Reactions of the Trichloromethyl Anion. Synthesis and Reactions of Dichloroprotoanemonin

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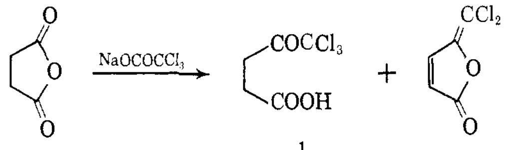
Abstract: Reaction of sodium trichloroacetate with succinic anhydride gives both 5,5,5-trichlorolevulinic acid (**1**) and 5,5-dichloro-4-hydroxy-2,4-pentadienoic acid lactone (**2**) (dichloroprotoanemonin). Direct conversion of **1** to **2** is effected by concentrated sulfuric acid. Possible mechanisms for these conversions are suggested. The unsaturated lactone **2** undergoes the Diels Alder reaction with anthracene and tetraphenylcyclopentadienone. On treatment of lactone **2** with acidified methanol, the ring is opened and the methyl ester of the dichloroketo acid is formed. Bromination of **2** gives a dibromide, which, from the nmr lines at τ 4.80 and 5.32 (singlets), is identified as the *trans*-addition product of bromine to the ring double bond. The infrared and nmr spectra for all of the compounds are discussed and interpreted in relation to the structural assignments.

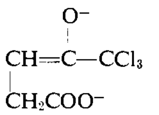
Recently we reported the trichloromethylation of anhydrides through reaction with sodium trichloroacetate.[1] We now wish to report that, in the case of succinic anhydride, in addition to the normal product, 5,5,5-trichlorolevulinic acid (**1**), an interesting side product, is also formed. This compound, isolated in 7–8% yield after purification, has been identified as 5,5-dichloro-4-hydroxy-2,4-pentadienoic acid lactone (**2**) (dichloroprotoanemonin).



1 2

The following evidence is consistent with the structural assignment of the lactone **2**. The compound readily sublimes under reduced pressure to give a white, crystalline solid. The two nonequivalent alkenic protons are clearly indicated by sharp infrared bands at 3020, 3060, and 3090 cm^{-1} (KBr) and by nmr doublets (CCl_4) in 1:1 ratio at τ 2.27 and 3.68 (J_{AB} = 8 cps). The lactone carbonyl absorbs in the infrared at 1770 cm^{-1} (KBr). The three double bond conjugated system is revealed by the intense ultraviolet maximum (ethanol) at 297 mμ (ϵ 21,000). The lactone **2** is a powerful vesicant and should be handled with extreme caution. This property is characteristic of this type of structure and is exhibited by the parent unchlorinated analog, protoanemonin, found in buttercups and other members of the *Ranunculus* species.[2]

The action of sodium trichloroacetate on succinic anhydride to form lactone **2** is a novel synthetic approach to the conjugated unsaturated lactone structure, and is another demonstration of the usefulness of the trichloromethyl anion in the synthesis of perchlorinated compounds. The mechanism of formation of lactone **2** from succinic anhydride is still somewhat obscure, but it is thought that the initial reaction is with the primary product, 5,5,5-trichlorolevulinic acid salt, through abstraction of the active proton by the trichloromethyl anion[3] to give the enol anion **3**. Further reactions, including one involving a 1,4-conjugate elimination of hydrogen chloride, could give rise to the final structure **2**. Several attempts were made to convert the salt of 5,5,5-trichlorolevulinic acid directly to the lactone **2** by the action of sodium trichloroacetate in hot DME, but, although some sort of reaction occurred, as evidenced by the change to the normal black color, none of the lactone **2** could be detected in the extract by vpc. This may indicate that the mechanism involves a participation by the parent anhydride, perhaps through a displacement by one of the enol anions **3** or **4**. Such a step could aid in the displacement of the oxygen by the carboxylate anion to form the lactone.



$$\begin{array}{l} \quad\;\; \mathrm{O^-} \\ \quad\;\; | \\ \mathrm{CH{=}C{-}CCl_3} \\ | \\ \mathrm{CH_2COO^-} \end{array}$$

