[CONTRIBUTION NO. 1550 FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

1-Methoxyvinyl Esters.[1] II.[2] An Oxygen-18 Study of Anhydride Formation

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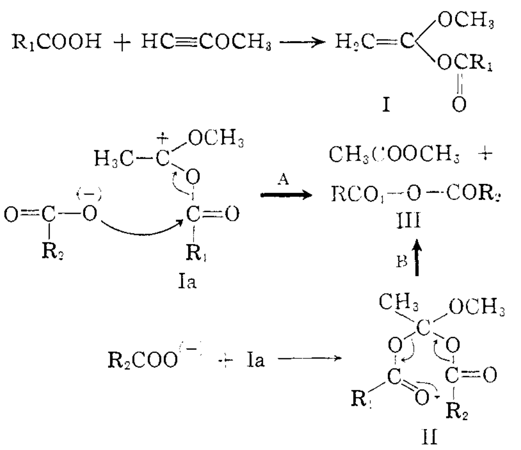
The mechanism of anhydride formation in the reaction of carboxylic acids with alkoxyacetylenes has been studied using O^{18} labeled benzoic acid and 1-methoxyvinyl benzoate. Anhydride formation is shown to occur *via* an intermediate orthoester which decomposes intramoleculary. Limitations in the use of this reaction for the formation of unsymmetrical anhydrides are discussed.

The reaction of alkoxyacetylenes with carboxylic acids under mild conditions has been found[4] to lead smoothly to the corresponding anhydrides in good yield. We have recently shown, using methoxyacetylene, that this procedure may be controlled so as to permit isolation of the intermediate 1-methoxyvinyl esters.[1,2]

The present report is concerned with the reaction of 1-methoxyvinyl benzoate, (I, R = C_6H_5) with O^{18}-labeled benzoic acid. This study is of interest in connection with the mechanism of the alkoxyvinyl ester–anhydride conversion, and, as will be shown below, discloses limitations in the use of the reaction of I with carboxylic acids for the preparation of unsymmetrical anhydrides.

Two paths, A and B, may be considered for the conversion of the intermediate I to the anhydride III. Path A represents a direct intermolecular acylation similar to that postulated for the formation of anhydrides from the reaction of acids with carbodiimides.[5] In path B, previously suggested,[4b] the orthoester II decomposes by way of a cyclic intramolecular transition state.

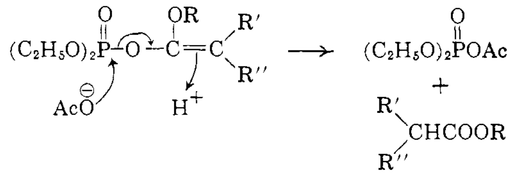


One should be able to distinguish between these two reaction paths by allowing I to react with a carboxylic acid having isotopically labeled oxygen. Path A would yield methyl acetate containing none of the excess O^{18}, while path B would result in a distribution of the excess O^{18} between the anhydride and the methyl acetate.

Experimentally, when equimolar amounts of 1-methoxyvinyl benzoate and benzoic acid containing 1.06 atom per cent. Excess O^{18} per oxygen were mixed at 80°, benzoic anhydride (98%) and methyl acetate (91%) were isolated. The methyl acetate was converted to N-benzylacetamide, thereby eliminating the one oxygen atom which cannot participate in the reaction and, simultaneously, obtaining a solid derivative. The total atom per cent. excess O^{18} in the benzoic acid (2.12) was recovered in the anhydride and amide (2.11), thus showing that nothing unusual had occurred in the conversion of methyl acetate to N-benzylacetamide. The individual analyses for O^{18} in the anhydride and amide were virtually identical[6] (0.53 and 0.52 atom per cent. excess per oxygen, respectively) and were also equal to one-half of that originally present in the benzoic acid.

The above results are those expected for anhydride formation exclusively by path B. (Had path A alone been involved, the anhydride would have contained all of the excess O^{18}, or 0.71 atom per cent. per oxygen.)

