Sesquiterpene Lactones of *Xanthium* Species. Xanthanol and Isoxanthanol, and Correlation of Xanthinin with Ivalbin

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Examination of a number of specimens of several *Xanthium* species has disclosed the existence of chemical differences between species and between individual *X. strumarium* chemovars. Two new lactones, xanthanol and isoxanthanol, have been isolated and related to xanthinin and to ivalbin, a lactone from *Iva* species. The xanthinin–ivalbin and xanthumin–gafrinin series are differentiated in the stereochemistry of the lactone ring fusion.

The genus *Xanthium* (family *Compositae*, tribe *Ambrosieae*), the common cocklebur, includes a number of species as well as what appear to be chemovariable members of the widely distributed *X. strumarium* L. We have examined a number of *Xanthium* specimens, including some designated as *strumarium* and some by other specific epithets, and have found xanthinin (**1**)[1] in some, xanthumin (**2**)[2] in others, and in others mixtures of xanthinin and xanthumin. Besides these two known sesquiterpene lactones two new lactones have been isolated from a specimen identified as *X. strumarium* L. collected at La Paz, B.C., Mexico.[3]

In the earlier study[1] of *X. strumarium* L. (*X. pennsylvanicum*)[4] xanthinin was the only compound found. Recent reexamination of several *Xanthium* specimens with the aid of thin layer chromatography disclosed the presence in some (but not all) plants of additional constituents, two of which have been isolated.

Xanthanol (**3**) has the composition of a dihydroxanthinin (Chart I). Its spectral properties are similar to those of xanthinin but differ from those of the latter in showing the absence of a carbonyl group and the presence of a hydroxyl group. Xanthanol yields an acetate (**4**), and is converted into xanthinin by chromic acid oxidation.

Isoxanthanol (**5**) is isomeric with xanthanol, and it was clear from the spectra of **3** and **5** that they were closely related in structure. The nmr spectra of both **5** and **3** show signals for two secondary methyl groups (δ 1.28, J = 7 cps; δ 1.20, J = 6.0 cps, in **5**), but the complex signal at δ 3.7 present in the spectrum of **3** is absent in **5**, being replaced by a well-defined triplet at δ 4.05. This suggested that **3** and **5** are related by an interchange of the hydroxyl and acetoxyl groups and this was confirmed by the preparation of the acetate of **5**, identical with **4**.

Oxidation of **5** with manganese dioxide converted it into the ketone, **6**. Although this ketone could not be crystallized it could be obtained in a chromatographically (tlc) pure state. The ultraviolet spectrum was that of an α,β-unsaturated ketone, and the nmr spectrum was in accord with the structure shown. A vinyl proton in a β position to the carbonyl group (δ 7.1) and a quartet centered at δ 2.95 (J = 6.5, 11.5 cps), the latter showing the geminal coupling of the methylene group at C-3, are in agreement with the structure **6**.

Although **6** could not be crystallized even when seeded with a specimen of the ivalbin-derived compound[5] of the same gross structure, the two compounds give nmr spectra nearly identical in all respects. The compounds show different optical rotations. That they differ only in the configuration of the CHOAc grouping was shown by the smooth conversion of **6**, by passing it over an alumina column, into the dienone **7**, identical with the compound obtained from ivalbin.

Xanthanol or isoxanthanol can be converted into a mixture of the two with aqueous alkali as a result of the 1,3 exchange of acetoxyl and hydroxyl groups similar to that observed in the case of gafrinin.[6] The oxidation of gafrinin with manganese dioxide yielded some xanthumin as a result of the isomerization of the 2-hydroxy-4-acetoxy compound into the 2-acetoxy-4-hydroxy compound. No xanthinin was formed during the oxidation of **5** to **6**, and it is possible that the manganese dioxide used in the oxidation of gafrinin may have contained a trace of alkali.

Because of the ready isomerization of **3** and **5** the possibility exists that one of them is an artefact. It is believed, however, that both **3** and **5** are natural products, for they are both observable on thin layer chromatograms of crude extracts of the plant prior to chromatographic separation procedures, and they have not been observed to undergo interconversion during the usual manipulations.

