minum hydride in 60 ml. of anhydrous ether, there was added a solution of 0.8 g. of the enol ether of cortisone acetate in 20 ml. of benzene. The material reacted vigorously with the formation of a precipitate. After stirring and refluxing the mixture for 2 hours, small chips of ice were added to destroy the excess reagent. The mixture was then acidified with cold dilute hydrochloric acid and extracted with ether. The ethereal layer was washed with small portions of water, and the combined aqueous fractions were salted and again extracted with ether. The ether solution was concentrated to about 10 ml. and treated with a mixture of 30 ml. of methanol and 5 ml. of 2% hydrochloric acid for 12 hours. This solution was concentrated *in vacuo* to about 5 ml. volume, salt water and ether were added and the organic layer was separated. The residue, 0.6 g. of hygroscopic tetrolone, remaining after removal of solvent from the dried ethereal solution was acetylated by treatment with 1 ml. of acetic anhydride and 3 ml. of pyridine for 10 hours at room temperature. This was then gently warmed *in vacuo* to remove excess reagents and anhydrous ether was then added to crystallize the product which separated slowly as clusters of prisms melting at 218–223°. The first crop, 0.36 g., was recrystallized several times from acetone yielding prisms, m.p. 226–227° dec. in air; m.p. 230–231° in vac.; log $\epsilon_{max.}$ 4.3 at 241 mμ in methanol; $[\alpha]^{23}D$ +163° (8.1 mg. made up to 2 ml. with acetone, αD +0.663°, l, 1 dm.).

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.97; H, 8.09. Found: C, 66.63; H, 7.95.

CHICAGO 39, ILL.

RECEIVED SEPTEMBER 21, 1950

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE JOHNS HOPKINS UNIVERSITY]

Synthetic Approaches to 1,2,3,4-Cyclobutanetetracarboxylic Acid

BY EVANS B. REID AND MILTON SACK[1]

In this paper it is shown that the alleged 1,2,3,4-cyclobutanetetracarboxylic acid is in reality fumaric acid. Attempts to prepare this cyclic acid by degradation of certain isomers of 1,3-dicarboxy-2,4-cyclobutanediacetic acids were unsuccessful. A new synthesis of ethyl 1,1,2,2,3,4-cyclobutanehexacarboxylate is described, and from this ester 1,2,3,4-cyclobutanetetracarboxylic acid, of unknown stereochemical form, has been obtained. The infrared absorption spectra of several highly substituted cyclobutanes have been determined and the characteristic cyclobutane absorptions have been noted.

In 1932 Owen and Simonsen[2] reported the formation of ethyl 1,2,3,4-cyclobutanetetracarboxylate as a *by-product* from the interaction of ethyl diazoacetate with methylheptenone in the presence of copper bronze. The same ester was again obtained when ethyl 4-methyl-3-pentenoate replaced methylheptenone in the above reaction.[3] The identification of this cyclic ester rested upon the analysis of the parent acid and the molecular weight of the methyl ester. Later, Ranganathan[4] prepared the supposed ethyl 1,2,3,4-cyclobutanetetracarboxylate, as the *main product*, from the interaction of ethyl α-isopropylacrylate with ethyl diazoacetate and copper bronze, under the conditions of Owen and Simonsen. Beyond these three reports the literature affords no other reference to this cyclic compound.

Certain stereochemical studies in this Laboratory required the preparation of 1,2,3,4-cyclobutanetetracarboxylic acid in quantity, and we therefore repeated the synthesis of Ranganathan[4] several times. However, the product, after hydrolysis, bore such a striking resemblance to fumaric acid that we were led to make a direct comparison between this unsaturated acid and the supposed 1,2,3,4-cyclobutanetetracarboxylic acid. The results of this clearly established the fact that the supposed cyclic acid of Ranganathan[4] was in reality fumaric acid. As a further check, the acid was transformed into its methyl ester by the method of Owen and Simonsen.[2] The ester proved to be methyl fumarate.[5]

Comparison of the properties of fumaric acid with those given by Owen and Simonsen[2,3] for their alleged cyclobutane acid, revealed complete agreement except for the molecular weight of the methyl ester. The English authors obtained, by the Rast method, a value very close to that calculated for the tetrabasic cyclic ester. We therefore carried out the Rast determination[6] on methyl fumarate, and obtained values approximating that of the cyclic ester, *i.e.*, nearly twice that of methyl fumarate. It is apparent that the Rast method is not reliable for this determination, probably due to strong association of the unsaturated ester. We thus are led to believe that neither 1,2,3,4-cyclobutanetetracarboxylic acid nor its esters have ever been prepared.

