[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

# Xanthinin. II. The Structures of Xanthinin and Xanthatin

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Xanthinin, $C_{17}H_{22}O_5$, and xanthatin, $C_{15}H_{18}O_3$, have been found to be $\alpha$-methylenic lactones containing a single carbocyclic ring. Evidence is presented for the nature of all of the structural elements, and complete structures are proposed. The compounds are formulated as sesquiterpenoid lactones related to the known azulenogenic guaianolides.

In the first paper of this series[1] were described the isolation and characterization of xanthinin from *Xanthium pennsylvanicum*, and its conversion into xanthatin. Xanthinin is an acetoxy ketolactone which loses the elements of acetic acid with the formation of an $\alpha,\beta$–$\gamma,\delta$-dienone (xanthatin). The composition of xanthatin, $C_{15}H_{18}O_3$, indicated that the compound possessed, in addition to the keto and lactone carbonyl groups, the lactone ring, and the two carbon–carbon double bonds, a total of two additional rings or double bonds.

Hydrogenation and quantitative bromination studies indicated that of these two remaining structural elements, one was a double bond, and that xanthinin and xanthatin were monocarbocyclic compounds. Hydrogenation of xanthinin resulted in the uptake of amounts of hydrogen (about 3 moles) that suggested that both addition and hydrogenolysis were occurring. Hydrogenolysis could be accounted for, since the easily eliminated acetoxy group was probably in a position allylic to one of the double bonds; and indeed it was found that acetic acid is present in the solutions after hydrogenation. However, under conditions in which hydrogenation was allowed to proceed to completion no crystalline products could be isolated.

When hydrogenation was allowed to proceed to the uptake of one mole of hydrogen only, and then interrupted, crystalline dihydroxanthinin was isolated. The formation of dihydroxanthinin did not involve the saturation of the double bond that eventually becomes part of the dienone system of xanthatin, since by the removal of acetic acid from dihydroxanthinin, dihydroxanthatin, having an ultraviolet absorption spectrum nearly identical with that of xanthatin, was formed. It was thus apparent that a double bond hitherto unrecognized had been disclosed, and that xanthinin and xanthatin each contained but one carbocyclic ring.

That the double bond that is reduced in the formation of dihydroxanthinin is present in an exocyclic methylene group was shown by the presence in the dihydro compound of an additional carbon-linked methyl group (Table III, Experimental part) over those present in xanthinin itself. This was confirmed by the isolation of formaldehyde (as the dimedone derivative) by ozonization of xanthinin, and by other experiments described herein.

An examination of the infrared absorption spectrum of xanthinin failed to reveal the characteristic absorption of the aliphatic $>C{=}CH_2$ grouping at about 890 cm.$^{-1}$ [2] despite the clear indication, reinforced by subsequent observations, of the presence of this group. It seemed probable that the behavior of the methylene group was altered by its presence in a situation other than that of a simple 1,1-disubstituted olefin, and that it might exist in conjugation with the lactone carbonyl group. This expectation was borne out by an examination of the ultraviolet absorption spectra of xanthinin and the dihydro compound.

Xanthinin possesses no prominent ultraviolet absorption until the low wave length region is reached, when strong end absorption is observed in the 220–210 m$\mu$ region. This is characteristic of $\alpha$-methylenic $\gamma$-lactones,[3,4] and distinguishes them from $\alpha,\beta$-unsaturated $\gamma$-lactones in which the double bond is intracyclic. In the latter case, absorption maxima near 215–225 m$\mu$ are observed.[3,5] Dihydroxanthimin and dihydroxanthatin lack the pronounced end absorption of their unreduced counterparts, an indication that the reduction of an $\alpha$-methylenic $\gamma$-lactone to an $\alpha$-methyl lactone has occurred (Table I).

TABLE I

EXTINCTION COEFFICIENTS OF XANTHININ AND DERIVATIVES

| Compound | Molar extinction coefficient, $\epsilon$ In 95% ethanol 220 m$\mu$ | In 95% ethanol 215 m$\mu$ | In water 220 m$\mu$ | In water 215 m$\mu$ |
|---|---|---|---|---|
| Xanthinin | 5974 | 9037 | 8823 | 12193 |
| Dihydroxanthinin | 401 | 925 | 2031 | 3332 |
| Xanthinin-pyrazoline | .. | 2500 | .. | ... |

The presence of the conjugated exocyclic methylene group was further established by the reaction of xanthinin with diazomethane, with the formation of a pyrazoline.[4,6] The pyrazoline showed the same loss of end absorption, compared with xanthinin, as did the dihydro compound, again showing that the $\alpha,\beta$-ethylenic linkage had disappeared in its formation.

Diazomethane also added to xanthatin with the formation of a compound that still retained the characteristic ultraviolet absorption maximum (276 m$\mu$) of xanthatin itself. This substance, therefore, is the pyrazoline analogous to that derived from xanthinin, and resulted from the addition of diazomethane to the methylene group of the lactone. When the reaction of diazomethane with xanthinin or xanthatin was carried out in methanol–ether, rather than in dry ether alone, two molecules of diazomethane were added with the formation from either xanthinin or xanthatin of the same compound. It is apparent that elimination of acetic acid took place in the reaction with xanthinin. The bis-pyrazoline possesses a markedly different ab-

(1) T. A. Geissman, Peter Deuel, E. K. Bonde and F. A. Addicott, THIS JOURNAL, **76**, 685 (1954).

