arranged mixtures of (II). The weights of bromosultone obtained from 0.2-g. mixtures of (I) and (II) were as follows: 0% (I), very small amount of oil; 10% (I), small amount of oil; 20% (I), 0.10 g.; 30%, 0.12 g.; 40%, 0.13 g.; 50%, 0.14 g.; 60%, 0.16 g.; 70%, 0.19 g.; 80%, 0.21 g.; 90%, 0.22 g.; 100%, 0.235 g. (95% yield). The oil formed from (II) on treatment with potassium tribromide solution contaminates the bromosultone so that all samples from mixtures of the two salts are low melting. A mixture of sodium 2-hydroxy-3-phenyl-2-methylpropane-1-sulfonate with (I) did not alter the quantity or purity of bromosultone obtained from the latter. No solid bromosultone was obtained on addition of potassium tribromide solution to solutions of (II) (sodium salt) which were allowed to stand at room temperature with or without the addition of alkali (5% NaOH solution) or acid (10% HCl solution) for periods of from one to seven days. Heating at 100° caused as much as 70% rearrangement in twenty-four hours in acid or basic solution but no change in neutral solution. No rearrangement was observed after three hours at 100° in acid, basic or neutral solution.

Sodium 2-Hydroxy-3-phenyl-2-methylpropane-1-sulfonate.—3-Phenyl-2-methyl-2-hydroxy-1-bromopropane was prepared from 13 g. (0.1 mole) of 2-benzyl-1-propene according to the directions of Read and Reid.[30] The crude bromohydrin was added slowly to a saturated solution containing 12 g. (0.1 mole) of sodium sulfite in 10% sodium hydroxide. The mixture was stirred and heated on the steam-bath for forty-eight hours. Working up the reaction mixture gave 9 g. (0.035 mole) of organic sodium salt, which was extremely soluble in water and slightly soluble in alcohol (35% yield of crude salt). Separation from inorganic salts was difficult.

The S-benzylthiouronium salt was prepared and crystallized with difficulty from alcohol-water mixtures, m. p. 132.5–133°.

Anal. Calcd. for $C_{18}H_{24}O_4N_2S_2$: N, 7.07. Found: N, 6.66.

The *p*-toluidine salt crystallized from a solution containing 1 g. of hydroxysulfonate, 0.4 g. of *p*-toluidine, 1 ml. of concd. HCl and 5 ml. of water after five days, m. p. 148–149°.

Anal. Calcd. for $C_{17}H_{23}O_4NS$: neut. equiv., 337. Found: neut. equiv., 328.

Acknowledgment.—The authors wish to express their appreciation to Professors C. D. Hurd and R. H. Baker for reading and criticizing the manuscript.

Summary

1. Sulfonation of 2-benzyl-1-propene with dioxane sulfotrioxide gives about 50% of 3-phenyl-2-methyl-2-propene-1-sulfonic acid and 25% of 2-benzyl-2-propene-1-sulfonic acid. It is believed that the remaining 25% of the sulfur trioxide added to the double bond of the olefin to give β-benzyl-β-methylethionic anhydride, which would account for the presence of 12% of barium sulfate in the neutralization products.

2. A mechanism for the reaction of dioxane sulfotrioxide with olefins is proposed, which accounts for the presence of both unsaturated and hydroxy sulfonic acids in the neutralization products. The unsaturated sulfonic acids are believed to be formed by addition of a molecule of sulfur trioxide to the number one carbon of the olefin to give a dipolar intermediate, which stabilizes itself by transfer of a proton from one of the number three carbon atoms to an oxygen atom. Addition of a second molecule of sulfur trioxide to the intermediate accounts for the formation of alkyl ethionic anhydrides, which on hydrolysis give hydroxy sulfonic acids and sulfuric acid.

3. Details of the mechanism and the possibility of a cyclic structure for the intermediate are discussed.

(30) Read and Reid, *J. Chem. Soc.*, 1487 (1928).

EVANSTON, ILL. RECEIVED MARCH 7, 1945

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE VICK CHEMICAL COMPANY]

The Synthesis of a Clavacin Isomer and Related Compounds[1]

BY BRUNO PUETZER, CYRIL H. NIELD AND RICHARD H. BARRY

In November, 1943, Raistrick and co-workers[1a] described the isolation of a crystalline antibiotic from the culture filtrate of *Penicillium patulum Bainier* which they named patulin. This antibacterial substance was first isolated in an impure state by Wiesner[2] and Waksman, Horning and Spencer[3] from the culture media of *Aspergillus clavatus* and was named clavacin by Waksman. The identity of patulin with clavacin and antibiotic substances isolated from several other mold cultures has been established.[4] On the basis of studies on the chemical degradation of this compound, structure I was assigned[1] to it. The strongest evidence presented by Raistrick in favor of I, was the decomposition of patulin by dilute sulfuric acid to formic acid and in 10% yield to tetrahydro-γ-pyrone-carboxylic acid-2. The Bergel group[4b] state that the proposed formula I does not entirely agree with all the results of their studies on the chemistry of the compound. They also refer to the possibility of tautomerism between I and several isomeric structures (I, II, III and IV), and, on the basis of their results, they conclude that clavacin exists in solution chiefly in forms III and IV.

