2-Carbethoxy-3-tosyloxythieno[3,2-*b*]pyrrolyl-6-glyoxylic Acid (XII).—To a suspension of 0.139 g. (0.3 mmole) of the glyoxylic ester VII in 5 ml. of 95% ethanol was added at room temperature 0.12 ml. (0.6 mmole) of 5 *N* sodium hydroxide solution, whereupon a clear, yellow solution was formed. After standing at 25° for 1.5 hr., a slightly yellow, amorphous precipitate began to separate; the reaction mixture was allowed to stand at room temperature 4 hr., after which time 3 ml. of water was added. The resulting clear, orange solution was then neutralized with ice-cold 6 *N* hydrochloric acid and concentrated under reduced pressure to about 2 ml. The crude acid XII, precipitated as an oily product, solidified upon cooling and scratching to form light tan crystals. The product was filtered, washed with water, and dried *in vacuo* over phosphorus pentoxide, affording 0.10 g. (75%) of the crude acid XII. Purification of XII was achieved by dissolving the crude product in 2.5 ml. of hot 95% ethanol and adding 8 ml. of water until the solution remained faintly turbid. Upon slow cooling over a period of 11 hr., the pure acid XII crystallized in slightly tan, cotton-like crystals, m.p. 215–217 dec.; the material contained 0.5 mole of water of crystallization, which was not removed by drying overnight at 78° (0.025 mm.). Infrared (KBr pellet) 3190 (N–H), 1720 and 1645, sh ($CO–CO_2H$), 1663 (carbethoxy C=O), 1390 and 1174 ($—O—SO_2^-$), 1268 $cm.^{-1}$ (C—O stretch).

Anal. Calcd. for $C_{18}H_{15}NO_8S_2{\cdot}1/2H_2O$: C, 48.42; H, 3.61; N, 3.14. Found: C, 48.58; H, 3.56; N, 3.14.

2-Carbethoxy-3-hydroxythieno[3,2-*b*]pyrrolyl-6-glyoxylic Acid (IX). (A) **From 2-Carbethoxy-3-acetoxy-6-ethoxyalylthieno[3,2-*b*]pyrrole (VIII).**—To a suspension of 0.27 g. (0.76 mmole) of the ester VIII in 10 ml. of 95% ethanol and 2 ml. of water was added at room temperature 0.612 ml. (3.06 mmoles) of 5 *N* sodium hydroxide, and the resulting orange-colored solution was heated on a steam bath under reflux for 10 min. The solution was allowed to stand at room temperature for 13 hr., after which time the precipitated orange solid (Na salt) was dissolved by addition of 11 ml. of water to the mixture. After neutralization of the excess base with ice-cold 6 *N* hydrochloric acid the clear solution was poured into 10 ml. of ice water and the colorless, microcrystalline precipitate was collected, washed with water, and dried *in vacuo*. The yield of crude IX was 0.22 g. (96%). An analytical sample, obtained by very slow cooling of a solution of IX in a minimum amount of ethanol–water (1:3), formed fluffy, colorless needles, which turned bright yellow upon drying *in vacuo*, m.p. (on a preheated hot stage) 244–246° dec., darkening at 239°. Two additional recrystallizations from ethanol–water did not affect the melting point or infrared spectrum. The product was obtained as a monohydrate after drying for 16 hr. over phosphorus pentoxide *in vacuo* (0.05 mm.) at room temperature. A solution of IX in 95% ethanol gave a positive ferric chloride test[34] (intense dark green color). Infrared (KBr pellet): 3380 (broad, O—H), 3260 (N—H), 1715 and 1624 ($CO—CO_2H$), 1658 (carbethoxy C=O), 1265 and 1237 $cm.^{-1}$ (C—O stretch).

Anal. Calcd. for $C_{11}H_9NO_6S{\cdot}H_2O$: C, 43.85; H, 3.86; N, 4.65. Found: C, 43.72; H, 3.84; N, 4.62.