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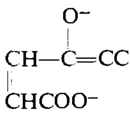
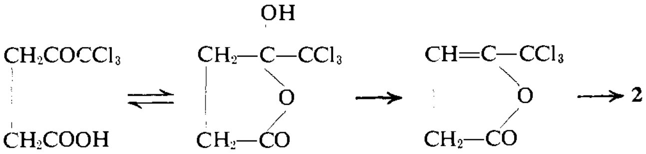


$$\begin{array}{l} \quad\;\; \mathrm{O^-} \\ \quad\;\; | \\ \mathrm{CH{-}C{=}CCl_2} \\ | \\ \mathrm{CHCOO^-} \end{array}$$

4

Conversion of 5,5,5-trichlorolevulinic acid directly to the lactone **2** is possible by the action of cold concentrated sulfuric acid over a period of several days. The mechanism for this conversion must be quite different from the preceding and possibly involves an initial dehydration of the hydroxy lactone tautomer of **1** to give **5**, which then undergoes a 1,4-conjugate elimination of hydrogen chloride to give the product **2**.



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The details of both of these mechanism are currently being explored.

As a dienophile in the Diels–Alder reaction, lactone **2** is of somewhat lower reactivity than maleic anhydride and failed to add either cyclopentadiene or furan. Refluxing lactone **2** with anthracene in xylene was successful in forming the anthracene adduct **6**. The lactone carbonyl group was evident by the infrared peak at 1810 cm^{-1} (Nujol). The nmr spectrum ($DCCl_3$)

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[1] A. Winston, J. P. M. Bederka, W. G. Isner, P. C. Juliano, and J. C. Sharp, *J. Org. Chem.*, **30**, 2784 (1965).

[2] M. Bergmann, *Ber. Schweiz. Botan. Ges.*, **54**, 339 (1944); *Chem. Abstr.*, **41**, 2463 (1947).

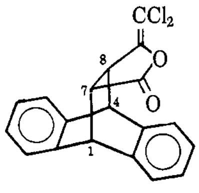
[3] W. M. Wagner, H. Kloosterziel, and A. F. Bickel, *Rec. Trav. Chim.*, **81**, 933 (1962).

was in good agreement with the extensive data reported on the dibenzobicyclo[2.2.2]octadiene system[4] and is consistent with structure **6**. The following assignments were made: multiplet at τ 2.7, aromatic hydrogen; doublet at 5.06 ($J_{4,8}$ = 2.6 cps), C-4 hydrogen; doublet at 5.27 ($J_{1,7}$ = 3.5 cps), C-1 hydrogen; quartet at 6.43 ($J_{7,8}$ = 10 cps, $J_{4,8}$ = 2.7 cps), C-8 hydrogen; quartet at 6.65 ($J_{7,8}$ = 10 cps, $J_{1,7}$ = 3.4 cps), C-7 hydrogen. In this case, as well as in the others reported here, the lower field lines of each set are assigned to the protons nearer the dichloromethylene groups which would be deshielded to a greater extent than the ones nearer the carbonyl.

With tetraphenylcyclopentadienone in refluxing bromobenzene, the product was the cyclohexadiene derivative **7**, formed by loss of carbon monoxide from the Diels–Alder adduct. The infrared peak for the lactone carbonyl appeared at 1820 cm^{-1} (Nujol). The nmr spectrum (DMF) had a multiplet at τ 3.0 for the aromatic protons and two doublets at 4.91 and 5.32 (J_{AB} = 9 cps) for the two aliphatic protons.

Treatment of the lactone **2** with methanol and acid afforded an oily methanolysis product. Infrared bands (neat) at 3080 (alkene hydrogen), 1775 (ketone carbonyl), and 1730 cm^{-1} (ester carbonyl) indicated that the compound was the open chain keto ester **8** and not the cyclic pseudo ester. The nmr spectrum confirms the structural assignment. The alkene hydrogens appeared as doublets at τ 2.69 and 3.55 (J_{AB} = 5.75 cps). Singlets appeared at τ 4.13 for the dichloromethyl proton and at 6.67 for the methyl ester.