Xanthumin and xanthinin differ in the stereochemistry of the lactone ring system. Both compounds yield (−)-(*S*)-methylsuccinic acid on chromic acid oxidation; xanthatin (**8**) and the corresponding dienone from xanthumin[2] are different compounds; xanthumin has been shown to possess a *cis*-fused lactone ring;[2] and, if the assumption is made that xanthinin and xanthumin, like all other lactones of the class derived from plants of the Compositae, possess a β-oriented C-7/11 bond, the absolute stereochemistry of both compounds is defined as in the structures written in this paper, with the sole exception of the configurations of the –CHOH and –CHOAc groupings in all of the compounds of the two series.

Lactones of *Xanthium* Species and Varieties.—

(1) P. G. Deuel and T. A. Geissman, *J. Amer. Chem. Soc.*, **79**, 3778 (1959).

(2) H. Minato and I. Horibe, *J. Chem. Soc.*, 7009 (1965).

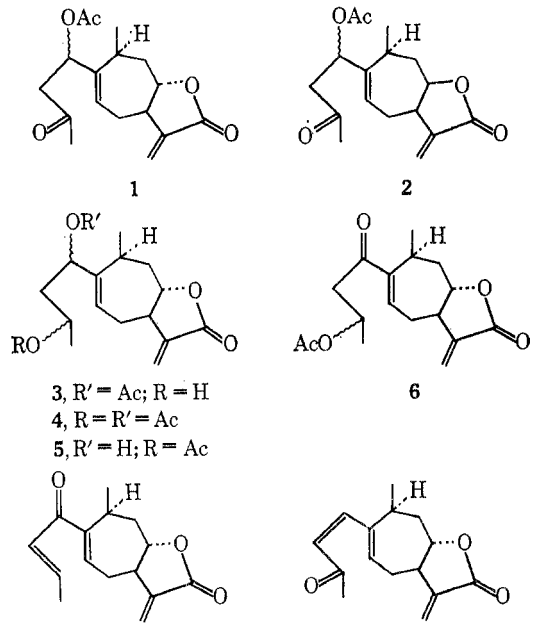
(3) All of the specimens used, with the exception of those designated by the symbols -SX and -SY (Table I), were furnished by Dr. W. Payne, who provided the identification for all of the plants used. Professors M. Mathais and K. C. Hamner, Department of Botany, UCLA, also provided help in establishing the identity of the material.

(4) The plant used in the early work, then called *X. pennsylvanicum*, was a variety from northern Illinois. While this plane is morphologically indistinguishable from *Xanthium* collected in Los Angeles, the two varieties show distinctly different photoperiodic responses (K. C. Hamner, private communication).

(5) W. Herz, H. Chikamatsu, N. Viswanathan, and V. Sudarsanam, *J. Org. Chem.*, **32**, 682 (1967).

(6) L. A. P. Anderson, W. T. deKook, W. Nel, and K. G. R. Pachler, *Tetrahedron*, **24**, 1687 (1968).

CHART I



Examination of two collections of *X. strumarium* L., growing in Los Angeles and morphologically indistinguishable, led to the surprising observation that one of them contained essentially only xanthumin, the other largely xanthinin along with a small amount of xanthumin. Study of a number of *Xanthium* specimens provided by Dr. W. W. Payne[3] gave the results shown in Table I. It is to be noted that xanthinin and xanthumin show nearly identical behavior on tlc, but it is fortunate that the compounds crystallize with ease from partially refined plant extracts. They possess quite different melting points, and the melting point of once-recrystallized material provided a reliable index of composition. Pure xanthumin has mp 99–100°, pure xanthinin has mp 126°, and xanthinin contaminated with xanthumin was found to have a melting point between about 110 and 120°, which could be raised to over 120° by repeated recrystallization.