(B) **From 2-Carbethoxy-3-acetoxythieno[3,2-*b*]pyrrolyl-6-glyoxylyl Chloride (VI).**—To a suspension of 0.343 g. (1 mmole) of glyoxylyl chloride VI in 20 ml. of water was added 1 ml. (5 mmoles) of 5 *N* sodium hydroxide at room temperature. The resulting clear orange solution was heated on a steam bath for 15 min., then allowed to stand at room temperature for 23 hr. and finally neutralized with ice-cold 6 *N* hydrochloric acid. The mixture was chilled for 30 min. and the pale yellow precipitate was collected, washed with a small amount of water, and dried *in vacuo*; wt. 0.28 g. (93%). Purification of the crude product by the method given under procedure A afforded yellow needles, m.p. 243–245° dec. A mixture melting point determination and the infrared spectrum (KBr) confirmed the identity of the product with the acid IX prepared according to procedure A.

The Structure of Xanthinin

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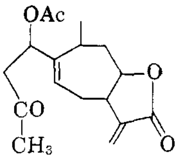
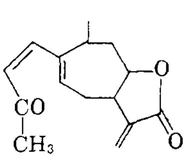
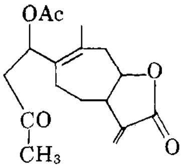
The structures of xanthinin (I) and xanthatin (II), sesquiterpene lactones derived from *Xanthium pennsylvanicum* (cocklebur), were first proposed by Deuel and Geissman in 1957.[1] In the same year, Dolejš and his collaborators[2] described their studies on these compounds and agreed that the structure for II was correct, but proposed the structure III for xanthinin. Structures III and I differ only in the position assigned to one of the double bonds. In the work of Deuel and Geissman the assignment was made on the basis of the characteristic infrared absorption associated with the $—CH{=}\overset{|}{C}—$ grouping, while the Czech workers arrived at the alternative conclusion from the results of an oxidative degradation.


I


II


III

The structure of xanthinin has now been reexamined with the aid of NMR. The results are clear and unequivocal, and substantiate the structure (I) originally put forward by Deuel and Geissman. The relevant portions of the NMR spectrum are shown in Fig. 1. The presence of the secondary methyl group is shown by the symmetrical doublet at $\tau = 8.9$. No methyl group singlet of the type $CH_3—C{=}C$, as would be required for structure III,

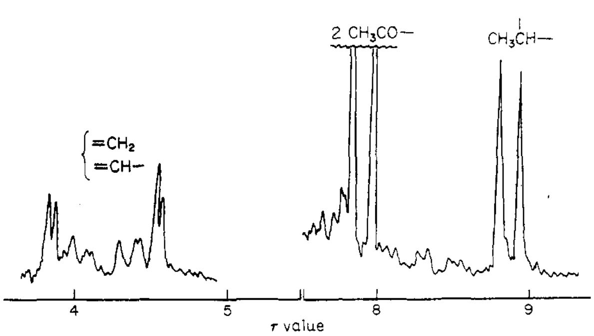


Fig. 1.—NMR spectrum of xanthinin (60 mc. $CDCl_3$), shown for τ = 4 to 5, 8 to 9 regions.

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[1] P. G. Deuel and T. A. Geissman, *J. Am. Chem. Soc.*, **79**, 3778 (1957).

[2] L. Dolejš, V. Herout, and F. Šorm, *Chem. Listy*, **51**, 1521 (1957); *Coll. Czech. Chem. Commun.*, **23**, 504 (1958).

is present. In addition, the vinyl proton region (near $\tau = 4$) shows both the pair of doublets associated with the exocyclic methylene group of the lactone and additional vinyl peaks for $=CH—$, probably affected by the adjacent $—CH_2$-grouping and perhaps by the side chain, in the same region of the spectrum. Were structure III the correct one, there would be no additional vinyl hydrogen signals besides those of the $=CH_2$ group.

The explanation for the results of the degradation experiments described by the Šorm group is obscure, but there can be no doubt that xanthinin has indeed the structure I, despite the Czech findings.

Configurations of 1- and 7-Acetylthio-4-androstene-3,17-diones

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In a previous paper[1] the preparation of a number of 1α- and 7α-acetylthio-Δ^4-3-oxo steroids was reported. At that time the configurations at 1 and 7 were assigned on the basis of analogy in the absence of more definitive evidence. Since NMR spectra have now been used to assign configurations in a similar series of steroidal esters,[2] we decided to examine the curves of some of the sulfur compounds. The substituted 4-androstene-3,17-diones were chosen as readily available models whose NMR spectra should not be too complicated.