Bromination of lactone **1** in carbon tetrachloride or acetic acid proceeded slowly to give a crystalline dibromide. The two nmr lines ($DCCl_3$), appearing at τ 4.80 and 5.32 (singlets), can only be interpreted as indicating a *trans* addition of bromine to the ring double bond to give lactone **9**. The chemical shifts are of the same magnitude as that of *trans*-dibromosuccinic anhydride, which has a singlet at τ 5.13 ($DCCl_3$). The lack of line splitting from the two vicinal protons can reasonably be attributed to a distortion of the ring by the mutual repulsion of *trans* bromine atoms to provide an angle between the hydrogens close to 90°, where the coupling constants approach zero. This is one of the few examples where the coupling of nonidentical protons on adjacent carbon atoms is not resolved. The additional strain is indicated by an infrared absorption for the lactone carbonyl group at 1840 cm^{-1} (KBr), one of the highest values observed for a γ-lactone. A single, sharp infrared peak at 3020 cm^{-1} (KBr), although somewhat high for an alkane C–H, is consistent with the shift expected from halogen substitution and the ring strain.



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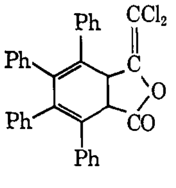

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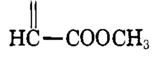
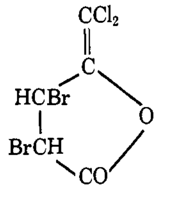


$$\begin{array}{l} HC\text{—}COCHCl_2 \\ \| \\ HC\text{—}COOCH_3 \end{array}$$

8



9

Lactone **1** readily undergoes free-radical copolymerization[5] with methyl methacrylate, methyl acrylate, vinyl acetate, vinylidine chloride, acrylonitrile, and styrene. Its reactivity as a monomer and the structure of the polymers are under current investigation. As an antibiotic, lactone **2** strongly inhibits growth of *Bacillus subtilis*, *Escherichia coli*, and *Staphylococcus aureus*.

Experimental Section

Melting points and boiling points are uncorrected. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. The ultraviolet spectrum was determined on a Beckman DU spectrophotometer. The infrared spectra were determined on Perkin-Elmer Models 137 and 137-G spectrophotometers. The nuclear magnetic resonance spectra were recorded on the HA-60, Varian Associates high-resolution spectrometer using tetramethylsilane as the internal standard.

5,5-Dichloro-4-hydroxy-2,4-pentadienoic Acid Lactone (2). Procedure A. A mixture of 100 g (1 mole) of succinic anhydride and 185.5 g (1 mole) of dry sodium trichloroacetate in 500 ml of anhydrous dimethoxyethane (DME) was stirred at room temperature for 10 hr. An additional 92.5 g (0.5 mole) of sodium trichloroacetate was added and the mixture was stirred for an additional 19 hr. The black reaction mixture was filtered, and the solid was washed several times with anhydrous ethyl ether. The DME filtrate and ether washings were combined and evaporated to give a thick, black oil. Sublimation of the oil at 70° (2 mm) gave 11.2 g (6.8%) of white crystals, mp 95.5°.

Anal. Calcd for $C_5H_2Cl_2O_2$: C, 36.38; H, 1.22; Cl, 42.99. Found: C, 36.57; H, 1.26; Cl, 43.29.

The dried solid from the reaction mixture was dissolved in water and acidified. A tan solid separated, which, upon recrystallization from benzene–hexane, afforded 35 g of white crystals of 5,5,5-trichlorolevulinic acid (**1**), mp 76.5–77.5° (lit.[1] mp 78–79.5°). An additional 8.5 g of the acid (total yield 20%) was obtained by further sublimation of the residue from the DME–ether extracts at 100° (2 mm).

Procedure B. A solution of 3.5 g (0.0016 mole) of 5,5,5-trichlorolevulinic acid (**1**) in 350 ml of 100% sulfuric acid was allowed to stand at room temperature for 14 days, and was then poured over ice. The acidity of the aqueous solution was adjusted to pH 4 with 25% sodium hydroxide. The solution (about 2 l.) was then extracted with ethyl ether, and the extracts were dried over magnesium sulfate. Evaporation of the ether gave an oily solid which on sublimation afforded 1.2 g (0.0073 mole, 45.5%) of lactone **2** and 1.85 g (53%) of unreacted acid **1**.