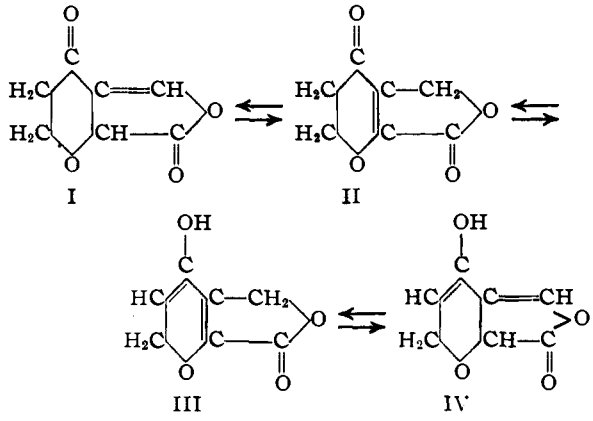
(1) A preliminary report on the subject matter of this paper was published in *Science*, March 23, 1945, 101, #2621, pp. 307–8, entitled "The Synthesis of a Clavacin Isomer" by Puetzer, Nield and Barry.

(1a) Raistrick, Birkinshaw, Bracken and Michael, *Lancet*, **2**, 625 (1943).

(2) Wiesner, *Nature*, **149**, 356 (1942).

(3) Waksman, Horning and Spencer, *Science*, **96**, 202 (1942).

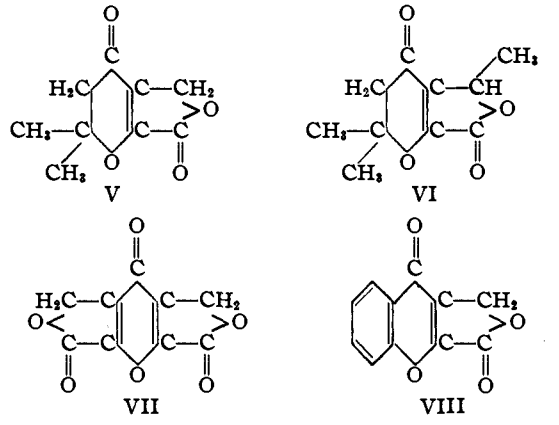
(4) (a) Bergel, Morrison, Moss, Klein, Rinderknecht and Ward, *Nature*, **152**, 750 (1943); (b) Bergel, Morrison, Moss and Rinderknecht, *J. Chem. Soc.*, 415 (1944); (c) Chain, Florey and Jennings, *Brit. J. Exp. Path.*, **23**, 202 (1942); (d) Chain, Florey and Jennings, *Lancet*, 1, 112 (1944); (e) Florey, Jennings and Philpot, *Nature*, **153**, 139 (1944); (f) Hooper, Anderson, Skell and Carter, *Science*, **99**, 16 (1944); (g) Anslow, Raistrick and Smith, *J. Soc. Chem. Ind.*, **162**, 236 (1943).



I II III IV

Prior to the appearance of the Bergel publication, the possibility of tautomerism between I and II occurred to us, and consequently we decided to investigate compounds of structure II.

We have synthesized II. This compound is not identical to clavacin and has only a slight bacteriostatic activity[5] up to dilutions of 1:2000. V, VI, VII and VIII were also prepared as representative derivatives of structure II. VII and VIII are not true derivatives of II, since they are in reality γ-pyrones, whereas II, V and VI are dihydro-γ-pyrones.



V VI VII VIII

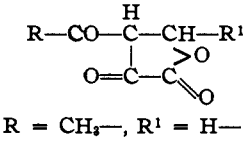
The general method of synthesis that was utilized involved condensation of an oxalic ester with the appropriate methyl ketone to yield a 2,4-diketo ester. This compound, in the form of its sodium enolate, was treated with the appropriate aldehyde to yield a α-keto-β-acyl-butyrolactone which was cyclized to the corresponding dihydropyrone.

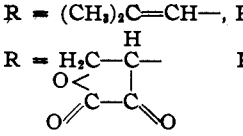
The reaction of 2,4-diketo esters with an aldehyde to form a α-keto-β-acyl-butyrolactone derivative was first reported by Claisen,[6] who prepared α-keto-β-acetyl-γ-phenyl-butyrolactone by heating ethyl acetopyruvate with benzaldehyde using piperidine as a catalyst. Similarly Meyer[7] prepared α-keto-β-(β,β-dimethylacryl)-γ-phenyl-butyrolactone from methyl 2,4-diketo-6-methyl-hepten-5-oate and benzaldehyde.

After our experimental work on these butyrolactone derivatives was finished a reference[8] to a paper[9] appeared in which experimental conditions similar to those which we have used for the α-keto-β-acyl-butyrolactones were described for the reaction of ethyl sodium oxalacetate with formaldehyde and acetaldehyde to give ethyl 3-keto-paraconate and ethyl 3-keto-5-methyl-paraconate, respectively.

We obtained a 90–93% yield of α-keto-β-acetyl-butyrolactone (IX) by treating ethyl sodium acetopyruvate with formaldehyde in aqueous solution. It was found that this reaction could be applied generally to acyl pyruvates for the preparation of α-keto-β-acyl-butyrolactones. The *p*H of the reaction mixture is important in this condensation. Thus, condensation does not occur at room temperature in acid solution, whereas the use of excess alkali effects the rapid hydrolysis of the 2,4-diketo esters. Aqueous or aqueous-alcoholic solutions of the sodium enolates of all the 2,4-diketo esters we have worked with were quite satisfactory for condensation with formaldehyde, which occurred rapidly even at 10°.