Turning to the question of synthesis, the most promising route to the cyclic tetracarboxylic acid, in its various forms, would appear to be through the 1,3-dicarboxy-2,4-cyclobutanediacetic acids.[7,8] Not only have all five stereoisomeric forms of the latter compound been isolated and characterized,[8] but precise conditions have been reported whereby the various forms may be interconverted.[8] Various factors, however, prevented the successful completion of these degradations. Thus, attempts to degrade the α- and β-forms of 1,3-dicarboxy-2,4-cyclobutanediacetic acid (II) (Fig. 1), in a manner analogous to that used in the case of *cis*-pinic acid,[9,10] were thwarted by the inertia of these acids toward bromination. Further, attempts to brominate the cyclic acid chloride directly[11,12] had to be abandoned since thionyl chloride yielded only the dianhydride (III). Likewise, phosphorus penta-

---

[1] From the doctoral dissertation of Milton Sack, The Johns Hopkins University, 1950.

[2] Owen and Simonsen, *J. Chem. Soc.*, 1424 (1932).

[3] Owen and Simonsen, *ibid.*, 1225 (1933).

[4] Ranganathan, *J. Indian Soc.*, **13**, 419 (1936).

[5] Other authors have noted the formation of fumaric esters from the decomposition of diazoesters with copper bronze catalyst, *viz.*, Loose, *J. prakt. Chem.*, [2] **79**, 505 (1909); Buchner and Schottenhammer, *Ber.*, **53**, 865 (1920).

[6] Shriner and Fuson, "The Systematic Identification of Organic Compounds," third ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 50.

[7] Guthzeit, Weiss and Schaefer, *J. prakt. Chem.*, **80**, 393 (1909).

[8] Ingold, Perren and Thorpe, *J. Chem. Soc.*, **121**, 1765 (1922).

[9] Baeyer, *Ber.*, **29**, 1908 (1896).

[10] Perkin and Simonsen, *J. Chem. Soc.*, **95**, 1174 (1909).

[11] Fourneau and Nicolotch, *Bull. soc. chim.*, **43**, 1232 (1928).

[12] Schwenk, THIS JOURNAL, **70**, 3626 (1948).

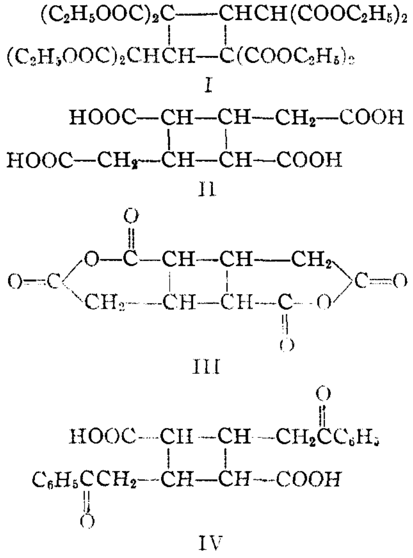

Fig. 1.

chloride failed to form the desired acid chloride from either the tetrabasic acid or its dianhydride.[13]

The cyclic tetrabasic acid (II), when subjected to oxidation according to the procedure of Windaus, *et al.*,[14] was mostly recovered unchanged. Direct oxidation of the octa-ester (I) failed to form the expected dihydroxy compound[15]; likewise, hydrolyses of the dibromide of (I) were futile.