It is, however, conceivable that complete exchange of the benzoyloxy groups of 1-methoxyvinyl benzoate and labeled benzoic acid may have occurred during the reaction, *e.g.*, *via* reversible decomposition of II, $R_1 = R_2 = C_6H_5$. In this event, all mechanistic paths leading to III would be indistinguishable by the isotope experiment. Conclusive evidence that *complete exchange* did not take place was provided from the reaction, also at 80°, of an excess of 1-methoxyvinyl benzoate (4 moles) with a sample of the same O^{18} labeled benzoic acid (1 mole). The methyl acetate re-



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[1] For a preliminary communication on this subject, see H. H. Wasserman and P. S. Wharton, *Tetrahedron*, **3**, 321 (1958). This paper is abstracted from the Doctoral Dissertation of P. S. Wharton, submitted to the Graduate School of Yale University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1959.

[2] Paper I in this series, H. H. Wasserman and P. S. Wharton, THIS JOURNAL, in press.

[3] Procter and Gamble Fellow, 1957–1958.

[4] (a) J. F. Arens and P. Modderman, *Proc. Koninkl. Ned. Akad. Wetenschap.*, **53**, 1163 (1950); *C. A.*, **45**, 6152 (1951); (b) G. Eglinton, E. R. H. Jones, B. L. Shaw and M. C. Whiting, *J. Chem. Soc.*, 1860 (1954).

[5] H. G. Khorana, *Chem. Revs.*, **53**, 145 (1953). Note also that F. Cramer and K.-G. Gartner, *Ber.*, **91**, 704 (1959), suggest an analogous direct acylation of an ethoxyvinyl phosphate ester to form the mixed phosphoric–carboxylic acid anhydride, *viz.* (see formulas →)

[6] Using an appropriate procedure, however, the analyses obtained from the experiments run at 80° were shown to differ by a small but definite amount, 0.010. Neglecting any isotope effect, this difference could be due to (a) exchange of 2% of the reacting acid with the forming anhydride, or (b) occurrence of 2% of anhydride formation by path A.

covered was converted to N-benzylacetamide which was found to contain 0.43 atom per cent. excess O^{18}. Although the exchange which occurred in this reaction was appreciable, almost one-third of that possible (involving *ca.* 20% of the labeled acid), it was *not* complete,[7] thus ruling out the possibility that the O^{18} results may have arisen from a combination of complete exchange and path A. Path B, then, represents the favored mechanism.[8]

Further information about the mechanism of anhydride formation can be derived from the experiment in which an excess of methoxyvinyl benzoate was used in the reaction with labeled benzoic acid. The exchange which was observed cannot be due to acid–anhydride interchange.[9] It is, therefore, likely that it occurs by the elimination of either of the equivalent benzoate residues from the orthoester II, R = C_6H_5, a possibility which is significant in connection with the possible utilization of 1-methoxyvinyl esters as reactive intermediates in the preparation of unsymmetrical anhydrides. It would appear that unsymmetrical anhydrides derived from two similar acids of the same strength cannot be prepared quantitatively from the reaction of 1-methoxyvinyl esters with carboxylic acids. Exchange of the acid residues would be expected in such cases, with the formation of substantial amounts of symmetrical anhydrides. However, in seeking to prepare unsymmetrical anhydrides where the acids involved are of different strengths, one would expect that the elimination of the stronger acid from the orthoester II would occur preferentially. Thus, it may well be possible to prepare the unsymmetrical anhydrides in almost quantitative yield (with little or no contamination), by adding the stronger acid to the 1-methoxyvinyl ester prepared from the weaker acid. Some experimental confirmation of this hypothesis was obtained from the spectral observations that negligible amounts of symmetrical anhydrides contaminated the unsymmetrical anhydrides formed in the reactions of 1-methoxyvinyl acetate with trichloroacetic and formic acids. In the latter reaction, 0.5% of acetic anhydride would have been detected in the infrared spectrum of the reaction mixture.[10]

Experimental[11,12]

Benzoic Acid-O^{18}.—Two samples of the acid were used,[13] m.p. 122–123°. Oxygen-18 analysis[14] of sample A: 1.261, 1.260, 1.263 and 1.259 atom per cent. O^{18} per oxygen; mean value, 1.26. Sample B: 1.293 and 1.303 atom per cent. O^{18} per oxygen; mean value, 1.30.