Condensation of methyl vinyl ketone with diethyl oxalate in the presence of sodium methylate was found to be complicated by addition of methanol across the double bond. The condensation of 3-ketobutyl methyl ether with dimethyl oxalate in the presence of sodium methylate was more satisfactory, although the yield of methyl β-methoxypropionyl-pyruvate was only 26.2%. The diketo ester reacted with formaldehyde in aqueous solution in the presence of one mole of sodium hydroxide to give α-keto-β-(β-methoxypropionyl)-butyrolactone (X). The same product was obtained directly by condensation of 3-ketobutyl methyl ether with diethyl oxalate in the presence of sodium methylate and treatment of the crude reaction product with formaldehyde. When X was heated in dioxane in the presence of sulfuric acid, methanol was eliminated and II was obtained.



IX R = CH_3—, R^1 = H—
X R = $CH_3OCH_2CH_2$—, R^1 = H—
XI R = $(CH_3)_2C{=}CH$—, R^1 = H—
XII R = $(CH_3)_2C{=}CH$—, R^1 = CH_3—
XIII R =  R^1 = H—
XIV R = *o*-$(HO)C_6H_4$—, R^1 = H—

(5) The activity was measured by a serial dilution method using *Staph. aureus* in an F. D. A. nutrient broth culture medium. V, VI, VII and VIII were also inactive in this test.

(6) Claisen, *Ber.*, **24**, 116 (1891).

(7) Meyer, *Ann.*, **398**, 58 (1913).

(8) *C. A.*, **38**, 4567[2] (1944).

(9) Gault and Durand, *Compt. rend.*, **216**, 848 (1943).

The sodium enolate of ethyl 2,4-diketo-6-methyl-hepten-5-oate, formed from mesityl oxide and diethyl oxalate, reacted with formaldehyde to give α-keto-β-(β,β-dimethylacryl)-butyrolactone (XI). This product could also be prepared by treatment of the butyl ester of 6,6-dimethyl-5,6-dihydro-γ-pyrone-carboxylic acid-2[10] with alcoholic sodium methylate and reaction of the sodium enolate of butyl 2,4-diketo-6-methyl-hepten-5-oate so obtained with formaldehyde. It had a bacteriostatic action on *Staph. aureus* in a dilution of 1:4000. The sodium enolate of ethyl 2,4-diketo-6-methyl-hepten-5-oate also reacted with acetaldehyde to yield XII. The isomerization of XI and XII to V and VI, respectively, was extremely facile. This cyclization could be brought about by heating with dilute aqueous alcoholic acids, heating in alcohol solution with piperidine as a catalyst, heating above the melting point, or in the case of XII at least, by heating in boiling water.

Condensation of disodium xanthochelidonic ester with aqueous formaldehyde gave 3,5-bis-hydroxymethyl-xanthochelidonic acid dilactone (XIII), a yellow solid which produced a deep jade-green color with ferric chloride solution. XIII was converted to VII by heating in a mixture of acetic and hydrochloric acids.

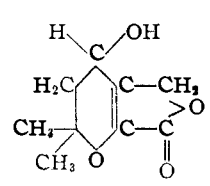
o-Hydroxyacetophenone was condensed with diethyl oxalate in the presence of sodium methylate to yield disodium-*o*-hydroxybenzoylpyruvic ester. This reacted with formaldehyde to yield XIV. Refluxing XIV in an acetic–hydrochloric acid mixture gave VIII.

The absorption spectrum of II is strikingly similar to that of clavacin.[11] It has a single maximum at 2760 Å., $E^{1\%}_{1cm}$ 604; V has the same type of curve with a maximum at 2800 Å., $E^{1\%}_{1cm}$ 497. The dihydropyrone derivatives showed no tendency to change to the isomeric structure represented by I. V distilled unchanged at 138°, 1 mm. The dihydropyrone derivatives, contrary to clavacin, are relatively stable to hot dilute mineral acids. Thus, when V was refluxed for six hours in 2 *N* sulfuric acid, 65% was recovered unchanged. V, when heated in aqueous solution at 230°, under pressure, underwent some decomposition, but a large part of it was recovered. V did not form an acetate when treated with acetic anhydride and sodium acetate in a manner similar to that used for clavacin (patulin).[1]

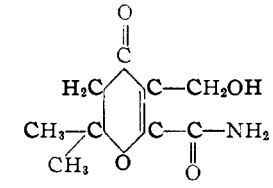
The dihydropyrone derivatives are sensitive to free alkali, an excess of which causes the pyrone ring to open. Thus, if II, V or VI are dissolved in aqueous alcohol and treated with excess sodium hydroxide at room temperature for a few seconds and the solution then acidified, it gives an intense red coloration with ferric chloride. This coloration is due to the presence of the isomeric butyrolactone derivatives. VII gives a greenish-red color under similar treatment. XIII gives a deep green color with ferric chloride but when subjected to the action of sodium hydroxide and then acidified, as above, it gives a greenish-red color with ferric chloride. The nature of this change has not been investigated. Opening of the pyrone ring in VIII requires gentle warming with aqueous-alcoholic sodium hydroxide.