Finally, the dianhydride (III) was converted by means of a Friedel and Crafts reaction to the dibenzoyl compound (IV).[16] Oxidation of this readily furnished benzoic acid, but no 1,2,3,4-cyclobutanetetracarboxylic acid could be isolated.[17]

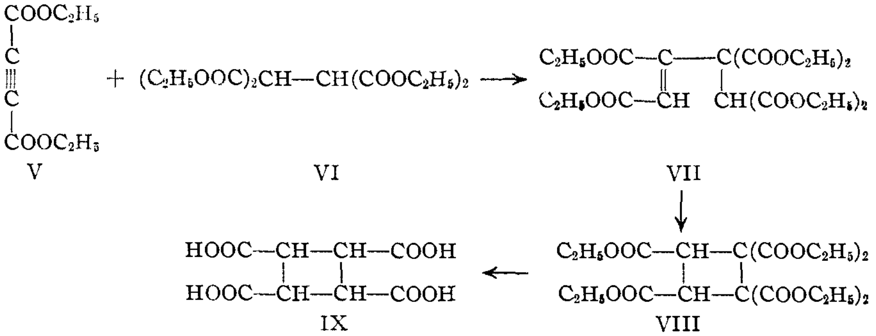

Fig. 2.

The discouraging results obtained with the above approach prompted a study of a more direct though less general route, employing ethyl 1,1,2,2,-3,4-cyclobutanehexacarboxylate (Fig. 2, VII). The latter has been obtained by Shibata[18] from the interaction of dibromosuccinic ester with the disodio salt of ethyl ethanetetracarboxylate (VI). Repetition of this synthesis showed that the low yield of product rendered the method unsuitable for the preparation of the cyclic ester in quantity.[19]

A superior method was therefore devised (Fig. 2), which involves the addition of ethyl 1,1,2,2-ethanetetracarboxylate (VI) to ethyl acetylenedicarboxylate (V). The reaction is catalyzed by a small amount of ethoxide ion; we regard the reaction as proceeding through successive Michael condensations, the second such being a cyclization of the primary addition product (VII).[20]

Although the cyclic hexaester was unstable toward base,[18] it was possible to hydrolyze the compound in acid solution. The hydrolysate consisted of a mixture of acids, some of which appeared to be unsaturated since they reacted instantly with permanganate. The hydrolysis mixture was repeatedly recrystallized until material was obtained that was free of unsaturates as evidenced by stability to permanganate for several hours. This substance gave analytical data and an infrared spectrogram in accord with 1,2,3,4-cyclobutanetetracarboxylic acid.

Infrared Data.[21]—In Fig. 3 are reproduced the infrared absorption spectra of the cyclobutane compounds described in this paper. The determinations were made on dry samples mulled in mineral oil, and the bands appearing at 3.3–3.4, 6.8–6.9, and 7.2–7.3 μ are due to the oil. Special interest attaches to the 900 cm.$^{-1}$ region, since cyclobutane itself gives a band in this zone,[22] and hydrocarbon-substituted cyclobutanes have been shown to absorb characteristically[23] between 908 and 918 cm.$^{-1}$. The spectra reproduced below show a characteristic absorption peaked in the 868–888 cm.$^{-1}$ region, and it is noteworthy that in *none* of the known cyclobutane derivatives studied here does absorption occur in the range noted for the alkyl-cyclobutanes.[23] It thus appears that substitution of one or more of the methylene hydrogens of *each* of the cyclobutane carbons results in a shift of the ring absorption to longer wave lengths.[24]

---

(13) A separate experiment showed that glutaric anhydride could be transformed into glutaryl chloride by means of phosphorus pentachloride, in 90% yield.

(14) Windaus, Klänhardt and Revery, *Ber.*, **55**, 3981 (1922).

(15) Compare Escola and Muotinen, *Suomen Kemistilehti*, **20B**, 16 (1947), *C. A.*, **42**, 122 (1948). Because of base-catalyzed ring-chain tautomerism (Ingold, Perren and Thorpe, ref. 8) our oxidations were carried out in acid solution.

(16) The structure of this product rests upon an analogous reaction of homophthalic anhydride (Graebe and Trumpy, *Ber.*, **31**, 375 (1898)); upon the fact that the compound is readily oxidized (compare Ellingboe and Fuson, THIS JOURNAL, **56**, 1774 (1934)); and upon its infrared absorption spectrum (*vide infra*).