In the previous paper,[1] the 7α-acetylthio compound was described as a glass. This result was apparently due to the presence in the starting 4,6-dien-3-one of an appreciable amount of 1,4-diene-3-one. The use of pure material gave, by chromatography and fractional crystallization, both the 7α- and 7β- isomers as crystalline solids. The molecular rotatory changes for the two compounds are consistent with the values reported for the corresponding oxygen esters.[2]

A definitive proof of the structures is proved by the NMR spectra.[3] The spectra of the thioesters (see Table I) are qualitatively quite similar to those of their oxygen analogs, whose structures have been discussed.[2] The peaks for the 7α- and 7β-acetoxymethyls and the 7β-hydrogen are quite close to Jackman's values for alicyclic acetates.[4] The acetylthio-methyls show a shift of about 0.25–0.30 p.p.m. to lower τ values, while the peaks of the protons on the same carbon atom as the sulfur atom are shifted 1.0–1.2 p.p.m. higher than the corresponding peaks in the oxygen analogs.

TABLE I

NMR SPECTRA OF ACETYLTHIO-4-ANDROSTENE-3,17-DIONES

	Position of Acetylthio Group			
	7α	7β	1α	1β
C_4-H	4.30	4.23	4.25	4.17
19-Methyl	8.75	8.79	8.60	8.70
18-Methyl	9.08	9.10	9.10	9.13
1- or 7-Thioacetyl methyl	7.65	7.68	7.68	7.67
1- or 7-Hydrogen	5.92	6.43 6.54	5.92	5.74

Since the β-isomer had been found at the 7-position, we decided to check the addition product from the 1,4-diene as well. A careful reëxamination of the preparation of 1α-acetylthio-4-androstene-3,17-dione also revealed the presence of the β- isomer in 9% yield. In the case of the 1-isomers, the NMR spectra did not provide conclusive evidence for the assigned configurations. The 1β-hydrogen gives a good singlet, but the 1α-hydrogen produces a peak intermediate in shape between a singlet and a multiplet, and the positions of the two peaks are reversed compared to those of the 7-isomers.

We then turned to rotations to provide more conclusive evidence. The molecular rotatory contribution of the 1β-acetylthio group is strongly negative as is the value for 1β-acetoxy 4-androstene-3,17-dione $-358°$,[5] while the contributions of the 1α-acetoxy and acetylthio groupings are positive.[1]

The rotatory dispersion curves[6] also confirm the configurational assignments. The curves for the 1α-compounds are very similar to each other and to 4-androstene-3,17-dione[7] (see Table II), but the amplitudes of the peaks of the 1β-isomers are considerably lower than those of the 1α-isomers.

The relative yield of the isomers may vary depending on the conditions of the reaction. In the addition of ethanethiolic acid to 17a-oxa-D-homo-1,4-androstadiene-3,17-dione, a total of 97% of the 1α-isomer was obtained. This high yield may be due to the long heating period or to the fact that the product had crystallized from the hot mixture.

Another compound, previously reported as a glass,[1] has now been obtained in crystalline form. This is 1α-acetylthiotestosterone, whose constants are given in the experimental section.

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(1) R. M. Dodson and R. C. Tweit, *J. Am. Chem. Soc.*, **81**, 1224 (1959).

(2) R. C. Tweit, A. H. Goldkamp, and R. M. Dodson, *J. Org. Chem.*, **26**, 2856 (1961).

(3) Very kindly determined and interpreted by Dr. N. L. McNiven of the Worcester Foundation for Experimental Biology. They were run at 60 mc. in deuterochloroform. The shifts are reported as τ values relative to tetramethylsilane as an internal standard [see G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958)].

(4) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, 1959, pp. 55–7.

(5) R. M. Dodson, S. Kraychy, R. T. Nicholson, and S. Mizuba, *J. Org. Chem.*, in press.

(6) Very kindly determined by Professor W. Klyne of Westfield College (University of London) and Professor C. Djerassi of Stanford University.

(7) C. Djerassi, E. W. Foltz, and A. E. Lippman, *J. Am. Chem. Soc.*, **77**, 4354 (1955).