The α-keto-β-acyl-butyrolactone derivatives are also unstable in the presence of free alkali. However, XI was readily prepared from V by treatment with 1 mole of alcoholic sodium methylate. Aqueous sodium carbonate and sodium bicarbonate can also be used for this conversion.

A possible method of conversion of compounds of structure II to that of structure I would involve reduction to a tetrahydropyrone derivative, bromination in the 3-position and removal of hydrogen bromide involving the hydrogen on the methylene carbon of the furan ring. In the case of V, reduction did not occur at room temperature and 50 pounds pressure. Reduction at 300 lb. pressure in the presence of either palladium–charcoal, platinum oxide, or Raney nickel catalyst proceeded to the unsaturated alcohol XV in almost quantitative yield. Hydrogenation stopped at this point. This alcohol was readily



XV



XVI

reconverted to IX by oxidation with chromic acid. XV reacted rapidly with bromine in aqueous suspension at 10° to give an unknown monobromo compound $C_9H_{13}BrO_5$. The bromine was removed readily by heating for a short time in an aqueous buffer to yield a compound, $C_9H_{14}O_6$. V did not react with bromine at room temperature. At 95° in acetic acid it reacted rapidly to give an almost quantitative yield of a monobromo derivative. V also reacted rapidly with excess concentrated ammonia to give the amide XVI, which reverted to V when heated in the presence of dilute mineral acid.

Experimental

α-Keto-β-acetyl-butyrolactone.—To a suspension of 100 g. of ethyl sodium acetopyruvate (95% pure[12]) in 200 ml. of water and cooled to 13°, 50 g. of 35% formaldehyde was added in one lot The temperature rose to 23° and most of the solid sodium salt dissolved. After stirring the mixture at 20–25° for one-half hour it was cooled to 10° and 140 ml. of 6 *N* hydrochloric acid was added. The product crystallized quickly and after stirring for fifteen minutes in an ice-bath it was filtered off, washed with three 50-ml. portions of ice water, and dried at 55°. The yield was

(10) Obtained from U. S. Industrial Chemicals, Inc., New York, N. Y., under the trade name of Indalone.

(11) Katzman, Hays, Cain, Van Wyk, Reithel, Thayer, Doisy, Gaby, Carroll, Muir, Jones and Wade, *J. Biol. Chem.*, **154**, 475 (1944).

(12) Obtained from U. S. Industrial Chemicals, Inc., New York, N. Y.

67.5 to 69.5 g. (90–93%), m. p. 127–128°. The product crystallized from water as a colorless monohydrate, m. p. 127–128°, which readily lost its water of crystallization at 50–55°. *Anal.* Calcd. for $C_6H_8O_4$: C, 50.71; H, 4.26; neutralization equivalent, 142.11. Found: C, 50.91; H, 4.31; neut. equiv., 141.1. This compound is strongly acidic, liberating carbon dioxide from sodium bicarbonate solution. Its aqueous solution gives a deep red color with ferric chloride solution. When heated in glacial acetic acid at 90° for a few minutes with introduction of dry hydrogen chloride it formed an acetate, m. p. 79°. *Anal.* Calcd. for $C_8H_8O_5$: C, 52.18; H, 4.38. Found: C, 52.38; H, 4.57.

3-Ketobutyl Methyl Ether.—The method of Koelsch[13] for the preparation of β-alkoxypropionitriles from acrylonitrile was applied to methyl vinyl ketone for the preparation of 3-ketobutyl methyl ether.

To a mixture of 28.0 g. of anhydrous methyl vinyl ketone and 45.0 ml. of methanol was added 0.70 g. of sodium methylate.[14] The solution was stirred at 35–37° until the temperature began to fall, and after an additional five minutes was treated with 2.0 ml. of glacial acetic acid and distilled; yield, 28.6 g. (70.12%), of a colorless liquid, b. p. 136–138°, 82–86° at 99 mm.

Methyl β-Methoxypropionyl-pyruvate.—To a suspension of 21.6 g. of sodium methylate in 250 ml. of anhydrous ether, a mix of 47.2 g. of dimethyl oxalate and 40.8 g. of 3-ketobutyl methyl ether was added at 0–5° in fifty minutes. The resulting solution was stirred at 0–5° for two hours and then 400 ml. of ice water was added, followed by 43.0 ml. of 50% sulfuric acid. The product was extracted with ether, and distilled, b. p. 124–126°, 7–8 mm.; yield, 22.0 g. (29.26%). Considerable resinous material remained in the flask. The product redistilled as a yellow oil, b. p. 108–109.5°, 2–3 mm. *Anal.* Calcd. for $C_5H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 50.66; H, 6.30; n^{25} 1.4830 (white light); d^{25}_{25} 1.1866.