(17) Compare Popoff, *Ann.*, **161**, 294 (1872).

(18) Shibata, *Ber.*, **43**, 2619 (1910).

(19) We wish to thank Mr. A. C. Smith, Jr., for carrying out this work at Middlebury College, Vt., 1944.

(20) We wish to thank Miss Eileen Luz for assistance in adapting this reaction to a large scale, Middlebury College, Vt., 1946.

(21) We are indebted to Dr. Lester P. Kuhn, of the Ballistics Research Laboratory, Aberdeen Proving Grounds, Md., for these determinations. The instrument used was a Baird Associates double beam infrared spectrophotometer.

(22) Wilson, *J. Chem. Phys.*, **11**, 369 (1943).

(23) Derfer, Pickett and Boord, THIS JOURNAL, **71**, 2482 (1949).

(24) Despite the fact that measurements made on dispersed material may differ unpredictably from those made on pure liquids or gases, or on true solutions, the same general shift toward longer wave lengths shown by all of these highly substituted cyclobutanes supports the above conclusion.

On the basis that the 1,2,3,4-tetrasubstituted cyclobutane ring shows absorption which is characteristic, in the 868–888 cm.$^{-1}$ region, the structure of the cyclobutane tetraacid isolated in the present work is substantiated (curve 6). Moreover the absence of absorption in the 1640 cm.$^{-1}$ range is clear proof that the compound was free of contamination with unsaturated material. The same cannot be said for the parent hexaester (curve 5) since the peak at about 1635 cm.$^{-1}$ is indicative of the presence of some unsaturated impurity. Undoubtedly this impurity was responsible for the sensitivity of the crude hydrolysate toward oxidation. The nature of this impurity is unknown, but the presence of some of the isomeric ethylenic ester (VII) would account satisfactorily for this behavior.

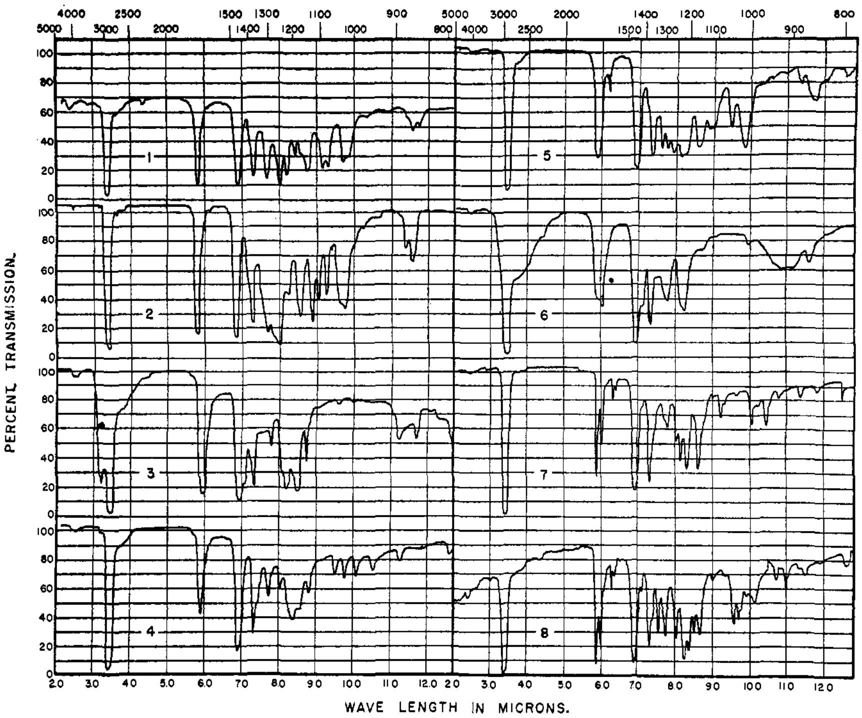

Fig. 3.

The following is a list of the significant absorption peaks in the above spectra.