1-Methoxyvinyl benzoate was prepared as previously described;[2] b.p. 95–96° (0.5 mm.), $n^{25}D$ 1.5181. The benzoic anhydride content of the distillate was determined as less than 0.1% by electrometric titration of 897 mg. (5 mmoles) in 20 ml. of a 1:1 mixture of pyridine and water. The amount of base consumed was 0.05 ml. of 0.129 *N* sodium hydroxide, equivalent to 0.7 mg. of benzoic anhydride. A blank showed a negligible correction. The method of determining anhydride in this system was checked by adding 12 mg. (0.106 meq.) of authentic anhydride to the aqueous pyridine solution. In the subsequent titration, 0.87 ml. of 0.129 *N* base (0.112 meq.) was consumed.

Reaction of Equimolar Amounts of Benzoic Acid-O^{18} and 1-Methoxyvinyl Benzoate.—Benzoic acid-O^{18} (sample A, 1.487 g., 12.18 mmoles) and 2.173 g (12.20 mmoles) of 1-methoxyvinyl benzoate were mixed in a small flask which was connected to a liquid nitrogen trap. The flask was placed in an oil-bath at 80° and the solution stirred (magnetically) for 20 minutes. After cooling the flask in ice-water, the system was evacuated to 1 mm. and the flask warmed to 35–40° for 15 minutes. The residue (pale yellow) was seeded with authentic benzoic anhydride and left for 6 hours at 1 mm. to give 2.170 g. (98%) of benzoic anhydride, m.p. 42-45°, mainly 44–45°. Crystallization at 5° from a mixture of 1.3 ml. of benzene and 3.0 ml. of pentane raised the m.p. to 45.2–45.7°. The methyl acetate which had collected in the liquid nitrogen trap, was transferred to a small flask by vacuum-line technique; yield 825 mg. (91%), b.p. 55°, $n^{25}D$ 1.3610. It was further characterized (a) by its infrared spectrum, which showed (neat, 0.25-mm. cell) the presence of less than 0.1% of benzoic acid and 1-methoxyvinyl benzoate, both of which absorb strongly at 14.02 μ; and (b) by gas chromatography, which also showed the complete absence of other volatile components. For O^{18} analysis, the methyl acetate was converted to N-benzylacetamide by heating it in a sealed tube with slightly less than the requisite amount of freshly distilled benzylamine, b.p. 181–182°, $n^{25}D$ 1.5413, for 5 to 6 hours at 140°. Removal of volatiles from the colorless product gave N-benzylacetamide, m.p. 62–63°. Crystallization at 5° from ether containing 2–3% ethanol raised the m.p. to 64.5–65.4°. Benzoic anhydride:[15] 0.730, 0.723, 0.724 atom per cent. O^{18} per oxygen; mean value, 0.73. N-Benzylacetamide:[15] 0.712, 0.716, 0.718; mean value, 0.72. Four more runs, three at 80° and one at 22° (24 hr.), were carried out with almost identical results.

Reaction of Benzoic Acid-O^{18} with Excess 1-Methoxyvinyl Benzoate.—The general procedure described for the reaction of equimolar amounts of the two reagents was followed. A mixture of 1.665 g. (13.63 mmoles) of benzoic acid-O^{18}, sample A, and 9.746 g. (54.70 mmoles) of 1-methoxyvinyl benzoate was heated and stirred at 80° for 20 minutes. The methyl acetate which had formed was collected in the liquid nitrogen trap at 1 mm. and 35° and then transferred to a small flask at 20 mm. and 50°; yield 529 mg. (51%), $n^{25}D$ 1.3609. The infrared spectrum showed that the distillate contained less than 0.15% of benzoic acid and 1-methoxyvinyl benzoate. N-Benzylacetamide: 0.632, 0.631 atom per cent. O^{18}; mean value, 0.63. A further run was carried out at 22° (19 hr.) with the same ratio of reactants. The results were similar but not identical; N-benzylacetamide: 0.593. 0.591 atom per cent. O^{18}; mean value, 0.59.

1-Methoxyvinyl acetate was prepared as previously described;[2] b.p. 79° (85 mm.), $n^{25}D$ 1.4122.

