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Reaction of Trichloromethyl Keto Acids and Lactols in Sulfuric Acid[1]

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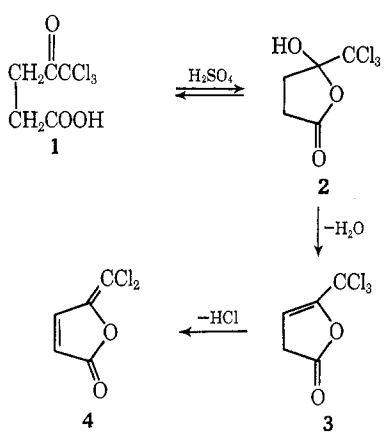
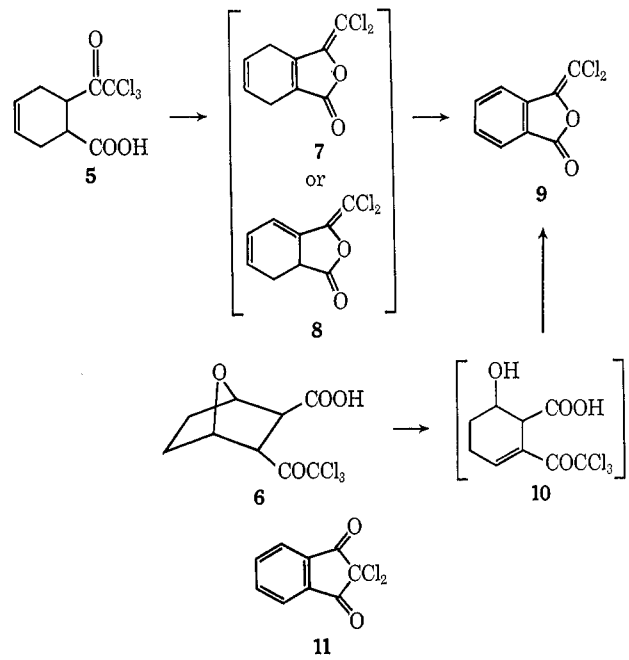
Earlier we suggested that the conversion of 5,5,5-trichlorolevulinic acid (**1**) to 5,5-dichloro-4-hydroxy-2,4-pentadienoic acid lactone (5,5-dichloroprotoanemonin) (**4**) in concentrated sulfuric acid proceeded by way of an initial cyclization to the lactol tautomer **2** followed in turn by a dehydration to **3** and a 1,4-conjugate elimination of hydrogen chloride to give **4** (Scheme I).[3]

SCHEME I



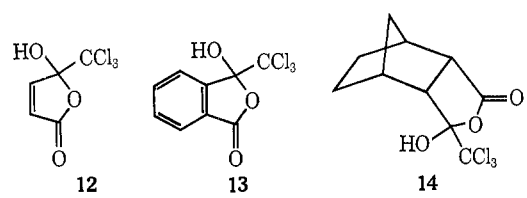
Although under normal conditions the open chain structure **1** is favored over the cyclic structure **2**,[4] protonation of the trichloroacetyl carbonyl group in the acid media would promote cyclization. To provide additional insight as to the course of this reaction and, at the same time, to explore the possibility of using this means as a general method for synthesizing halogen derivatives of protoanemonin, reactions of a variety of trichloromethyl keto acids or their cyclic lactol tautomers with concentrated sulfuric acid were examined.

Reaction of keto acid **5** was expected to give lactone **7** or **8**, but the evidence is clear that the aromatic structure **9** is formed. The analytical data reveal only four protons. The complex unsymmetrical multiplet centered at τ 2.2 in the nmr spectrum is consistent with an ABCD pattern of a unsymmetrical ortho disubstituted benzene. Infrared bands at 1795 (lactone C=O) and 1650 cm^{-1} (C=CCl$_2$) commonly occur in the spectra of protoanemonin derivatives.[3,5] As an alternate possibility, 2,2-dichloro-1,3-indandione (**11**), first reported by Zincke[6] in 1888, not only has a melting point of 124–125°, some 18° higher than ours, but is clearly inconsistent with the spectral data.



Reaction of *trans*-keto acid **6** also gave the aromatic dichloroprotoanemonin analog **9**, probably through an initial ring opening to keto acid **10**. Dehydration of **10** would bring the carbonyl and trichloroacetyl groups into coplanarity, which would favor cyclization to the lactol tautomer. A second dehydration and a dehydrohalogenation would lead to product **9**.