α-Keto-β-(β-methoxypropionyl)-butyrolactone, X.—Sodium methylate (21.6 g.) was suspended in 250 ml. of anhydrous ether at 2° and a mix of 40.8 g. of 3-ketobutyl methyl ether and 58.4 g. of diethyl oxalate was added below 5° in twenty minutes. The solution was stirred for one hour at 2–4°, and then 300 ml. of ice water and 40 ml. of 35% formaldehyde was added. The temperature was held at 5–10° for one-half hour, and the reaction mixture was acidified, using a slight excess of dilute sulfuric acid. The product was extracted with ether. When the dried ether extract was partially concentrated, a crystalline substance separated which was filtered off and washed with cold ether; yield, 22.3 g. (29.98%), m. p. 124°. The product was recrystallized from water as colorless crystals, m. p. 126°. *Anal.* Calcd. for $C_8H_{10}O_5$: C, 51.61; H, 5.42. Found: C, 51.68, 51.48; H, 5.86, 5.50.

This product was also obtained from methyl β-methoxypropionyl-pyruvate in the presence of one mole of sodium hydroxide. One and nine-tenths grams of methyl β-methoxypropionyl-pyruvate was shaken vigorously with a mix of 2.0 ml. of 5 *N* sodium hydroxide and 3.0 ml. of water to complete solution. The resulting solution was basic to litmus but acid to phenolphthalein. One milliliter of 35% formaldehyde was added and the solution was stirred vigorously for two minutes, cooled, and acidified with 50% sulfuric acid. The crystalline product which separated was filtered off, washed with a small quantity of ice water and dried to yield 0.450 g. of X, m. p. 123°. A mixed melting point with pure X, m. p. 126°, melted at 124°.

3-Hydroxymethyl-5,6-dihydro-γ-pyrone-carboxylic acid-2 Lactone, II.—One-quarter milliliter of concentrated sulfuric acid was added to 15.0 ml. of dioxane, followed by 5.0 g. of X. The solution was refluxed for six hours, set aside for one and one-half days, diluted with water to approximately 75.0 ml., and treated with an excess of solid sodium bicarbonate. The resulting solution was extracted four times with ethyl acetate. From these combined extracts was isolated 2.55 g. (65.5%, based on a recovery of 300 mg. of pure X by acidification and extraction of the alkaline aqueous solution) of a tan crystalline material, m. p. 81–82.5°. After recrystallization from a benzene–petroleum ether mixture the colorless product melted at 87°. *Anal.* Calcd. for $C_7H_6O_4$: C, 54.55; H, 3.92. Found: C, 54.60; H, 4.02.

α-Keto-β-(β,β-dimethylacryl)-butyrolactone, XI.—Eighty-six and four-tenths grams of sodium methylate was stirred in 1000 ml. of anhydrous ether at 2° and a mix of 233.6 g. of diethyl oxalate and 156.8 g. of mesityl oxide was added in one-half hour at 5–10°. The mixture was stirred for three hours at 5–10° and then stored in the refrigerator overnight. Ice water (750 ml.) was added, followed by 165 ml. of 35% formaldehyde. The temperature of the reaction was held at 15° for one-half hour, then 1500 ml. of water was added and the ether layer was separated. After extraction of the aqueous portion with ether, it was acidified with 440 ml. of 20% sulfuric acid. The solid was filtered at 10°, washed well with ice water, and dried at 55°; yield, 154 g. (52.90%), m. p. 143°. After two recrystallizations from isopropanol an almost colorless product was obtained, m. p. 149.5–150.5°. *Anal.* Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.17; H, 5.57.

This product was also obtained from butyl 5,6-dihydro-6,6-dimethyl-γ-pyrone-carboxylic acid-2.[9] A solution of 22.6 g. of the latter product in 55 ml. of methanol was treated slowly with 5.67 g. of sodium methylate at 20°. After fifteen minutes the mixture was cooled to 15° and 15.0 ml. of 35% formaldehyde was added. The temperature rose to 25°, the sodium salt dissolved, and another product separated. After one hour it was filtered off. The precipitate was treated with a mixture of 35 ml. of water and 10 ml. of 20% sulfuric acid. The product was filtered, washed with water and dried; yield, 6.8 g., m. p. 132–133°. An additional 1.3 g., m. p. 143°, was obtained from the alcoholic mother liquor, total yield, 8.1 g. (44.51%). After recrystallization from isobutyl acetate the product melted at 150°. A mixed melting point with XI, above, showed no depression.

3-Hydroxymethyl-5,6-dihydro-6,6-dimethyl-γ-pyrone-carboxylic Acid-2 Lactone, V.—The open-chain isomer, XI, was most conveniently isomerized to V by heating for a short time in aqueous-alcoholic hydrochloric acid as follows: Fifty grams of XI was refluxed for five minutes in a mixture of 50 ml. of 95% alcohol and 25 ml. of 6 *N* hydrochloric acid and 175 ml. of hot water added. A colorless solid, m. p. 83–84°, separated from the cooled solution; yield, 47.5 g. (95.0%). After recrystallization from aqueous alcohol the product melted at 84–85°. *Anal.* Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.48, 59.36; H, 5.82, 5.77. This product distilled without decomposition at 138°, 1 mm.

V was reconverted to XI in the following way: a solution of V, 1.82 g., in 25.0 ml. of methanol, was treated with 0.57 g. of sodium methylate. After fifteen minutes at room temperature, 50 ml. of water and 5 ml. of 20% sulfuric acid was added. A colorless crystalline product, m. p. 143°, separated, which produced a red coloration with ferric chloride solution. After recrystallization it melted at 150°. A mixed melting point with XI showed no depression.