TABLE I

Specimen no.	Plant[a]	Amt, g	Mp of once-recrystallized product, °C	Yield, g
1	*X. strumarium*[b]	160	118[g]	2.35
2	*X. strumarium*[c]	20	98–99[h]	0.25
3	*X. strumarium*[d]	40	123–124	0.50
4	*X. strumarium*[e]	26	123–124	0.54
5	*X. strumarium*[f]	10	123–124	0.12
6	*X. commune*	14	122–123	0.07
7	*X. chinense*	32	96–97	0.19
8	*X. chasei*[i]	19	99–99.5	0.12

[a] All plants mature, seed bearing. Leaves only used. [b] 10867-X-SA (TAG). [c] 91667-X-SY (TAG). [d] "*X. pennsylvanicum*" (used by K. C. Hamner for photoperiodism study). [e] La Paz, Mexico. Crude material before recrystallization, mp 116–118°. [f] Sonora, Mexico. Specimens 3–8 from W. W. Payne. [g] From mother liquors of recrystallization of crude xanthinin obtained xanthumin, mp 99–100°. [h] Last fractions from mother liquors, mp 98–99°. [i] Specimens no. 4, 5, 6 showed (in crude total lactone fraction) two prominent spots on tlc (xanthinin and xanthanol). Specimens 2 and 8 showed the higher R_f spot (xanthumin) only.

Experimental Section

Detailed presentation of nmr data is omitted. Values pertinent to the discussion have been given in the text.

Isolation of Xanthanol (3) and Isoxanthanol (5).—Powdered leaves (1 kg) of *Xanthium strumarium* L. from La Paz, Mexico,[3] were processed as previously described for the isolation of xanthinin.[1] After the separation of xanthinin (5.4 g, mp 126°) the residual mother liquors were concentrated and chromatographed on a column of silica gel (Baker, 1 kg, previously washed with a 0.01% solution of acetic acid in benzene), with the collection of 100-ml fractions.

Fractions 25–54 (benzene–ether, 20:1) yielded further xanthinin (3.8 g, mp 126°).

Fractions 62–84 contained a mixture of xanthanol and isoxanthanol which, after rechromatography twice, yielded xanthanol (500 mg) as colorless needles from ether–hexane: mp 78–79°; $[\alpha]^{26}D$ −87.3° (*c* 0.96, chloroform). The infrared spectrum ($CHCl_3$) showed absorption at 3500–3600, 1770, and 1725 cm^{-1}. The ultraviolet spectrum showed only the absorption typical of the α,β-unsaturated lactone.

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.20; H, 7.99.

Xanthanol Acetate (4).—Acetylation of 60 mg of xanthanol with pyridine–acetic anhydride gave xanthanol acetate (4): 60 mg; mp 69–70° (from ether–hexane); $[\alpha]^{25}D$ −30.0° (*c* 0.99, chloroform); infrared 1770, 1740 cm^{-1} (no absorption in the hydroxyl region).

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 65.12; H, 7.48.

Isoxanthanol (5).—Rechromatography of fractions 62–84 yielded, in addition to xanthanol, 275 mg of isoxanthanol: mp 101–102° (from ether–hexane); $[\alpha]^{25}D$ 27.9° (*c* 0.99, chloroform). Infrared peaks ($CHCl_3$) were observed at 3500–3600, 1700, and 1725 cm^{-1}.

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.11; H, 7.72.

Isoxanthanol Acetate (Xanthanol Acetate) (4).—Acetylation of isoxanthanol with pyridine–acetic anhydride yielded the acetate, mp 69–70°, identical with the acetate of xanthanol.

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 65.26; H, 7.43.

Xanthinin (1) from Xanthanol (3).—A solution of 100 mg of xanthanol in 10 ml of acetone was treated with chromic acid–aqueous sulfuric acid reagent[7] until the color of the reagent persisted. The solution was diluted with water and extracted with ether and the ether solution washed with water, dried over magnesium sulfate, and concentrated to 10 ml. Xanthinin separated as colorless needles (65 mg), and had mp 126–127°. It was identical with natural xanthinin by mixture melting point, infrared spectrum, tlc, and color reaction with HCl–ethanol.

Examination of the ether mother liquors failed to disclose the presence of the isomeric α,β-unsaturated ketone that would have been formed had acetyl migration taken place in the course of the oxidation, a process that was reported to occur in the oxidation of gafrinin with manganese dioxide.[8]

Fractions 85–115 (benzene–ether, 4:1) of the original silica column gave gum consisting mainly of xanthanol. Oxidation of this material yielded 2.35 g of xanthinin, mp 126°.