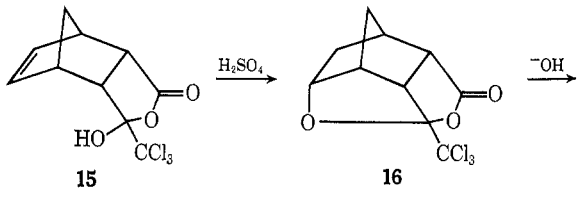
Lactols **12**, **13**, and **14** failed to react with concentrated sulfuric acid at room temperature even after prolonged reaction times and only starting materials were isolated. In accordance with the suggested mechanism (Scheme I), the failure of lactols **12** and **13** to react is consistent with the lack of appropriately placed hydrogens to provide for the dehydration and dehydrohalogenation steps. However, the stability of lactol **14** under these conditions must be due to other causes, since the required hydrogens are indeed present. We suggest that this stability is a direct result of the considerable strain energy involved in the ring distortion which would accompany a dehydration.



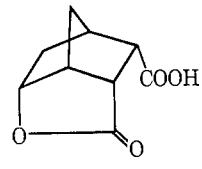
Unsaturated bicyclic lactol **15** failed to react normally with sulfuric acid to give an analog of dichloroprotoanemonin. However, a reaction did occur to give tetracyclic lactone **16**, the structure of which was consistent with the analytical data, spectral data, and

(1) From the Ph.D. dissertations of J. C. Sharp (1966) and R. F. Bargiband (1970).
(2) NASA Trainee, 1967–1970.
(3) A. Winston and J. C. Sharp, *J. Amer. Chem. Soc.*, **88**, 4196 (1966).
(4) A. Winston, J. P. M. Bederka, W. G. Isner, P. C. Juliano, and J. C. Sharp, *J. Org. Chem.*, **30**, 2784 (1965).
(5) A. Winston and R. N. Kemper, *Tetrahedron*, **27**, 543 (1971).
(6) T. Zincke, *Ber.*, **21**, 491 (1888).

the failure of the compound to react with bromine or to undergo catalytic hydrogenation. Confirmation of the structure was obtained by converting **16** to the known acid lactone **17**[7] by aqueous base.



15 **16**



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Although it has long been felt that for structure **15** the smaller hydroxyl rather than the trichloromethyl group would be directed under the bicyclic ring as shown, the ease of cyclization of **15** and **16** confirms the close proximity of the hydroxyl to the ring double bond.

The reaction of **15** with sulfuric acid is striking in that the solution takes on a beautiful deep blue color (see Experimental Section for details). This effect is not observed for any of the other compounds, even the closely related compound **14**, nor is color produced on dissolution of the product **16** in sulfuric acid. The origin of the blue color has not been confirmed, but initial results indicate that this effect is not really associated with the primary sequence of **15** and **16**. Inhibition of color formation by addition of small amounts of sodium azide as well as the appearance of an esr signal suggests that a radical is involved.

The results of this study support the proposed mechanism outlined in Scheme I for the conversion of trichloromethyl keto acids and lactols to 5,5-dichloroprotoanemonin analogs and are consistent with the requirements for hydrogen at C-2 and C-3. The synthetic utility of the reaction is, however, limited by unfavorable steric strain and competing side reactions inherent in concentrated sulfuric acid.

Experimental Section

The trichloromethyl keto acids and lactols were prepared as described in previous communications.[4,8] The 100% sulfuric acid was prepared by mixing appropriate amounts of 96.86% acid with fuming sulfuric acid. Melting points are uncorrected. Analyses were carried out by Galbraith Laboratories, Knoxville, Tenn. The ir and nmr spectra were obtained using Perkin-Elmer Model 137 and Varian Associates HA-60 instruments, respectively. Protoanemonin and 5,5-dichloroprotoanemonin are powerful vesicants and handling compounds of this type should be carried out with considerable care.[3]

General Procedure for Sulfuric Acid Reactions.—The trichloromethyl lactol or keto acid was dissolved in 100% sulfuric acid at room temperature and allowed to stand with intermittant stirring. The solution was poured over ice and the products were isolated by filtration or extraction into ether. The solid products were purified by crystallization or sublimation and characterized. The experimental details, the products isolated, and the yields of purified products are reported in Table I.

(7) H. Koch, J. Kotlan, and H. Markut, *Monatsh. Chem.*, **96**, 1646 (1965).
(8) A. Winston, J. C. Sharp, K. E. Atkins, and D. E. Battin, *J. Org. Chem.*, **32**, 2166 (1967).