α-Keto-β-(β,β-dimethylacryl)-γ-methyl-butyrolactone, XII.—To 21.6 g. of sodium methylate suspended in 250 ml. of anhydrous ether, was added a mix of 39.2 g. of mesityl oxide and 58.4 g. of diethyl oxalate at 5–10°. The temperature was held at 5–10° for one and one-half hours and then 400 ml. of ice water and 29.0 ml. of acetaldehyde was added. The reaction mixture was stirred for one-half hour at 10°, and acidified with 42.0 ml. of concentrated hydrochloric acid. The product was extracted with ether. The ether solution was, in turn, extracted several times with aqueous sodium bicarbonate solution. The combined aqueous extracts were extracted with ether, then petroleum ether, cooled to 10°, and acidified to yield a tan, crystalline product; yield, 22.8 g. (29.09%), m. p.

(13) Koelsch, THIS JOURNAL, **65**, 437 (1943).

(14) The sodium methylate used in these experiments, which is not less than 95% pure, was obtained from The Mathieson Alkali Works, Inc., Niagara Falls, N. Y.

100–101°. The crude material, after purification from petroleum ether–benzene (1:1), yielded colorless crystals, m. p. 102–103°. *Anal.* Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 60.97; H, 6.12.

3-(α-Hydroxyethyl)-5,6-dihydro-6,6-dimethyl-γ-pyrone-carboxylic Acid-2 Lactone, VI.—A mixture of 3.0 g. of XII, 3.0 ml. of 95% ethanol, and 1.5 ml. of 6 *N* hydrochloric acid was refluxed for five minutes. The enol test with ferric chloride was then negative. Ten milliliters of hot water was added. The product was filtered off at 5°, washed with ice water and dried at 55°; yield, 2.82 g. (94%), m. p. 141–142°; recrystallized from ethanol, colorless crystals m. p. 142°. *Anal.* Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 60.99; H, 6.27.

3,5-Bis-hydroxymethyl-xanthochelidonic Acid Dilactone, XIII.—To a suspension of 116 g. of sodium methylate in 1500 ml. of petroleum ether (b. p. 60°) in a three-liter flask equipped with an efficient agitator, a mix of 310 g. of diethyl oxalate and 58 g. of acetone was added. When the temperature reached 50°, an ice-bath was applied to maintain a temperature of 50–55°. The complete addition of the ketone–ester mix required ten minutes. The reaction mixture was stirred at 50–60° for one and one-half hours and then cooled to 20°. The canary-yellow salt was filtered off through cloth, washed with petroleum ether, and spread out on a filter paper to dry; yield, 303 g.[15]

Sixteen and seven-tenths grams of the crude disodium salt was placed in a test-tube. A small amount of crushed ice was added, followed by 10.0 ml. of 35% formaldehyde. The paste was stirred vigorously, and the temperature rose rapidly to 45°. The mixture became stiff. Sufficient ice water was added to allow stirring with a glass rod. After ten minutes, 13.5 ml. of concentrated hydrochloric acid was added and the yellow product was filtered off at 5°, washed with a small amount of ice water, and dried at 50–55°; yield, 4.3 g. (34.49%), m. p. 181–183° (dec.). It was recrystallized from acetone, in the form of yellow needles, m. p. 187° dec. *Anal.* Calcd. for $C_9H_6O_7$: C, 47.80; H, 2.67. Found: C, 47.62; H, 2.75.

This product is fairly soluble in water but is only slightly soluble in dilute (as low as 3%) hydrochloric acid and is almost insoluble in 20% salt solution. The condensation with formaldehyde must be carried out with a minimum of water, otherwise the yield is very low, and even the addition of salt does not improve it.

3,5-Bis-hydroxymethyl-chelidonic Acid Dilactone, VII.—A mixture of 1.40 g. of XIII, 10 ml. of glacial acetic acid, and 2 ml. of concentrated hydrochloric acid was refluxed for two hours and forty minutes, cooled, and diluted with water. The product was filtered off and washed with water; yield, 0.7 g. (54.35%). The solid was recrystallized from acetic acid and dried at 55°; colorless needles, m. p. 265°. This product, in alcoholic solution, gave no color with ferric chloride solution. *Anal.* Calcd. for $C_9H_4O_6$: C, 51.94; H, 1.94. Found: C, 51.45; H, 1.97.

α-Keto-β-(*o*-hydroxybenzoyl)-butyrolactone, XIV.—To 90 g. of sodium methylate suspended in 1000 ml. of petroleum ether (b. p. 60°) was added a solution of 102.0 g. of *o*-hydroxyacetophenone[16] and 120.5 g. of diethyl oxalate in 100 ml. of petroleum ether at 20–25° in the course of twenty minutes. The mixture was then heated at 50–60° for two hours. The disodium salt was filtered off, washed with petroleum ether and dried in the air; yield, 210 g. of yellow salt.

Fourteen grams of the salt was shaken in a flask with 100 ml. of water and 5.0 ml. of 35% formaldehyde was added. After shaking for fifteen minutes, nearly all of the salt had dissolved. The reaction mixture was filtered, and acidified with dilute sulfuric acid. The yellow product was filtered off and dried; yield, 5.0 g. (45.45%). The product was recrystallized from acetone–water and dried over phosphoric anhydride *in vacuo*, yellow crystals, m. p. 204° dec. *Anal.* Calcd. for $C_{11}H_8O_6$: C, 60.00; H, 3.66. Found: C, 59.88; H, 3.82. This product gave a deep brownish-red color with aqueous-alcoholic ferric chloride.