Diels–Alder Adduct 6 of Lactone 2 and Anthracene. A solution of 3.30 g (0.02 mole) of lactone **2** and 3.56 g (0.02 mole) of anthracene in 30 ml of anhydrous xylene was stirred and heated under reflux for 6 days. Addition of 10 ml of hexane and cooling caused a yellow solid to precipitate. Partial sublimation gave 0.45 g of anthracene. The residue was recrystallized from benzene to give 4.7 g (68.5%) of 9,10-dihydro-9,10-ethanoanthracene-11-carboxylic acid-12-(2,2-dichloro-1-hydroxyvinyl) γ-lactone (**6**), mp 205°.

Anal. Calcd for $C_{19}H_{12}Cl_2O_2$: C, 66.45; H, 3.53; Cl, 20.70. Found: C, 66.28; H, 3.58; Cl, 20.50.

Diels–Alder Adduct 7 of Lactone 2 and Tetraphenylcyclopentadienone. A solution of 3.30 g (0.02 mole) of lactone **2** and 7.68 g (0.02 mole) of tetraphenylcyclopentadienone in 50 ml of anhydrous xylene was stirred and heated under reflux for 7 days. On cooling, a mixture of a white solid and purple crystals separated. Several recrystallizations of the mixture from chloroform, followed by sublimation, gave 7.3 g (70%) of the white crystalline solid 2,3,4,5-tetraphenyl-2,4-cyclohexadiene-1-carboxylic acid-6-(2,2-dichloro-1-hydroxyvinyl) γ-lactone (**7**), mp 298.5°.

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(4) S. J. Cristol, T. W. Russell, J. R. Mohrig, and D. E. Plorde, *J. Org. Chem.*, 31, 581 (1966).

(5) A. Winston and G. T. C. Li, International Symposium on Macromolecular Chemistry, Prague, Czechoslovakia, Aug 30–Sept 4, 1965, Preprint P-95; *J. Polymer Sci.*, in press.

Anal. Calcd for $C_{33}H_{22}Cl_2O_2$: C, 75.85; H, 4.30; Cl, 13.46. Found: C, 75.88; H, 4.29; Cl, 13.53.

Methanolysis of Lactone 2. A solution of 1.65 g (0.01 mole) of lactone **2** and 0.5 ml of concentrated sulfuric acid in 100 ml of methanol was refluxed for 40 hr. The solution was concentrated to 25 ml, neutralized with sodium bicarbonate, and extracted with ethyl ether. The ether extract was decolorized, dried over magnesium sulfate, and evaporated to give about 2 ml of a light yellow oil. Vaccuum distillation afforded about 1 ml of methyl 5,5-dichloro-4-oxo-2-pentenoate (**8**), bp 100° (1.5 mm).

Anal. Calcd for $C_6H_6Cl_2O_3$: C, 36.54; H, 3.07; Cl, 36.05. Found: C, 36.45; H, 3.34; Cl, 36.18.

Bromination of Lactone 2. A solution of 0.825 g (0.005 mole) of lactone **2** and 0.275 ml (0.005 mole) of bromine in 30 ml of anhydrous carbon tetrachloride was stirred and refluxed for 3 days. The solvent was evaporated and the oily residue was sublimed to give 1.22 g (75%) of white crystals of the *trans*-2,3-dibromo-5,5-dichloro-4-hydroxy-4-pentenoic acid γ-lactone (**9**), mp 59°.

Anal. Calcd for $C_5H_2Br_2Cl_2O_2$: C, 18.48; H, 0.64; Br, 49.18; Cl, 21.88. Found: C, 18.67; H, 0.53; Br, 48.99; Cl, 21.53.

Acknowledgment. The authors are indebted to Dr. Willaim J. Pace and Dr. Melvin L. Farmer of the Union Carbide Corp., Charleston, W. Va., and to Mr. Robert Smith for recording the nmr spectra, to Dr. Robert G. Burrell of the Department of Microbiology, West Virginia University, for the biological testing, and to Mr. Ray Wilkins, undergraduate chemistry major, for some purifications. Partial support by the West Virginia University Cancer Research Committee and the American Cancer Society is greatly appreciated.