TABLE I
REACTION OF LACTOLS AND KETO ACIDS WITH CONCENTRATED SULFURIC ACID

Reactant	Wt, g	Reaction time, days	Compd isolated	Wt, g	Yield, %
5	0.10	9	**9**	0.06	70
6	0.20	2	**9**	0.10	70
12	0.30	17	**12**	0.05	17
13	0.30	34	**13**	0.27	90
14	0.30	7	**14**	Trace	
15	20.0	1 hr	**16**	14.8	74

2-(2,2-Dichloro-1-hydroxyvinyl)benzoic Acid Lactone (9).—Reaction of either *cis*-2-trichloroacetyl-4-cyclohexenecarboxylic acid (**5**) or *endo*-3-trichloroacetyl-7-oxabicyclo[2.2.1]heptane-*exo*-2-carboxylic acid (**6**) with concentrated sulfuric acid produced identical products as shown by comparison of their ir and nmr spectra. The solid was purified by sublimation to give white crystals of **9**: mp 107°; ir (Nujol) 1795 (C=O) and 1650 cm^{-1} (C=CCl_2);[5] nmr ($CDCl_3$) τ 2.2 unsymmetrical multiplet (arom H).

Anal. Calcd for $C_9H_4Cl_2O_2$: C, 50.20; H, 1.86; Cl, 33.00. Found: C, 50.06; H, 1.91; Cl, 32.83.

Reaction of 4,4-Dihydroxy-5,5,5-trichloro-2-pentenoic Acid Lactone (12), 3-Hydroxy-3-trichloromethylphthalide (13), and *endo-cis*-3-Trichloroacetylbicyclo[2.2.1]heptane-2-carboxylic Acid Lactol (14) with Sulfuric Acid.—The solids isolated were identified by their ir spectra as consisting entirely of the starting material.

5-Trichloromethyl-4,11-dioxatetracyclo[5.2.1.$1^{5,8}$.$0^{2,6}$]undecan-3-one (16).—Since this reaction was carried out somewhat differently from the others, a full description will be given. To 20.0 g (0.071 mol) of *endo-cis*-3-trichloroacetylbicyclo[2.2.1]-4-heptene-2-carboxylic acid lactol (**15**) was added 200 ml of concentrated sulfuric acid over a 15-min period with stirring. A very deep blue color appeared immediately, and the reaction was slightly exothermic. After all of the solid had dissolved, the flask was immersed in an ice–water bath and 600 ml of water was slowly added, whereupon a black solid was gradually formed. The solid was collected, washed well with water, and dried *in vacuo* at 60° for 4 hr, yielding 18.3 g of a black powder. Thin layer chromatography of the solid, using 100% ether, 70:30 ether–chloroform, or 60:40 ether–acetone as eluents showed only one migrating component. The solid was extracted with chloroform, the chloroform solution was treated with decolorizing charcoal, and the solvent was removed *in vacuo* at 50–60°, leaving a yellow oil, which rapidly crystallized upon cooling. Recrystallization from carbon tetrachloride–hexane gave 14.8 g (0.052 mol, 73.2%) of white crystals of lactone **16**, mp 149.5°, ir (KBr) 1795 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_9Cl_3O_3$: C, 42.36; H, 3.20; Cl, 37.52. Found: C, 42.50; H, 3.29; Cl, 37.29.

When this reaction was carried out in the presence of sodium azide, the same product, lactone **16**, was isolated but no blue color intermediate was observed. On dissolving lactone **16** in sulfuric acid, no blue color was observed nor was the blue color produced in any of the other sulfuric acid reactions. An esr spectrum of the blue sulfuric acid solution revealed a complex pattern centered at 3345 G and extending over a range of about 40 G. This signal faded after several days although the blue color remained essentially unaffected. When additional lactone **16** was added, the esr signal returned.

***endo-cis*-5-Hydroxybicyclo[2.2.1]heptane-2,3-decarboxylic Acid Lactone (17).**—A mixture of 7.0 g (35 mmol) of lactone **16** and 60 ml of 5% aqueous sodium hydroxide was heated under reflux for 4.5 hr. Acidification of the reaction mixture, evaporation of the water to dryness, and extraction of the resulting solid with ether yielded 5.46 g (30 mmol, 85%) of a tan solid. Sublimation afforded white crystals of **17**: mp 200–201° (lit.[7] mp 200–201°); ir (KBr) 1770 (lactone C=O) and 1692 cm^{-1} (acid C=O). The infrared spectrum was identical with that of an authentic sample of lactone acid **17** prepared by the method of Koch, *et al.*[7]

Registry No.—**5**, 2903-44-8; **6**, 28795-85-9; **9**, 28795-86-0; **15**, 28795-87-1; **16**, 28795-88-2.