is probable that in animal metabolism these compounds would be hydrolyzed to the carcinogenic amine and fluoroacetic acid. Fluoroacetic acid and its derivatives are known convulsant poisons.[3] Essentially, fluoroacetic acid is a Krebs cycle poison.[4] It has been postulated[5-7] that activated fluoroacetic acid and oxalacetic acid molecules react to form a fluorocitric acid which blocks the conversion of citric acid to α-ketoglutaric acid in the

TABLE I

Compound	M.p.,[a] °C.	Yield, %	Nitrogen, % Calcd.	Found
2-FA[b]-biphenyl	93–94	92	6.11	6.00
4-FA-biphenyl	179–180	95	6.11	6.06
4,4'-diFA-biphenyl	316–318 dec.	85	9.21	9.10
2-FA-naphthalene	106–107	90	7.82	7.60
2-FA-fluorene	168–169	97	5.81	5.99[c]
2,7-DiFA-fluorene	253–255	88	8.86	8.70
4-FA-2',3-dimethyl-azobenzene	155–157	96	14.7	14.5

[a] All melting points are uncorrected. [b] FA = Fluoroacetylamino. [c] Calcd.: C, 74.69; H, 4.98. Found: C, 74.97; H, 5.11.

(1) The work described in this paper was supported by a grant from the Sloan–Kettering Institute for Cancer Research.

(2) E. Sawicki and F. E. Ray, THIS JOURNAL, 75, 2519 (1953).

(3) H. McCombie and B. C. Saunders, Nature, 158, 382 (1946).

(4) C. Liebecq and R. Peters, Biochim. Biophys. Acta, 3, 215 (1949).

(5) P. Buffa and R. A. Peters, J. Physiol. (London), 110, 488 (1950).

(6) P. Buffa, R. A. Peters and R. W. Wakelin, Biochem. J., 48, 467 (1951).

(7) C. Martius, Ann., 561, 227 (1949).

body. On this basis the N-fluoroacetyl derivatives have been prepared to test their effect on living cells and malignant tumors. Table I lists these new fluoroacetyl derivatives.

Experimental

General Procedure. (a).—Nine and seven-tenths g. (0.01 mole) of fluoroacetyl chloride[8] was added dropwise to an ice-cold stirred solution of 0.01 mole of the monoamine in 5 ml. of benzene and 2 ml. of pyridine. The stirred mixture was warmed for 5 minutes and then 20 ml. of water was added. The benzene was evaporated at room temperature under a vacuum and the crude crystals were crystallized from heptane.

(b).—Nineteen and four-tenths g. (0.02 mole) of fluoroacetyl chloride was added dropwise to a stirred ice-cold solution of 0.01 mole of the diamine in 20 ml. of pyridine. The mixture was stirred an additional half hour at 0–10° and then poured into 100 ml. of ice-cold 25% sulfuric acid. The precipitate was crystallized from methyl cellosolve.

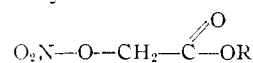(8) E. Sawicki and F. E. Ray, J. Org. Chem., in press (1953).

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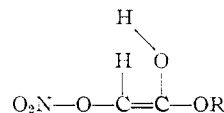## The Infrared Spectrum and Structure of Glycolate Nitrate Esters

BY W. D. KUMLER[1]

The structure of glycolate nitrate esters is expected to be mainly

$$O_2N—O—CH_2—\overset{\displaystyle \nearrow O}{C}—OR$$

but the possibility exists that some enol may be present.

$$O_2N—O—\underset{\overset{|}{H}}{C}=\underset{\overset{|}{O}\overset{|}{H}}{C}—OR$$

If this is the case the infrared spectrum should have a frequency in the 3 μ region corresponding to the O–H vibration.

The esters[2] used in this study were: isopropylglycolate nitrate, $n^{25}D$ 1.4163; n-butylglycolate nitrate, $n^{25}D$ 1.4235; s-butylglycolate nitrate, $n^{25}D$ 1.4270; isoamylglycolate nitrate, $n^{25}D$ 1.4250. The spectra were determined on the pure liquids with a Perkin–Elmer Model 21 Infrared Spectrograph with a sodium chloride prism, using a sodium chloride cell without a spacer.

In Fig. 1 is the spectrum of s-butylglycolate nitrate. It is to be observed, that there is a strong band at 3.43 μ due to C–H but also a weaker but rather broad band with a peak at 2.93 μ which is evidence of the presence of O–H. It would appear that there is some enol present in this molecule. The spectra of the other three esters all show this band near 2.93 μ. For comparison the spectrum of ethyl acetoacetate which is known to have about 7.7% enol in the liquid is shown in Fig. 2. It is to be noted that it has a similar band with a peak

(1) Requests for reprints should be sent to W. D. Kumler at the College of Pharmacy, University of California, San Francisco 22, California.

(2) J. G. Bird, H. K. Iwamoto, C. J. Carr and J. C. Krantz, Jr., J. Pharmacol. Expl. Therap., 97, 475 (1949).