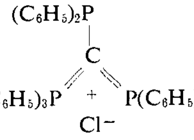
Mesomeric Phosphonium Dications

Gail H. Birum and Clifford N. Matthews

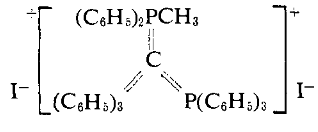
Contribution from the Monsanto Company Central Research Department,
St. Louis, Missouri 63166. Received May 26, 1966

Abstract: Mesomeric phosphonium monocation salts, $(C_6H_5)_2PC[P(C_6H_5)_3]_2{}^{+}X^{-}$ (**1**), and dication salts, $\{R(C_6H_5)_2PC[P(C_6H_5)_3]_2\}^{2+}2X^{-}$ (**2**), in which three phosphorus atoms are bonded to a single carbon atom have been synthesized. An unusual possibility of delocalization of two positive charges over three pentavalent phosphorus centers exists in **2**. Support for such charge distribution was provided by nmr measurements and by absence of evidence of formation of triphosphonium salts when various derivatives of **2** were treated with strong acids. Reactions accomplished at the trivalent phosphorus atom of **1** include addition of active halogen compounds, complexing with heavy metal salts, oxidation, and thiolation. An unusual case of spin coupling of phosphorus and hydrogen through intervening carbon and phosphorus atoms was observed in nmr studies on a solution of **2** (R = H) in trifluoroacetic acid.

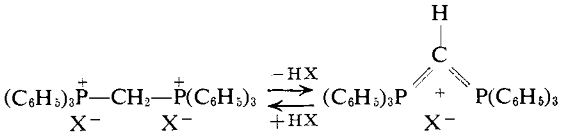
As part of an investigation of mesomeric phosphonium chemistry we have synthesized compounds in which three phosphorus atoms are bonded to a single carbon atom. The prototypes of these mesomeric compounds are the monocation salt **1a** and the dication salt **2a**. The monocation of **1a** is structurally related to the mesomeric cation of the known [(triphenylphosphoranylidene)methyl]triphenylphosphonium salts **4**[1-3] derived from diphosphonium salts **3**. The dication of **2a** has an unusual structure in which two positive charges can be delocalized over three pentavalent phosphorus centers.



1a



2a



3 **4**

The essential precursor for the synthesis of these mesomeric salts is hexaphenylcarbodiphosphorane **5** which is prepared by the dehydrobromination of **4** (X = Br).[1-3] Reaction of **5** with chlorodiphenylphosphine yielded **1a**,[4] which was converted to the diiodide **2a** by treatment with excess methyl iodide.[5] Other

$$\underset{\mathbf{5}}{(C_6H_5)_3P{=}C{=}P(C_6H_5)_3} + (C_6H_5)_2PCl \longrightarrow \mathbf{1a}$$

$$\mathbf{1a} + 2CH_3I \longrightarrow \mathbf{2a} + CH_3Cl$$

salts[6] such as **1b–e** (see Table I) and **2b–e** (see Table II) were obtained from **1a** and **2a**, respectively, by metathesis.

Evidence for structure **1** is provided by elemental analyses (Table I) and nmr spectra of several representative salts. Proton nmr spectra of **1a** contain two complex multiplets, centered at about −7.5 and −7.2 ppm in a 3:1 area ratio, characteristic of aryl protons.

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(1) F. Ramirez, N. B. Desai, B. Hansen, and N. McKelvie, *J. Am. Chem. Soc.*, **83**, 3539 (1961).

(2) C. N. Matthews, J. S. Driscoll, J. E. Harris, and R. J. Wineman, *ibid.*, **84**, 4349 (1962).

(3) J. S. Driscoll, D. W. Grisley, Jr., J. E. Pustinger, J. E. Harris, and C. N. Matthews, *J. Org. Chem.*, **29**, 2427 (1964).

(4) D. Seyferth and K. A. Brändle, *J. Am. Chem. Soc.*, **83**, 2056 (1961), have reported that bromodiphenylphosphine reacts with triphenylphosphinemethylene to produce diphenylphosphinemethyltriphenylphosphonium bromide.

(5) We have found that phosphonium chlorides and bromides are readily converted by methyl iodide to the corresponding iodides.

(6) A convenient systematic way of naming these and related compounds is to regard them as derivatives of **4**, *i.e.*, as substituted [(triphenylphosphoranylidene)methyl]triphenylphosphonium salts, so that **1a** is [(diphenylphosphino)(triphenylphosphoranylidene)methyl]triphenylphosphonium chloride, and **2a** is (diphenylmethylphosphoranylidene)methylenebis(triphenylphosphonium iodide).