Interconversion of Xanthanol and Isoxanthanol.—A solution of 2 mg of xanthanol in 5 ml of ether was shaken with 5 ml of 0.1 *N* aqueous potassium hydroxide for 10 min. The ether solution was separated, washed with water, dried ($MgSO_4$), and evaporated. Thin layer chromatographic examination of the residual material disclosed that it was a mixture of xanthanol and isoxanthanol. Treatment of pure isoxanthanol in the same way gave the same mixture of the isomers.

Oxidation of Isoxanthanol (5) to 6.—A solution of 60 mg of isoxanthanol in methylene chloride was stirred with 1.5 g of active manganese dioxide[8] for 24 hr at 20°. The filtered solution was evaporated to an oily residue which was purified by chromatography on silica gel (washed with acetic-acid-containing benzene). The product (6) was an oil which could not be crystallized but which showed a single compact spot on tlc and gave an

(7) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(8) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. H. Jansen, and T. Walker, *ibid.*, 1094 (1952).

nmr spectrum that was in complete accord with the structure assigned. Crystallization could not be induced by seeding the oil with a crystal of the corresponding ketone from the ivalbin series. There was no trace of xanthinin in the crude products of this oxidation reaction (by tlc).

Anhydrodehydroivalbin (7) from Isoxanthanol—The oily ketone (6, 20 mg) was chromatographed in ether solution over a column of alumina (Woelm, activity II). The eluate was evaporated and the residue recrystallized from ether–hexane to yield colorless needles of the dienone (VI): mp 117–118°; $[\alpha]^{25}D$ 63° (*c* 0.23, chloroform) [lit.[5] mp 117–118°; $[\alpha]D$ 59° (*c* 0.195, chloroform)]. A mixture melting point with a specimen of anhydrodehydroivalbin was undepressed, and the two materials showed identical behavior on tlc.[9] The uv spectrum showed λ_{max} 244 mμ (ε 12,300) [lit.[6] λ_{max} 245 mμ (13,000)].

Extraction of Assay Specimens (Table I). 1.—A sample of 20 g of dried, ground leaves of *X. strumarium* (no. 91667-X-SY) was extracted with chloroform and the solvent removed. The tarry residue was dissolved in 10 ml of ethanol to which was added 50 ml of hot water. The clear aqueous portion was decanted from tar, treated with a few drops of lead acetate, clarified by filtration through Celite, and extracted with chloroform. The chloroform layer showed a single spot on tlc. Evaporation of the solvent left a gum which crystallized when ether was added. The product was collected and washed with cold ether; it formed colorless needles, mp 98–99° (250 mg).

2.—A 160-g sample of *X. strumarium* (no. 10867-X-SA) was worked up in the same way. The residue from the last chloroform extract yielded 2.35 g of crystals which had mp 112–114°. Mixture with pure xanthinin (mp 126°) gave a melting point of 116–120°, and with xanthumin (mp 99–100°) gave a melting point of 95–97°. One recrystallization from ethanol raised the melting point to 118–119°.

The ether mother liquors from the first crop of crystalline material were evaporated and the residual oil covered with ether and placed in the refrigerator. The crystals which separated were collected and recrystallized several times, yielding 0.44 g of pure xanthumin, mp 99–100°.

(−)-(*S*)-Methylsuccinic Acid. A. From Xanthinin.—To 500 mg of xanthinin was added 20 ml of a solution prepared by dissolving 34 g of chromic oxide in 200 ml of water and 20 ml of concentrated sulfuric acid. The solution was refluxed for 2.3 hr, cooled, and extracted continuously with ether. The ether extract was dried and evaporated and the oily residue dissolved in benzene. The crystalline product (65 mg) that separated was recrystallized from benzene to give 58 mg of methylsuccinic acid, mp 110–111°. A mixture of this material with authentic (±)-methylsuccinic melted at 108–111°. The rotation was $[\alpha]^{26}D$ 7.7° (*c* 3.64, H_2O). The nmr spectrum of the compound was identical with that of the authentic material.

B. From Xanthumin.—The same procedure was used for the oxidation of 500 mg of xanthumin to yield 50 mg of methylsuccinic acid, mp 110.5–111°. A mixture melting point of the two acids from the natural sources was undepressed. The rotation was $[\alpha]^{26}D$ 5.5° (*c* 2.04, H_2O).[10]

Registry No.—**1**, 17954-90-4; **3**, 17976-42-0; **4**, 17954-91-5; **5**, 17968-60-4; **7**, 17968-61-5; (−)-(*S*)-methylsuccinic acid, 2174-58-5.