	Compound	Cyclobutane (cm.$^{-1}$)	C=C	C=O[a]
1.	Ethyl 1,1,3,3-tetracarbethoxy-2,4-cyclobutanedimalonate (α-form)	870		1735 ester
2.	Ethyl 1,1,3,3-tetracarbethoxy-2,4-cyclobutanedimalonate (β-form)	875		1725 ester
3.	1,3-Dicarboxy-2,4-cyclobutanediacetic acid (α-form)	888		1690 acid
4.	Methyl 1,3-dicarbomethoxy-2,4-cyclobutanediacetate (α-form)	888		1712 ester
5.	Ethyl 1,1,2,2,3,4-cyclobutanehexacarboxylate	885	1635	1720 ester
6.	1,2,3,4-Cyclobutanetetracarboxylic acid	868		1690– 1710 acid
7.	Methyl 2,4-diphenacyl-1,3-cyclobutanedicarboxylate	888		1675 benzoyl 1710 ester
8.	Ethyl 2,4-diphenacyl-1,3-cyclobutanedicarboxylate	875		1675 benzoyl 1710 ester

Acknowledgment.—One of the authors (M.S.) gratefully acknowledges receipt of a grant-in-aid from the Hynson, Westcott and Dunning Fund.

Experimental

The Alleged 1,2,3,4-Cyclobutanetetracarboxylic Acid.—Ethyl α-isopropylacrylate[25] and copper bronze were treated with ethyl diazoacetate according to the procedure of Ranganathan.[4] Hydrolysis of the resultant ester gave only fumaric acid, m.p. and mixed m.p. 289–290° (dec.). The methyl ester of the hydrolysis product was prepared.[2] It was pure methyl fumarate, m.p. and mixed m.p. 102°.

Determination of the molecular weight of methyl fumarate by the Rast method[6] gave 236 and 246. Theory requires 144. Owen and Simonsen[2] obtained 279.8 for their product, as against 288 which theory requires for methyl 1,2,3,4-cyclobutanetetracarboxylate.

Ethyl 1,1,3,3-Tetracarbethoxy-2,4-cyclobutanedimalonate.—Ethyl α,γ-dicarboxyglutaconate was prepared from ethyl sodiomalonate and chloroform.[27] Self condensation of the glutaconic ester in the manner described by Guthzeit, *et al.*,[7] furnished the α-form of the cyclic octaester. It had the reported m.p. 103°. Isomerization of the α- to the β-form, m.p. 87°, was accomplished by keeping the α-ester in benzene containing piperidine.[7]

1,3-Dicarboxy-2,4-Cyclobutanediacetic Acids.—The mixture of isomeric acids was obtained by extended acid hydrolysis of the above octaester (α-form) according to the recommended procedure.[3] In our hands the fractional crystallization procedure[7] for separating the two isomers was satisfactory only on a small scale; we were, however, unable to devise a superior method for obtaining the β-isomer. In order to prepare the α-isomer in quantity and in a pure state it was necessary to esterify the crude mixture of acids, using methanol saturated with hydrogen chloride. Distillation of the mixture of esters at 1.0–2.0 mm. furnished a viscous colorless oil, b.p. 176–180°. The oil solidified on standing, m.p. 72–74°, and was shown to be the methyl ester of the α-acid. Hydrolysis of this ester by boiling with 3 *N* hydrochloric acid gave the α-acid, m.p. 229–231° (dec.).[7] The yield of α-acid was about 65%, based on the ester. It proved impossible to distil the methyl ester of the β-acid, due to decomposition. Contrary to Ingold, *et al.*,[8] the dianhydride could not be prepared in yields above 30% from the mixture of isomeric acids, and hydrolysis of the dianhydride gave poor yields of the α-acid.

2,4-Diphenacyl-1,3-cyclobutanedicarboxylic Acid.—A mixture of 11.2 g. (0.05 mole) of the dianhydride of α-acid, 27 g. (0.02 mole) of aluminum chloride, and 150 ml. of dry benzene was stirred under reflux until the evolution of hydrogen chloride became negligible (eight hours). The brown reaction mixture was acidified with 250 ml. of 2 *N* hydrochloric acid (which did not appear to change the nature of the viscous product). Steam distillation removed the benzene and caused the deposition of crystalline material. The yield of dry product was 13 g. (30%). The product was dissolved in base and carefully precipitated by the addition of dilute hydrochloric acid. It had m.p. 231–232°.