(2) N. Sheppard and D. M. Simpson, *Quart. Revs.*, **6**, 1 (1952).

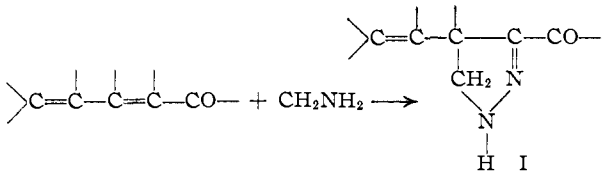
(3) E. E. van Tamelen, C. E. Osborn, Jr., and S. R. Bach, THIS JOURNAL, **77**, 4625 (1955).

(4) E. E. van Tamelen and S. R. Bach, *ibid.*, **77**, 4683 (1955).

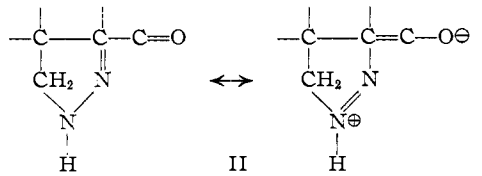
(5) W. G. Dauben and P. D. Hance, *ibid.*, **75**, 3352 (1953).

(6) K. F. W. Hansen, *Ber.*, **64**, 943 (1931).

sorption spectrum from that of xanthatin, having a principal maximum at 314 mμ. This suggests that the relevant structural fragment (I) is formed



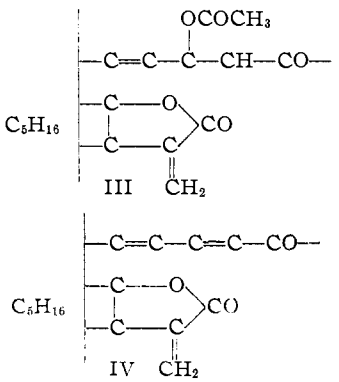
and that the 314 mμ absorption maximum is the result of participation of such contributing forms as II



Dihydroxanthinin, as would be expected from these conclusions regarding the structure of the lactone moiety, was recovered unchanged after treatment with diazomethane in ether solution. In methanol, however, a monopyrazoline having the spectral characteristics ($\lambda_{max}$ 314 mμ) of the bis-pyrazoline of xanthatin is formed.

The formulation of the lactone ring as 5-membered derives from a consideration of the infrared absorption spectra (Table II). The carbonyl absorption of the lactone, recurring in the spectra of xanthinin, xanthatin and their derivatives, is found at 1755–1765 cm.$^{-1}$, typical of γ-lactones and different from that (about 1740 cm.$^{-1}$) characteristic of 6-membered lactones. The observation that the lactone carbonyl frequency does not change materially or systematically upon removal of the α,β-unsaturation by hydrogenation or diazomethane addition is not unusual.[4,5]

The foregoing observations can be summarized in the following partial structures for xanthinin (III) and xanthatin (IV)



Evidence regarding the nature of the five carbon atoms not specified as to structure in III and IV is found in the results of oxidation procedures. These were of two kinds: hypoiodite oxidation and chromic acid oxidations under conditions that were essentially those of the Kuhn–Roth carbon-linked methyl group determination.

Both xanthinin and xanthatin, when treated with sodium hypoiodite, give iodoform and xanthatic acid, $C_{14}H_{16}O_4$. This confirms the presence of the grouping $-COCH_3$, and spectral data indicate that the conjugated system in xanthatin is C=C–C=C–$COCH_3$. The formation of xanthatic acid from xanthinin under these alkaline conditions is accompanied by the loss of acetic acid in a reaction analogous to that in which xanthatin is formed from xanthinin.

TABLE II

INFRARED SPECTRAL DATA FOR XANTHININ AND DERIVATIVES

| Compound | Absorption peaks in cm.$^{-1}$ Lactone CO | Other CO and C=C | $R_2C=$ CHR[d] |
|---|---|---|---|
| Xanthinin[a] | 1765 | 1720 | 814 |
| Xanthatin[a] | 1766 | 1660, 1609, 1590 | 812 |
| Dihydroxanthinin[b] | 1757 | 1720 | 807 |
| Dihydroxanthatin[b] | 1760 | 1653, 1606, 1587 | 820 |
| Xanthatic acid[c] | 1756 | 1670, 1608 | 827 |
| Dihydroxanthatic acid[c] | 1765 | 1677, 1613 | 815 |
| Methyl xanthate-pyrazoline[b] | 1770 | 1715sh, 1700, 1618 | 834 |

[a] Film. [b] Chloroform. [c] Potassium bromide disk. [d] For six olefins of the type $R_2C=CHR$, where the substituents are simple alkyl groups, Sheppard and Simpson[2] give 801, 812, 823, 824, 825 and 833 cm.$^{-1}$.