Acknowledgments.—This work was supported by a Grant GM-14240-02 from the U. S. Public Health Service. Analyses were by Miss Heather King, UCLA. We are grateful to Professor W. W. Payne for plant material and valuable consultation and to Professor Werner Herz for specimens of compounds of the ivalbin series.

(9) Specimens of acetyldehydroivalbin and anhydrodehydroivalbin were kindly provided by Professor W. Herz.

(10) The polarimetry was checked by measuring the rotation of xanthinin, $[\alpha]^{26}D$ 54.5° (lit.[1] $[\alpha]^{26}D$ 52°). Since the melting point of pure (−)-(*S*)-methylsuccinic acid is reported to be 115°, some racemization took place during the oxidation. M. Matell [*Arkiv. Kemi*, **5**, 17 (1952)] reported $[\alpha]^{23}D$ 6.1° for methylsuccinic acid obtained by the oxidation of active 2-methyl-4-pentenoic acid, from which it was calculated that the product was a mixture of 63% (−) and 37% (±) acid.

Thermal and Photochemical Rearrangements of Azine Oxides. I. A Novel Pyrolytic Decomposition to Nitriles

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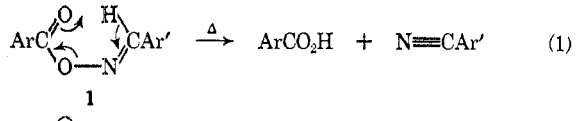
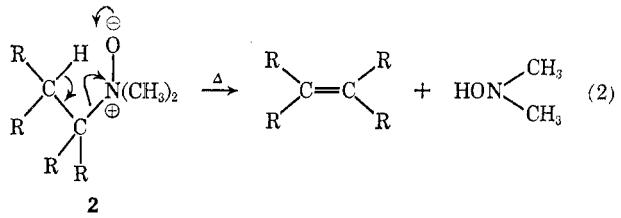
An investigation of the pyrolytic decomposition of aldazine monoxides has led to the discovery of a new eliminative process which results in fragmentation of the monoxide to 1 equiv each of nitrile and oxime. A new, easy process for preparing pure aromatic azine monoxides in good yields, utilizing CF_3CO_3H as the oxidizing agent in a buffered solution, is described and discussed along with attempts to extend such preparations to aliphatic systems. An unsymmetrical azine oxide is prepared and characterized for the first time, and its pyrolysis is discussed.

Pyrolyses of either benzoyl-α-benzaldoximes, **1**,[1] amine oxides, **2**,[2] or nitronate esters, **3**[3] (eq 1–3), result cleanly in elimination processes, ostensibly *via* cyclic transition states as shown below. Aldazine



(1)

1



(2)

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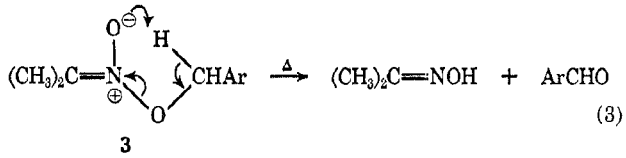

(3)

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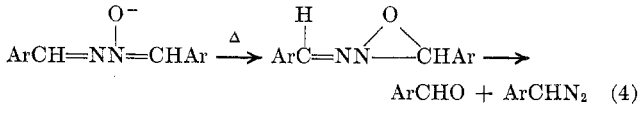
monoxide systems, on the other hand, while bearing much analogy to the above systems, have been reported[4] upon pyrolysis to fragment as in eq 4 to aldehydes and diazo compounds, presumably *via* oxazirane intermediates.



(4)

We wish at this time to present some results from our current research into the chemistry of azine oxides.

(1) J. H. M. Hill and L. D. Schmookler, *J. Org. Chem.*, **32**, 4025 (1967).
(2) A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 361 (1960).
(3) H. B. Hass and M. L. Bender, *J. Amer. Chem. Soc.*, **71**, 1767 (1949).
(4) L. Horner, W. Kirmse, and H. Fernekess, *Chem. Ber.*, **94**, 279 (1961).