Anal. Calcd. for $C_{22}H_{20}O_6$: C, 69.47; H, 5.26; neut. equiv., 190. Found: C, 69.66; H, 5.40; neut. equiv., 192.

The methyl ester was prepared by treating a suspension of the keto-acid in ether with diazomethane. The ester, which was insoluble in ether, was recrystallized from chloroform, giving shiny needles, m.p. 176°. Zeisel determina-

---

[25] Rasmussen, Tunnicliff and Brattain, THIS JOURNAL, **71**, 1068 (1949); Rasmussen and Brattain, *ibid.*, **71**, 1073 (1949).

[26] Blaise and Luttringer, *Bull. soc. chim.*, [3] **33**, 760 (1905).

[27] Ingold and Perren, *J. Chem. Soc.*, **119**, 1582 (1921).

tion for the ester, $C_{24}H_{24}O_8$, gave 15.31. Theory requires 15.20.

The ethyl ester was obtained on concentrating the ethanolic solution used to recrystallize the keto-acid. After recrystallization from chloroform, it had m.p. 133–134°. The Zeisel determination gave, for $C_{26}H_{28}O_8$, 20.71. Theory requires 20.64. Hydrolysis of the ester with aqueous ethanolic sodium hydroxide regenerated the keto-acid, m.p. 228–230°.

Ethyl Acetylenedicarboxylate.—Ruhemann and Beddow[28] report that this ester may be prepared in very high yield by direct esterification of acetylenedicarboxylic acid with ethanol and hydrogen chloride. Repetition of their procedure, however, furnished a product whose analysis and physical constants accorded very closely with those of ethyl chlorofumarate. Our product contained 15.95% Cl, had b.p. 96–100° at 6.0 mm., $n^{25}\mathrm{D}$ 1.4600. Ethyl chlorofumarate[29] has b.p. 119° at 12 mm., $n^{24}\mathrm{D}$ 1.4598, and contains 17.16% Cl. Clearly the main product from the above esterification was ethyl chlorofumarate.

The acetylenic ester was prepared in 65% yield by an adaptation of the azeotropic distillation method of Mitchovitch.[30] It had b.p. 106–107° at 12–13 mm.

Ethyl 1,1,2,2,3,4-Cyclobutanehexacarboxylate.—The method of Shibata[18] furnished this ester in about 5% yield. The method was very tedious, requiring manual separation of the hexaester from starting material and by-products. For the preparation of the cyclic ester in quantity, the following method was devised. Under anhydrous conditions and with stirring, a mixture of 34 g. (0.2 mole) of ethyl acetylenedicarboxylate, 66 g. (0.2 mole) of ethyl 1,1,2,2-ethanetetracarboxylate,[31] and 10 ml. of absolute ethanol was warmed to 45° to effect a clear solution. One and five-tenths grams (0.065 atom) of sodium dissolved in 24 ml. of absolute ethanol was added dropwise, with rapid stirring. After the addition of about 10 drops of the ethoxide solution, the internal temperature of the reaction mixture suddenly rose to 92° and then slowly subsided as the rest of the catalyst was added. As the temperature rose, the color of the solution changed to greenish-yellow and then to dark brown. The reaction mixture was poured into 100 ml. of 3 *N* hydrochloric acid and exhaustively extracted with ether. Evaporation of the ether left a mixture of solid and oil. The solid was collected and recrystallized from 80% ethanol. The deposition of crystals (typical square tablets) was slow. After one day, 28.5 g. of the hexaester, m.p. 78°, was obtained. A second crop (16 g.) was obtained four days later. The residual oil yielded about 4 g. of solid which was recrystallized. The total yield was about 48%. On slow recrystallization (two to four weeks), massive tablets, some with edges measuring 2 cm., were obtained, m.p. 78°.

Anal. Calcd. for $C_{22}H_{32}O_{12}$: C, 54.10; H, 6.56. Found: C, 54.07; H, 6.77.