Xanthatic acid shows an absorption maximum at 252 mμ (ethanol) (ε 21,400), in good agreement with the value reported for sorbic acid (254 mμ, ε 24,800),[7] and indicates that xanthatic acid is an α,γ-dienoic acid whose derivation from xanthatin may be represented as

C=C–C=C–$COCH_3$ ⟶ C=C–C=C–COOH

That the lactone grouping of xanthatin is preserved in xanthatic acid is shown by the positive hydroxamic test and by titration experiments. Xanthatic acid can be titrated in ethanol solution to a sharp end-point with the consumption of exactly one equivalent of alkali. When excess alkali is added and the solution is heated, back-titration shows that two equivalents of base are consumed.

Dihydroxanthatic acid was prepared in two ways: by catalytic hydrogenation of xanthatic acid, or by hypoiodite oxidation of dihydroxanthinin. Dihydroxanthatic acid has an absorption maximum at 252 mμ (ε 22,400) and thus possesses the same conjugated system as xanthatic acid. The C-methyl values are in harmony with these observations: xanthatic acid shows 0.54 and dihydroxanthatic acid 1.39 C-methyl groups. Moreover, xanthatic acid shows a greater absorption in the short wave length region than does the dihydro acid, the values for Δε being 7304 (220 mμ) and 9080 (215 mμ).[8]

When xanthatic acid was treated with diazomethane in ether, a nitrogen-containing compound was formed. This substance is the pyrazoline formed by the addition of diazomethane to the α,β-unsaturated system of the lactone, with concomitant esterification of the carboxyl group; it displays an ultraviolet absorption maximum at 262 mμ (ε 25,700), in agreement with its formulation as the

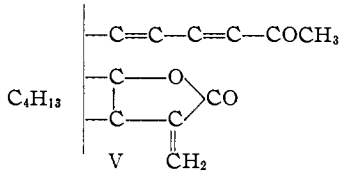
(7) A. E. Gillam and R. E. Stearn, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," E. Arnold, London, 1955.

(8) The value Δε is the difference between the molar extinction coefficients of the unsaturated acid and the dihydro acid at the indicated wave length.

methyl $\alpha,\gamma$-dienoate. The very low absorption of the pyrazoline in the 210–220 m$\mu$ region, like that of dihydroxanthinin, shows again that the addition of diazomethane is accompanied by the loss of the $\alpha,\beta$-unsaturation in the lactone grouping.

Both xanthatic and dihydroxanthatic acids show infrared absorption curves that confirm the above conclusions. The lactone carbonyl bands of 1755 cm.$^{-1}$ for xanthatic acid and 1765 cm.$^{-1}$ for the dihydro acid are in agreement with their formulation as $\gamma$-lactones. Xanthatic acid shows a weak absorption at 1410 cm.$^{-1}$ which is assigned to in-plane $=CH_2$ deformations[9]; this band is absent from the spectrum of dihydroxanthatic acid.

Since xanthatin can now be formulated as V, the remaining questions concern the nature of the residual four-carbon fragment and the manner in which the structural elements shown are assembled.

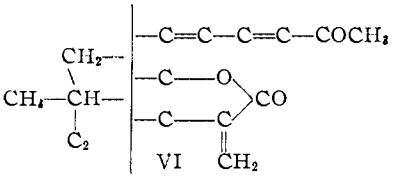


V

Since the C-methyl determination on xanthatin shows value of 1.44, the presence of two methyl groups is suggested. One of these is in the $-CO-CH_3$ grouping and would be expected to give nearly the theoretical amount of acetic acid. The other, from which only about 0.5 mole of acetic acid is formed, is probably present in a secondary, saturated location. In a very illuminating study of the Kuhn–Roth oxidation, Eisenbaum, McElvain and Aycock[10] have demonstrated that certain simple substances are remarkably resistant to the conditions of this method, and suggested that such acids as succinic, glutaric and adipic may be end-products of the degradation of more complex substances. Model studies were carried out in the course of the present investigation, and it was found that succinic, glutaric and adipic acids could be isolated from proline, cyclopentanone and cyclohexanone, respectively, after simulated C-methyl determinations on these compounds.

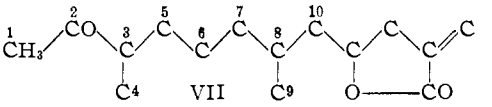
The oxidation of xanthinin with a chromic–sulfuric acid mixture gave a 29% yield of methylsuccinic acid. This compound was identified by analysis of it, its monoanilide and the *l*-quinine salt, and by mixed melting point determinations using the latter and an authentic sample. Melting point data on the acid and its anilide were inconclusive, probably because the "natural" acid was a mixture of racemic and active forms. Markownikov[11] reported the isolation of partially racemized (+)-methylsuccinic acid from oxidations of several terpene derivatives. Ladenburg[12] has stated that the *l*-quinine salt formed from *rac*-methylsuccinic acid is that of the dextrorotatory form. In the present experiments the *l*-quinine salt of the "natural" and synthetic samples of methylsuccinic acid were identical in melting point and behavior.