Formic Acetic Anhydride.—Methoxyvinyl acetate (1.060 g., 9.13 mmoles) and 422 mg. (9.16 mmoles) of formic acid (purity greater than 99% as determined by titration) were mixed at −20°. (Mixing at room temperature resulted in an explosive reaction.) The intensity of absorption at 8.9 μ in the infrared spectrum of the reaction solution showed the presence of less than 0.5% of acetic anhydride. In the

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(7) For complete exchange one would expect a value of 0.21; for no exchange, a value of 0.53 atom per cent. excess O^{18}.

(8) The O^{18} experiments were repeated at 22° with almost the same results as those obtained from the runs at 80°, indicating that temperature has little effect on the course of the reaction.

(9) The extent of exchange due to acid–anhydride interchange cannot have been greater than in the experiment using equimolar amounts of reactants where it was shown to be 4% (ref. 6). This figure is much smaller than the 20% exchange observed.

(10) Although it is possible that acetic trichloroacetic anhydride might have resulted from an initial mixture of anhydrides (*cf.* J. M. Tedder, *Chem. Revs.*, **55**, 787 (1955)), formic acetic anhydride must have arisen directly, since formic anhydride is not kown to exist.

(11) All b.p.'s and m.p.'s are uncorrected. The latter were determined in soft glass capillary tubes in a Hershberg apparatus.

(12) Infrared spectra were recorded on a Perkin–Elmer model 21 spectrophotometer.

(13) The acid was kindly supplied by Prof. W. von E. Doering.

(14) By the method of W. von E. Doering and E. Dorfman, THIS JOURNAL, **75**, 5595 (1953).

(15) These triplicate analyses of benzoic anhydride and N-benzylacetamide were determined on the same day as follows. A sample of benzoic anhydride-O^{18} was first burned to remove memory effects in the apparatus. Benzoic anhydride and N-benzylacetamide were then burned alternately, this procedure enabling a good comparison to be made between analyses from samples of almost identical oxygen-18 contents.

carbonyl region, bands at 5.57, 5.63 and 5.72 μ (CCl_4) were present. Evaporative distillation at 1 mm. and −50° failed to achieve a good separation of the formic acetic anhydride from methyl acetate.

Acetic Trichloroacetic Anhydride.—A solution of 1.114 g. (6.82 mmoles) of freshly sublimed trichloroacetic acid (purity determined as 99.8% by titration) in 1 ml. of dry ether was treated dropwise over 20 minutes at 0° with 811 mg. (6.98 mmoles) of 1-methoxyvinyl acetate; yield, after leaving overnight at −20° and 1 mm., 1.387 g. (99%), m.p. mainly[16] −6 to −4°, 5.42 and 5.63 μ (CCl_4). In the absence of solvent, polymerization of the 1-methoxyvinyl acetate was found to occur to an appreciable extent.

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[16] A very small amount of liquid was present even at −20°. A. R. Emery and V. Gold, *J. Chem. Soc.*, 1456 (1950), report a m.p. of *ca.* −5°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS & SCIENCES OF THE UNIVERSITY OF LOUISVILLE]

Synthesis and Characterization of the Geometric and Structural Isomers of 3,7-Dimethyl-2,4,6-octatrienoic Acid. I

BY RICHARD H. WILEY, E. IMOTO, R. P. HOUGHTON AND P. VEERAVAGU

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The *trans–trans* structure of dehydrogeranic acid (VI), m.p. 187°, prepared by a Reformatsky reaction with 6-methylhepta-3,5-dien-2-one (I) and the structure of its 2-*cis* isomer VIII, m.p. 161°, prepared by decarboxylation of the 4-carboxyoctatrienoic acid (VII), have been established and their infrared and ultraviolet absorption characteristics have been determined. The carboxy acid VII has absorption characteristics establishing that it has the 2-*cis*:4-*cis* configuration. The Reformatsky reaction between senecialdehyde and methyl γ-bromosenecioate gives rearranged products (IX,X) whose structures also have been established by absorption characteristics.