3-Hydroxymethyl-chromone-carboxylic Acid-2 Lactone, VIII.—XIV was refluxed for one hour with a 5:1 mixture of glacial acetic acid and concentrated hydrochloric acid The ferric chloride enol test gradually became negative. Upon cooling, a colorless crystalline product separated which was recrystallized from dilute acetic acid, m. p. 242°. *Anal.* Calcd. for $C_{11}H_6O_4$: C, 65.35; H, 2.99. Found: C, 65.46; H, 3.33.

3-Hydroxymethyl-4-hydroxy-5,6-dihydro-6,6-dimethyl-1,4-pyrane-carboxylic Acid-2 Lactone, XV.—A solution of 18.2 g. of V in 150 ml. of ethyl acetate was shaken with hydrogen at 300 pounds pressure in the presence of 0.3 g. of a palladium charcoal catalyst. After four hours and twenty minutes, one molar equivalent of hydrogen had been absorbed, and no further absorption took place. The catalyst was filtered off and the solvent was removed under reduced pressure, leaving 18.4 g. of a colorless solid, m. p. 114–115°. The crude product was recrystallized from benzene; yield, 15.5 g. (84.24%), m. p. 120.5–121.5°. *Anal.* Calcd. for $C_9H_{12}O_4$: C, 58.68; H, 6.57. Found: C, 58.42; H, 6.71. The same product was obtained when Raney nickel catalyst was used at 300 pounds pressure, either at room temperature or 150° in alcoholic solution, or when platinum oxide catalyst was used at 300 pounds pressure in ethanol–acetic acid solution. This product, in contrast to the ketone from which it was derived, is only slightly soluble in benzene at room temperature. It gave no coloration with ferric chloride solution after treatment with sodium hydroxide and reacidification in the manner previously described for the dihydro-γ-pyrone derivatives.

Oxidation of 3-Hydroxymethyl-4-hydroxy-5,6-dihydro-6,6-dimethyl-1,4-pyrane-carboxylic Acid-2 Lactone, XV.—A solution of 1.65 ml. of concentrated sulfuric acid, 18.0 ml. of water and 3.6 g. of sodium dichromate dihydrate was heated to 35° and 1.84 g. of XV was added while the mixture was stirred rapidly. The temperature rose quickly to 50–55° and an oil separated in a few minutes, which crystallized when the solution was cooled. The product was filtered off and washed with ice water; yield, 0.950 g., m. p. 83–84°. A mixed melting point with V showed no depression.

Bromination of 3-Hydroxymethyl-4-hydroxy-5,6-dihydro-6,6-dimethyl-1,4-pyrane-carboxylic Acid-2 Lactone, XV.—A mixture of 12.48 g. of XV and 70.0 ml. of water was cooled, with stirring, to 5°. About 4.1 ml. of bromine was added slowly, below 10°, until the permanent light yellow color of bromine persisted. Absorption of the bromine was rapid, and a colorless crystalline product separated which was filtered off, washed with ice water, and dried over sulfuric acid; yield, 17.2 g. (90.8%), m. p. 153–154° dec. The product was recrystallized from 95% ethanol, m. p. 159° dec. *Anal.* Calcd. for $C_9H_{13}BrO_6$: C, 38.45; H, 4.66; Br, 28.43. Found: C, 38.34; H, 4.64; Br, 28.86. This neutral compound lost no water when heated at 84°, 1 mm. pressure, for nine hours. When heated with a neutral aqueous phosphate buffer for a few minutes it dissolved and a colorless, neutral product, m. p. 193°, was isolated by extraction of the aqueous solution with ethyl acetate. *Anal.* Calcd. for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.51; H, 6.49. The compound lost no water when heated at 100°, or when heated for eight hours at 84°, 1 mm. pressure. It slowly reacted with dilute sodium hydroxide. When treated with excess sodium hydroxide in aqueous solution and the solution reacidified in a manner described for the dihydro-γ-pyrone derivatives, it gave a very weak green coloration with ferric chloride solution.

Bromination of 3-Hydroxymethyl-5,6-dihydro-6,6-dimethyl-γ-pyrone-carboxylic Acid-2 Lactone, V.—A solution of 18.2 g. of V in 100.0 ml. of glacial acetic acid was

(15) This procedure was found to be considerably more convenient than that of Riegel and Zwilgmeyer, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons Co., Inc., New York, N. Y., 1943, p. 126, in which alcohol is used as a reaction medium. In the latter case filtration of the sodium salt is difficult, whereas if petroleum ether is used, filtration is rapid. Ester interchange during the condensation is of no consequence since alcohol is eliminated with lactone formation when the product reacts with formaldehyde.

(16) Rosenmund and Schnurr, *Ann.*, **460**, 56 (1928).

heated to 95°. A solution of 5.5 ml. of bromine in 25.0 ml. of acetic acid was added. The reaction was rapid and the mixture boiled spontaneously for a short time. The solution was cooled to room temperature and diluted with 600 ml. of ice water. The colorless product was filtered off at 5°, washed with ice water and dried at 55°; yield, 25.5 g. (97.66%). The product was purified for analysis by recrystallization from an isopropanol–ethyl acetate mixture, m. p. 142–143°. *Anal.* Calcd. for $C_9H_9BrO_4$: C, 41.40; H, 3.47; Br, 30.61. Found: C, 41.50; H, 3.72; Br, 30.95.