These data allow the structural information to be expressed in formula VI for xanthatin



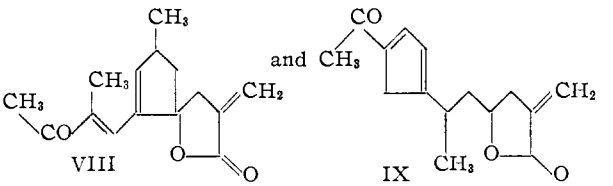
VI

The presence of the $\alpha$-substituted lactone grouping and an additional methyl group strongly suggests that xanthatin, $C_{15}H_{18}O_3$, is sesquiterpenoid in character. If this were the case, and the skeleton of the compound were constructed of isoprene units arranged in a regular way as in VII, the C-methyl data would require that one of the carbon



VII

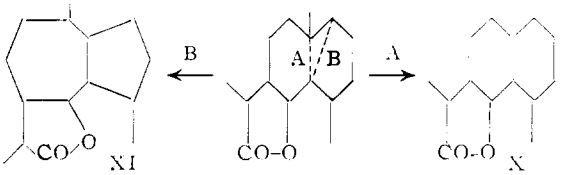
atoms 4 and 9 be utilized in ring formation. Now the ultraviolet absorption maximum of xanthatin is 276 m$\mu$, which corresponds best to a dienone system that is linear and bears two alkyl substituents, or that contains a ring of at least six members in which the $\gamma,\delta$-double bond is found.[13] Such structures as VIII and IX for xanthatin fail on one or the other of these requirements.



VIII and IX

A consideration of biogenetical relationships allows the proposal of a structure that not only accommodates all of the experimental evidence but relates these lactones to others to which their kinship can scarcely be doubted.

**Xanthium** is a genus of the *Compositae*, the family from which have been isolated a large number of lactones, many of them of known, sesquiterpenoid structure, and others whose empirical formulas strongly suggest that they are members of the same class. Those whose structures have been determined have been shown to belong to two groups: (1) those, of which santonin[14] is typical, which are naphthalenogenic on dehydrogenation (X); and (2) those which are guaianolides and give azulenes on dehydrogenation (XI). The formal relationship between these two classes can be seen in the scheme:



XI X

(9) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1954.

(10) E. J. Eisenbaum, S. M. McElvain and B. F. Aycock, THIS JOURNAL, **76**, 607 (1954).

(11) W. Markownikov, *Chem. Zentr.*, **74**, II, 288 (1903).

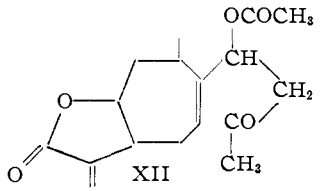
(12) A. Ladenburg, *Ber.*, **31**, 525, 937 (1898).

(13) R. B. Woodward, THIS JOURNAL, **63**, 1123 (1941).

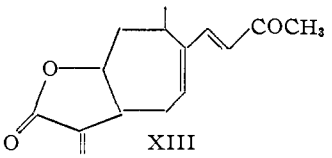
(14) J. L. Simonsen and D. H. R. Barton, "The Terpenes," Vol. 3, 2nd Ed., Cambridge University Press, Cambridge, Mass., 1952.

It is further to be noted that xanthinin, a $C_{17}$-compound, is related to xanthatin as prochamazulene,[15] tenulin,[16] pyrethrosin[17] and isotenulin[16] are related to basic $C_{15}$-sesquiterpenoid lactones; and, indeed, prochamazulene, pyrethrosin and tenulin are isomeric with xanthinin.

These considerations of the similarities in constitution, chemical nature and plant origin between xanthinin and the above-mentioned azulenogenic lactones suggest that the *Xanthium* lactone possesses a structure which, while not constructed on an azulene skeleton, is a monocarbocyclic congener of this type of compound. Structures XII and XIII are proposed for xanthinin and xanthatin. They accommodate all of the experimental evidence, possess the same basic carbon skeleton (except for the open 5-membered ring) as the known guaianolides, and may be regarded as being derived from a common type of precursor either by ring opening or by the failure of a ring-closing step in the biosynthesis.

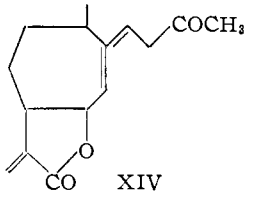



XII




XIII

An alternative structure (XIV, given for xanthatin) cannot be excluded from consideration, and indeed bears a closer analogy in respect to the position of oxygenation of the ring to the known guaianolides than do structures XII and XIII. However, the position of oxygenation of the ring in XII




XIV

and XIII finds its counterpart in tenulin and helenalin,[18] both of which bear two ring-oxygenated positions, one of which is at the carbon shown oxygenated in XII and XIII. Indeed, in the formula advanced for helenalin the lactone ring is constructed as it is in XII and XIII.

The present preference for structure XII for xanthinin rather than the corresponding derivative of XIV is based upon two observations: (1) while methylsuccinic acid was isolated from the oxidation of xanthinin and xanthatin, no $\alpha$-methylglutaric acid could be found. Since $\alpha$-methylglutaric acid appears to be nearly as stable as methylsuccinic acid to the oxidizing conditions used,[10] it would have been expected as a product from XIV, but not from XIII. (2) There was no evidence of the presence of an acidic compound, other than acetic acid, among the products of hydrogenation of xanthinin—a result that suggests that the lactone oxygen atom is not attached in the allylic position shown in XIV, in which it would be subject to hydrogenolysis.