There are four geometrical isomers and five isomeric cyclized structures of 3,7-dimethyl-2,4,6-octatrienoic acid. Two of the former—m.p.'s. 187°[1-3] and 137°[1]—and four of the latter—m.p.s. 63°,[4] 111°,[5] 117°,[6] and 130°[4]—have been reported. With the possible exception of the 187° acid, which has been assigned[1] the *trans–trans* structure on the basis of its identity with a natural occurring[3] dehydrogeranic acid, the evidence for the structural assignments for these compounds is somewhat incomplete. A recent study[7] of the nuclear magnetic resonance properties of isomeric systems similar to the acyclic types has provided a new basis for structural assignments in such systems. The syntheses of the 3,7-dimethyl-2,4,6-octatrienoic acids, by Reformatsky and decarboxylation reactions, have been examined and the nuclear magnetic resonance characteristics of the isomeric products have been evaluated. These studies will be described in this and a subsequent paper with reference to a recent clarification[8] of the stereochemistry of the analogous 3-methyl-5-phenylpentadienoic acid system. The effect of these compounds on the enzymatic biosynthesis of cholesterol will be reported elsewhere.

3,7-Dimethyl-2-*trans*:4-*trans*-6-octatrienoic Acid (VI).—An acid having this structure has been isolated from the oil of the wood of *Callitropsis arancarioides* where it is found as the geranyl ester.[3] The acid is reported to have a m.p of 185–186° and a maximum in the ultraviolet at 311 mμ (log ε 4.55). The carbon skeleton was established by hydrogenation to DL-tetrahydrogeranic acid and by synthesis.[1,2] The synthesis involved a Reformatsky reaction with 6-methylhepta-3,5-dien-2-one (I) and bromoacetate followed by dehydration and saponification of the hydroxy ester II. This acid was assigned the 2-*trans*:4-*trans* structure and an isomeric acid, m.p. 137°, which was also obtained,[1] was assigned the 2-*cis*:4-*trans* structure. This assignment is in question since it is known[8,9] that Reformatsky syntheses of similar structures often give mixtures of isomers crystallizing as low melting complexes. We have confirmed this synthesis of the acid which we have observed to melt at 187°, but have not obtained the 137° acid. The heptadienone was prepared by condensation of senecialdehyde with acetone or, somewhat more conveniently, by decarboxylation of the acetoacetic ester obtained from diketene and 2-methylbut-3-yn-2-ol.[10] The Reformatsky reaction gives an excellent yield of the hydroxy ester II which on dehydration gives different products under different conditions. Dehydration in ether with *p*-toluenesulfonic acid gives a readily polymerizable ester which has maxima in the infrared at 1727 (saturated ester carbonyl stretching), 1706 (unsaturated ester carbonyl stretching), 966 (C–H out of plane deformation of *trans* —CH=CH—) and 885 cm.$^{-1}$ (C–H out of plane deformation of terminal methylene). Although undoubtedly a mixture of isomers this material probably contains some of the ester III or IV. An abnormal dehydration of a Reformatsky product to give a non-conjugated unsaturated ester has been reported previously.[11] If the dehydration is run in benzene, an ester, m.p. 17–23°, is obtained in 86% yield which on saponification gives 55% yield of the 187° acid. Esterification of the acid with diazomethane gives the pure methyl ester, m.p. 38–39°. The acid absorbs in the ultraviolet at 308 mμ (log ε 4.56); the ester at 311 mμ (log ε 4.50). The acid absorbs in the

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[1] R. Kuhn and M. Hoffer, *Ber.*, **65**, 651 (1932).

[2] F. G. Fischer and K. Löwenburg, *Ann.*, **494**, 263 (1932).

[3] R. S. Cahn, A. R. Penfold and J. L. Simonsen, *J. Chem. Soc.*, 3134 (1931).

[4] G. Wendt, *Ber.*, **74**, 1242 (1941).

[5] O. Jeger and G. Büchi, *Helv. Chim. Acta*, **31**, 134 (1948).

[6] G. Merling and R. Welde, *Ann.*, **366**, 215 (1909).

[7] L. M. Jackman and R. H. Wiley, *Proc. Chem. Soc.*, 196 (1958).

[8] R. H. Wiley, *J. Chem. Soc.*, 3831 (1958).

[9] R. Stoermer, F. Grimm and E. Laage, *Ber.*, **50**, 959 (1917).

[10] R. N. Lacey, *J. Chem. Soc.*, 827 (1954).

[11] L. Crombie, S. H. Harper and K. C. Sleep, *ibid.*, 2743 (1957); *cf. Chemistry & Industry*, 1538 (1954).