3-Hydroxymethyl-5,6-dihydro-6,6-dimethyl-γ-pyrone-carboxylic Acid Amide-2, XVI.—V (80.0 g.), was added in five minutes to 400.0 ml. of 28% ammonium hydroxide (temp., 15°). The mixture was stirred for fifteen minutes, at the end of which time the temperature was 3°. The colorless crystalline product was filtered off, washed with ice water, and dried in the air; yield, 74.0 g. (84.01%), m. p. 153–154° dec. The compound was recrystallized from isopropanol and dried at 55°, m. p. 157–158° dec. *Anal.* Calcd. for $C_9H_{11}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.18; H, 6.73; N, 6.73. This product evolved ammonia when heated with water. When heated for a short time with dilute hydrochloric acid it reverted to V.

Summary

1. The synthesis of a clavacin isomer, 3-hydroxymethyl-5,6-dihydro-γ-pyrone-carboxylic acid-2 lactone is described. It has been shown that this compound does not exist in equilibrium with clavacin, in confirmation of the earlier tentative exclusion of it by less direct evidence.

2. A number of homologs and derivatives possessing the same isomeric structure have also been made. The chemical properties of these compounds as well as those of several intermediate α-keto-β-acyl-butyrolactones are recorded.

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The Preparation of L-Sorbose from Sorbitol by Chemical Methods

BY WILLIAM R. SULLIVAN

L-Sorbose is usually prepared by the bacterial oxidation of sorbitol.[1] Two chemical syntheses have been reported. Votoček and Lukeš[2] and Talen[3] oxidized sorbitol with bromine water, and from the resulting sirup were able to obtain L-gulosazone, which was considered to indicate that L-sorbose had been formed in the oxidation. Gätzi and Reichstein[4] treated L-xylonyl chloride with diazomethane and obtained L-sorbose by acid hydrolysis of the intermediate diazo ketone.

A synthesis based on the oxidation of carbon atom 5 of D-sorbitol derivatives, in which the other positions are protected by suitable substituents, is reported in this paper. A search of the literature indicates that this represents a novel approach to the synthesis of ketose sugars.

1,3:2,4-Diethylidene-D-sorbitol (II)[5] is prepared by the partial hydrolysis of triethylidene sorbitol (I). Under suitable conditions 6-tosyl-[6] or 6-benzoyl-1,3:2,4-diethylidene-D-sorbitol (III) may be prepared in substantial yield, the diesters being formed simultaneously to some extent. The remaining free hydroxyl group on carbon atom 2 is then oxidized to the carbonyl stage by chromium trioxide in acetic acid solution. From the open-chain sorbose derivative (IV) so obtained, the ethylidene groups are removed by hydrolysis with dilute mineral acid to give 1-tosyl- or 1-benzoyl-L-sorbose (V). The structue of these products is proved by their synthesis from the known 2,3:4,6-diisopropylidene-L-sorbose (VI) and by the hydrolysis of 1-benzoyl-L-sorbose to the free sugar, L-sorbofuranose.

In the preparation of diethylidene sorbitol, the intermediate triethylidene compound (I) is handled satisfactorily in the form of a crude sirup. The crystalline compound has been isolated and found to melt at 96–97°. The melting point of 174–176° reported by Appel[5] for triethylidene-D-sorbitol suggests that two forms may exist, possibly as *cis–trans* or other isomers.

When the hydrolysis of the tosyl or benzoyl esters of diacetone-L-sorbose (VII) is carried out with 50% acetic acid, the intermediate monoacetone compounds (VIII) are the major products, while the use of dilute mineral acid leads to removal of both isopropylidene residues. The isopropylidene residue of the intermediates (VIII) is considered to be at positions 2 and 3, because the failure to reduce Fehling solution before hydrolysis with mineral acid proves that the carbonyl group is not free.

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Experimental[7]

1,3:2,4-Diethylidene-D-sorbitol (II).—The method of Appel[5] gave yields of about 26%. In an experiment on a

(1) Bertrand, *Bull. soc. chim.*, [3] **15**, 627 (1896); Wells, Stubbs, Lockwood and Roe, *Ind. Eng. Chem.*, **31**, 1518 (1939).

(2) Votoček and Lukeš, *Rec. trav. chim.*, **44**, 345 (1925).

(3) Talen, *ibid.*, **44**, 891 (1925).

(4) Gätzi and Reichstein, *Helv. Chim. Acta*, **21**, 186 (1938).

(5) Appel, *J. Chem. Soc.*, 425 (1935). See also Gätzi and Reichstein[4] for final proof of structure.

(6) Since the completion of the experiments here reported, the preparation of 6-tosyl-1,3:2,4-diethylidene-D-sorbitol has been described by Vargha and Puskás, *Ber.*, **76**, 859 (1943). These authors apparently did not isolate the di-ester from the reaction mixture and therefore the details, while similar, are included here.

(7) Melting points were determined with an uncalibrated set of Anschütz thermometers. The analyses were done in the Roche Microanalytical Laboratory under the direction of Dr. Al Steyermark.