With the structures XII and XIII for xanthinin and xanthatin in consideration, supporting evidence was found upon further scrutiny of the infrared spectral data. In the spectra of all of the compounds examined in this study is observed a prominent band in the neighborhood of 820 cm.$^{-1}$ (Table II). This band corresponds to the hydrogen-deformation frequency characteristic of trisubstituted olefins of the type $R_1R_2C{=}CHR_3$,[2] and is excellent confirmatory evidence for the presence in the compounds of a carbon–carbon double bond of the kind shown in XII and XIII (and XIV) as a part of the seven-membered ring.

The structures proposed for the xanthium lactones accommodate all the experimental evidence that is at hand, and in addition allow the reconciliation of some negative results. Numerous experiments aimed at the formation of naphthalene or azulene derivatives by dehydrogenation failed to yield any products of these types.

Further evidence will be required to establish structures XII and XIII, and studies of these and related lactones of the *Compositae* are continuing.

## Experimental

**Xanthinin** was isolated from *Xanthium pennsylvanicum* in the manner described in the first paper in this series.[1]

**Xanthatin** was prepared by a method that is superior to that first used.[1] A solution of 1.24 g. of xanthinin and 2.3 g. of sodium acetate in 20 ml. of ethanol was refluxed for 40 minutes, 10 ml. of alcohol being allowed to distil from the solution during this period. The mixture was made slightly acid (litmus) with hydrochloric acid and water was added until the sodium chloride had dissolved. Xanthatin (0.96 g., 96%) crystallized on cooling, m.p. 114.5–115.5° after recrystallization from absolute ethanol.

**Catalytic Hydrogenation of Xanthinin and Xanthatin.**—In attempts to prepare reduction products of xanthinin, experiments were performed in which the extent of hydrogen uptake was determined. (a) Reduction of 55.2 mg. of xanthinin in glacial acetic acid with 8.8 mg. of platinum oxide resulted in the absorption of 2.95 moles of hydrogen per mole of xanthinin. In a repetition of this experiment, 3.17 moles was absorbed. (b) In ethanol, with platinum oxide, 2.90 moles of hydrogen was absorbed. (c) Xanthatin absorbed 3.14 moles of hydrogen in glacial acetic acid and 2.87 moles in ethanol. In none of these experiments could a crystalline hydrogenation product be obtained. The oily materials that resulted gave no indication of acidic character.

**Dihydroxanthinin.**—A solution of 1.50 g. of xanthinin in 35 ml. of absolute ethanol was hydrogenated at atmospheric pressure in the presence of 27 mg. of platinum oxide. The reaction was interrupted when the amount of hydrogen corresponding to 1.0 mole had been absorbed (about 2 hours), and after removal of the catalyst the filtrate was concentrated and cooled. The yield of dihydroxanthinin from a series of runs using a total of 15.03 g. of xanthinin was 8.02 g. (45%). Dihydroxanthinin forms colorless crystals (from ethanol), m.p. 117–118°.

*Anal.* Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.13; H, 7.80.

The combined mother liquors from the first crystallizations of dihydroxanthinin were evaporated and the residue dissolved in ether. This solution was found to contain 2.64

(15) V. Herout and F. Šorm, *Coll. Czech. Chem. Comm.*, **18**, 854 (1953); **19**, 792 (1954); Z. Čekan, V. Herout and F. Šorm, *ibid.*, **19**, 798 (1954).

(16) E. P. Clark, THIS JOURNAL, **61**, 1836 (1939); **62**, 597, 2154 (1940); D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 142 (1956).

(17) Thoms, *Pharm. Ztg.*, 503 (1891); W. G. Rose and H. L. Haller, *J. Org. Chem.*, **2**, 484 (1937).

(18) R. Adams and W. Herz, THIS JOURNAL, **71**, 2546, 2551, 2554 (1949); G. Büchi and D. Rosenthal, *ibid.*, **78**, 3860 (1956).

meq. of titratable acid (compared to 49.05 millimoles of xanthinin reduced), and from it, by appropriate manipulations, 1.17 millimoles of *p*-bromophenacyl acetate was obtained, m.p. 83–85°.

**Dihydroxanthatin.**—To a solution of 0.53 g. of dihydroxanthinin in 15 ml. of boiling absolute ethanol was added 0.60 g. of sodium bicarbonate. The mixture was refluxed for one hour, filtered and acidified with dilute hydrochloric acid. Colorless crystals of dihydroxanthatin formed at once. Recrystallized from ethanol, the compound forms colorless leaflets, m.p. 138–140°.

*Anal.* Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.47; H, 8.14.

**Ozonization of Xanthinin: Isolation of Formaldimedon.**—A solution of 0.152 g. of xanthinin in 30 ml. of methylene chloride was ozonized at Dry Ice-acetone temperature for 105 minutes. The reaction solution was added to the contents of a water trap used on the outlet from the ozonization flask and the mixture was refluxed for 20 minutes. The water layer was separated and distilled into an ice-cooled receiver.

An aliquot of 60 ml. of the total 200 ml. of distillate was added to a hot solution of 300 mg. of dimedon in 30 ml. of water. The formaldimedon that separated weighed 11.0 mg. (0.254 mole $CH_2O$ per mole xanthinin), and melted at 190–190.5°. There was no depression on mixing with an authentic sample, m.p. 189°.