Mixed m.p. determinations with material prepared by the method of Shibata (78°) showed no depression. With both ethyl ethanetetracarboxylate and ethyl ethylenetetracarboxylate mixed m.p. determinations showed considerable depression. In accord with the observation of Shibata, basic solutions rapidly attacked the ester, forming bubbles on the surface of the compound.

1,2,3,4-Cyclobutanetetracarboxylic Acid.—The hydrolysis of the cylic hexaester was carried out using 10 ml. of concentrated hydrochloric acid for each gram of ester. The mixture was refluxed until a clear solution resulted (about three days). Evaporation of the hydrolysis solution left a yellow oil which was dissolved in the minimum amount of concentrated hydrochloric acid. White amorphous acidic material slowly deposited, m.p. 204–210° (dec.). This material was immediately attacked by permanganate solution. After several slow recrystallizations from water pure compound was obtained in the form of a white microcrystalline powder. When heated at the rate of 2° per minute, the m.p. was 226–228° (dec.), but heating at the rate of one degree per three minutes caused the substance to melt at 216–217° (dec.). The product was stable to dilute permanganate solution for five to six hours. The yield of product was about 15%.

Anal. Calcd. for $C_8H_8O_8$: C, 41.38; H, 3.45; neut. equiv., 58. Found: C, 41.48; H, 3.56; neut. equiv. 59.2.

During the m.p. determinations a sublimate was observed to form above the decomposing sample. The identity of this sublimate, m.p. 75–85°, is unknown.

Baltimore 18, Maryland Received July 7, 1950

---

(28) Ruhemann and Beddow, *J. Chem. Soc.*, **77**, 1121 (1900).

(29) Auwers and Harries, *Ber.*, **62**, 1678 (1929); Gladstone, *J. Chem. Soc.*, **59**, 290 (1891); Perkin, *ibid.*, **53**, 695 (1888).

(30) Mitchovitch, *Bull. soc. chim.*, [5] **4**, 1661 (1937).

(31) Bischoff and Rach, *Ber.*, **17**, 2781 (1884).

[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

Ketene Acetals. XXIV. The Preparation and Properties of Ketene Divinylacetal and Related Compounds

By S. M. McElvain and A. N. Bolstad

Ketene divinylacetal (IV) has been prepared by a stepwise dehydrochlorination of chloroacetaldehyde di-(β-chloroethyl)-acetal (I). The first dehydrochlorinations occur at the β-chloroethyl groups to yield the vinyl β-chloroethyl- and divinylacetals of chloroacetaldehyde (II) and III). While relatively stable to water and alcohols in the absence of acid, IV reacts vigorously with both in the presence of a trace of acid. IV is quite resistant to ionic polymerization, and to alkylation with benzyl bromide. At −70° IV reacts with hydrogen chloride to yield a stable addition product, $CH_3C(OCH{=}CH_2)_2Cl$ (VIII), the properties of which lead to the conclusion that a similar structure reported recently by Vogel and Schinz (ref. 4) is erroneous. With ethylene chlorohydrin, IV yields an orthoester that undergoes dehydrochlorination to trivinyl orthoacetate (VII). The relationships of the structures to the boiling points of this orthoester, ketene divinylacetal (IV), and their more saturated analogs is discussed.

In paper XV of this series the preparation and properties of ketene diphenylacetal were described.[1] The lower anioniod reactivity of this compound at the methylene carbon, as compared to that of ketene diethylacetal, was ascribed to a loss in the activating effect of the oxygens of the former compound through their polarization into the phenyl groups. To further extend the study of the effect of unsaturated groups attached to the acetal oxygens the preparation of ketene divinylacetal was undertaken.

Ketene divinylacetal (IV) was prepared by the step-wise dehydrochlorination of chloroacetaldehyde di-(β-chloroethyl)-acetal (I). The initial dehydrochlorinations, which were carried out in *t*-butyl alcohol solution with potassium *t*-butoxide, occur at the β-chloroethyl groups; the two intermediate vinylacetals (II and III) were separated and characterized by analyses and by the amount of acetaldehyde liberated when each was refluxed

---

(1) S. M. McElvain and B. Fajardo-Pinzon, This Journal, **67**, 650 (1945).