Another 60-ml. aliquot of the distillate was analyzed for formic acid by Harper's method.[19] The result showed that 0.112 mole of formic acid was formed per mole of xanthinin.

**Reaction of Xanthinin and Xanthatin with Diazomethane.** (**A**).—The diazomethane generated from 3.9 g. of nitrosomethylurea was added to a solution of 1.24 g. of xanthinin in a total of 500 ml. of dry ether. The solution was kept at room temperature for an hour and at 3° for 25 hours, and then evaporated until the diazomethane had been removed and the solution was colorless. The crystalline product that separated on cooling weighed 1.26 g. (90%) and melted at 130–132° with gas evolution. The reaction also was carried out in dioxane–ether; the yield was 0.18 g. from 0.24 g. of xanthinin.

*Anal.* Calcd. for $C_{18}H_{24}O_5N_2$: C, 62.05; H, 6.94; N, 8.04. Found: C, 62.02; H, 6.94; N, 8.17.

(**B**).—When dihydroxanthinin was treated with diazomethane in dioxane–ether solution, no adduct could be isolated, and 84% of (recrystallized) starting material was recovered.

(**C**).—From 79 mg. of xanthatin and excess diazomethane in dioxane–ether was obtained the pyrazoline, m.p. 144.5–146° after recrystallization from methanol.

*Anal.* Calcd. for $C_{16}H_{20}O_3N_2$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.66; H, 6.90; N, 9.92.

The compound had a $\lambda_{max}$ at 276 m$\mu$, showing that the dienone chromophore of xanthatin was unaltered.

(**D**).—An ethereal solution of diazomethane was added to a solution of 0.30 g. of xanthinin in absolute methanol (10 ml.). After 20 hours at room temperature the solution was evaporated, affording 0.10 g. of product, yellow crystals, m.p. 170–73° with gas evolution. This compound no longer gives the purple-red color with hydrochloric acid that is characteristic of xanthinin and xanthatin; $\lambda_{max}$ 314 m$\mu$ (95% ethanol).

*Anal.* Calcd. for $C_{17}H_{22}O_3N_4$: C, 61.80; H, 6.71; N, 16.96. Found: C, 61.52; H, 6.70; N, 16.77.

(**E**).—The same "dipyrazoline" was obtained from xanthatin and diazomethane in methanol–ether solution.

*Anal.* Found: C, 61.67; H, 7.06; N, 17.28.

(**F**).—Dihydroxanthinin (0.30 g.) in 10 ml. of methanol was treated with excess ethereal diazomethane. After 6 hours the ether was removed by distillation, and the product allowed to crystallize. The yield was 14.1 mg. of slightly yellowish needles, m.p. 139–142° dec., $\lambda_{max}$ 314 m$\mu$ (95% ethanol).

*Anal.* Calcd. for $C_{16}H_{22}O_3N_2$: C, 66.18; H, 7.64. Found: C, 66.01; H, 7.48.

**Xanthatic Acid.**—To a solution of 12.5 g. of iodine in 125 ml. of 20% potassium iodide solution was added 10% aqueous sodium hydroxide until the color of the iodine was discharged. The resulting solution was added to 5.0 g. of xanthinin and, while stirring, sodium hydroxide was added until the solution of the xanthinin was complete. After 30 minutes the solution was acidified carefully until iodine reappeared, then made basic and the precipitated iodoform collected by filtration. The reaction required 24 hours to go to completion. Acidification yielded 3.82 g. of crude xanthatic acid; 4.0 g. of iodoform was obtained, and was identified by melting point and mixed melting point with authentic material.

After three recrystallizations from absolute ethanol, 1.36 g. of xanthatic acid, m.p. 300° dec., was obtained.

*Anal.* Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.37; H, 6.52.

Xanthatic acid gives a positive hydroxamic acid test, but does not give a red color with concentrated hydrochloric acid. It had $\lambda_{max}$ 252 m$\mu$ (log $\epsilon$ 4.33) in 95% ethanol, 260 m$\mu$ (log $\epsilon$ 4.33) in 9.5% ethanol.

***p*-Nitrobenzyl Xanthatate.**—A solution of 105 mg. of xanthatic acid in 0.7 ml. of 4% sodium hydroxide solution was brought to slight acidity (litmus) with hydrochloric acid and added to a solution of 96 mg. of *p*-nitrobenzyl bromide in 3 ml. of ethanol. After one hour of refluxing, the volume of the solution was reduced by distillation and cooled. The product (59.5 mg.) formed colorless crystals from ethanol, m.p. 140–142°.

*Anal.* Calcd. for $C_{21}H_{21}O_6N$: C, 65.78; H, 5.52. Found: C, 65.74; H, 5.71.

**Titration of Xanthatic Acid.** (**A**).—A solution of 110.5 mg. of xanthatic acid in 5 ml. of ethanol containing 10.0 ml. of 0.118 *N* sodium hydroxide was heated at 75° for 20 minutes and titrated to the phenolphthalein end-point with 2.75 ml. of 0.102 *N* hydrochloric acid. The base consumed corresponded to 2.00 equivalents per mole of xanthatic acid.

(**B**).—A cold solution of 235.8 mg. of xanthatic acid in 50 ml. of ethanol was titrated to a phenolphthalein end-point with 8.24 ml. of 0.115 *N* sodium hydroxide. This corresponds to 0.998 equivalent of base per mole of xanthatic acid. The pink phenolphthalein color faded after about 5 minutes.

**Dihydroxanthatic Acid.** (**A**).—The hydrogenation of 167 mg. of xanthatic acid in 15 ml. of ethanol (with platinum oxide, 7.6 mg.) was stopped after 20.0 ml. (0.81 mole) of hydrogen had been taken up. The solution was filtered and concentrated, and yielded on cooling 21.4 mg. of dihydroxanthatic acid, m.p. 232–239° (crude product).

(**B**).—The oxidation of 0.89 g. of dihydroxanthinin with an alkaline solution of 2.21 g. of iodine was carried out as described for the preparation of xanthatic acid. The crude dihydroxanthatic acid weighed 450 mg. After several recrystallizations there was obtained 296 mg., m.p. 240–243°; iodoform (0.51 g.) also was isolated. Dihydroxanthatic acid had $\lambda_{max}$ 252 m$\mu$ (log $\epsilon$ 4.35) in 95% ethanol, and $\lambda_{max}$ 260 m$\mu$ (log $\epsilon$ 4.35) in 9.5% ethanol.

*Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.06; H, 7.53.

***p*-Nitrobenzyl dihydroxanthatate** was prepared as described for the corresponding derivative of xanthatic acid. The compound melted at 135–136.5°.

*Anal.* Calcd. for $C_{21}H_{23}O_6N$: C, 65.44; H, 6.02. Found: C, 65.61; H, 6.09.

**Chromic Acid Oxidations.**—An oxidizing solution was prepared by dissolving 33.6 g. of chromium trioxide in 200 ml. of water and 20 ml. of concentrated sulfuric acid. When 600 mg. of succinic acid was refluxed with 100 ml. of this solution for 1.5 hours, 47% of the succinic acid was recovered. From 1.5 g. of cyclohexanone and 150 ml. of the oxidizing solution (2 hours), 1.21 g. (73%) of adipic acid was isolated; from 1.0 g. of cyclopentanone and 100 ml. of the oxidizing solution (2 hours), 1.14 (73%) of glutaric acid was isolated; and from 1.53 g. of proline and 100 ml. of oxidizing solution, 0.11 g. (8%) of succinic acid was isolated.

**Methylsuccinic Acid.** (**A**).—A solution of 1.95 g. of xanthinin in 140 ml. of the oxidizing solution was refluxed for 2.25 hours. The excess chromic acid was reduced with 40% formaldehyde and the aqueous solution extracted continuously with ether. After evaporation of the ether, the residual oily material was dissolved in hot benzene and allowed to cool. The product weighed 0.25 g., melted at 109–111° (reported[19] m.p. 111°), and after recrystallization from water melted at 115–117°. Mixed with *dl*-methylsuccinic acid (m.p. 115–117°) the m.p. was 103–113°. The variation in melting point (recrystallized from carbon tetrachlo-

(19) S. H. Harper, *J. Chem. Soc.*, 595 (1942).

ride the sample melted at 104–106°) appears to be due to the fact that the compound is a mixture of the active and racemic acids.[11]

*Anal.* Calcd. for $C_5H_8O_4$: C, 45.45; H, 6.10. Found: C, 45.30; H, 6.26.

(B).—Oxidation of xanthatin under the above conditions gave an 18% yield of methylsuccinic acid, m.p. 112–114°; mixed with *dl*-methylsuccinic acid the m.p. was 105–114°.

**Monoanilide of Methylsuccinic Acid (from Xanthinin).**—A solution of 85 mg. of methylsuccinic acid in 0.75 ml. of thionyl chloride was refluxed for 45 minutes. The excess thionyl chloride was removed and to the residue was added a solution of 0.5 g. of aniline in 5 ml. of benzene. After 5 minutes refluxing a precipitate appeared. This was collected, washed with dilute hydrochloric acid, dissolved in 5% sodium hydroxide solution, and reprecipitated with dilute acid. Recrystallized from ethanol–benzene, the anilide melted at 150–151.5°.

*Anal.* Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.85; H, 6.59; N, 6.74.

Authentic *dl*-methylsuccinanilic acid was prepared, and had m.p. 147–149° (reported 148–149°,[20] 147°[21]), and a mixture of the two melted at 140–144°. Again, the presence of a mixture of active and racemic forms in the product derived from xanthinin is probably responsible for the differences in melting point.

**Quinine Salt of *d*-Methylsuccinic Acid (from Xanthinin).**—To a hot aqueous solution of 0.114 g. of the methylsuccinic acid from the oxidation of xanthinin was added an equivalent amount of *l*-quinine. On cooling, the solution deposited the crystalline salt, m.p. 168–169.5°. The quinine salt derived from authentic *dl*-methylsuccinic acid was made in the same way, and melted at 168–169.5° (reported[12,22] 169–171°). The two samples showed no depression in melting point on mixing.

The quinine salt crystallizes with water and after drying at room temperature over phosphorus pentoxide (16 hours) melted at 184–186° and analyzed for the monohydrate.

*Anal.* Calcd. for $C_{20}H_{24}N_2O_2 \cdot C_5H_8O_4 \cdot H_2O$: C, 67.65; H, 7.32. Found: C, 67.63; H, 7.30.

After drying at 138° ($P_2O_5$, 27 hours) the salt melted at 188–190° and was anhydrous.

*Anal.* Calcd. for $C_{20}H_{24}N_2O_2 \cdot C_5H_8O_4$: C, 69.20; H, 7.23. Found: C, 68.97; H, 7.27.

The salt from the synthetic acid, treated in the same way, formed the monohydrate (m.p. 182–184°; found: C, 67.64; H, 7.48) and the anhydrous form (m.p. 188–189°; found: C, 69.11; H, 7.36).

**Carbon-linked methyl groups were** determined by the use of the procedure of Barthel and LaForge.[23] In Table III are collected the C-methyl values for the compounds analyzed.

TABLE III

| Compound | C-Methyl groups |
|---|---|
| Xanthinin | 2.45 |
| Xanthatin | 1.44 |
| Dihydroxanthinin | 2.96 |
| Dihydroxanthatin | 1.95 |
| Xanthinin-pyrazoline | 2.55 |
| Xanthatin-pyrazoline | 1.47 |
| Xanthatin-dipyrazoline | 1.42 |
| Xanthatic acid | 0.53 |
| Dihydroxanthatic acid | 1.39 |
| Methyl xanthatate pyrazoline | 0.64 |

**Ultraviolet absorption spectra** were determined with a Beckman model DU spectrophotometer.

**Infrared absorption spectra** were determined with a Perkin–Elmer model 21 recording spectrophotometer equipped with a sodium chloride prism. Samples were in chloroform solution, as a film, or in a potassium bromide disk as noted in Table II.

(20) W. A. Bone and C. H. G. Sprankling, *J. Chem. Soc.*, **75**, 839 (1899).

(21) D. Vorländer, P. Weissheimer and F. Sponnagel, *Ann.*, **345**, 232 (1906).

(22) I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Eyre and Spottiswoode, Ltd., London, 1953.

(23) W. F. Barthel and F. B. LaForge, *Ind. Eng. Chem., Anal. Ed.*, **16**, 434 (1944).

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[CONTRIBUTION OF THE DEPARTMENT OF RESEARCH AND DEVELOPMENT, U. S. NAVAL POWDER FACTORY]

# The Reaction of Thiopseudoureas with 1,3-Diamino-2,2-bis-(hydroxymethyl)-propane[1]

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The reaction of 1,3-diamino-2,2-bis-(hydroxymethyl)-propane with the salts of 2-methyl-2-thiopseudourea or with 1-nitro-2-alkyl-2-thiopseudourea formed the following products: the salt of 1,3-bis-(guanidino)-2,2-bis-(hydroxymethyl)-propane, the salt of 1-guanidino-3-amino-2,2-bis-(hydroxymethyl)-propane, 1,3-bis-(nitroguanidino)-2,2-bis-(hydroxymethyl)-propane, 2-nitrimino-5,5-bis-(hydroxymethyl)-1,3-diazacyclohexane and 2-imino-5,5-bis-(hydroxymethyl)-1,3-diazacyclohexane, which may have formed from the nitrimino compound by a secondary reaction involving the addition of ammonia and the elimination of nitramide. These compounds when nitrated yielded 1,3-bis-(nitroguanidino)-2,2-bis-(nitroxymethyl)-propane and 2-nitrimino-5,5-bis-(nitroxymethyl)-1,3-diazacyclohexane. The 1,3-diamino-2,2-bis-(hydroxymethyl)-propane was prepared from the diacetate of 1,3-dibromo-2,2-bis-(hydroxymethyl)-propane by the Gabriel synthesis.

Both straight chain and cyclic guanidine and nitroguanidine derivatives of 2,2-bis-(hydroxymethyl)-1,3-propanediol have been prepared by the reaction between 1,3-diamino-2,2-bis-(hydroxymethyl)-propane and 1-nitro-2-alkyl-2-thiopseudoureas[2] or the salts of 2-methyl-2-thiopseudoreas.[3–5] The 1,3-diamino-2,2-bis-(hydroxymethyl)-propane used in the synthesis of these compounds was prepared from the diacetate of 1,3-dibromo-2,2-bis-(hydroxymethyl)-propane by the Gabriel synthesis. 1,3-Bis-(phthalimido)-2,2-bis-(hydroxymethyl)-propane could not be prepared from 1,3-dibromo-2,2-bis-(hydroxymethyl)-propane. The recovery of over 50% of the potassium phthalimide used in this reaction as phthalimide indicated that hydrogen bromide had split from the 1,3-dibromo-2,2-bis-(hydroxymethyl)-propane with the probable formation of an oxacyclobutane ring. Phthalimide would then be formed by the reaction between hydrogen bromide and potassium phthal-

(1) Published with permission of the Bureau of Ordnance, Navy Department. The opinions and conclusions are those of the authors.

(2) L. Fishbein and J. A. Gallaghan, THIS JOURNAL, **76**, 1877 (1954).

(3) B. Rathke, *Ber.*, **17**, 297 (1884).

(4) H. L. Wheeler and G. S. Jamieson, *J. Biol. Chem.*, **4**, 111 (1907).

(5) W. Schoeller and H. Schotte, U. S. Patent 1,805,889 (1931).