1294. *Studies on Sesquiterpenoids. Part XI.*[1] *Structure and Stereochemistry of Xanthumin, a Stereoisomer of Xanthinin*

By Hitoshi Minato and Isao Horibe

Xanthumin isolated from *Xanthium strumarium* L. is represented by the formula (II) and is a stereoisomer of xanthinin. Its stereochemistry is discussed.

Geissman,[2-4] Šorm,[5] and their co-workers isolated xanthinin (I), a sesquiterpene lactone, from the leaves of *Xanthium pennsylvanicum* and suggested structure (I) for it. Xanthinin was also obtained from the leaves of *Xanthium italicum* Mor. by Tóth *et al.*[6] Although we could not isolate xanthinin from the aerial part of Japanese-grown *Xanthium strumarium* L., we obtained a new sesquiterpene lactone, a stereoisomer of xanthinin (I), and named it " xanthumin," whose structure and stereochemistry are now described.

Xanthumin (II), m. p. 100·5—101°, $[\alpha]_D$ −48·2°, had the molecular formula, $C_{17}H_{22}O_5$, and showed maximum absorption at 207·5 mμ (ε 14,300) in the ultraviolet spectrum and at 1756 (γ-lactonic C=O), 1735 (acetate), and 1721 cm.$^{-1}$ (ketonic C=O) in the infrared spectrum. Moreover, as xanthumin (II) showed methyl signals at τ 7·82 (CH_3CO–) and τ 8·00 (–O·$COCH_3$) in the n.m.r. spectrum and gave iodoform on oxidation by sodium hypoiodite, five oxygen atoms of xanthumin are present as an acetyl group, an acetoxyl group, and a γ-lactonic function.

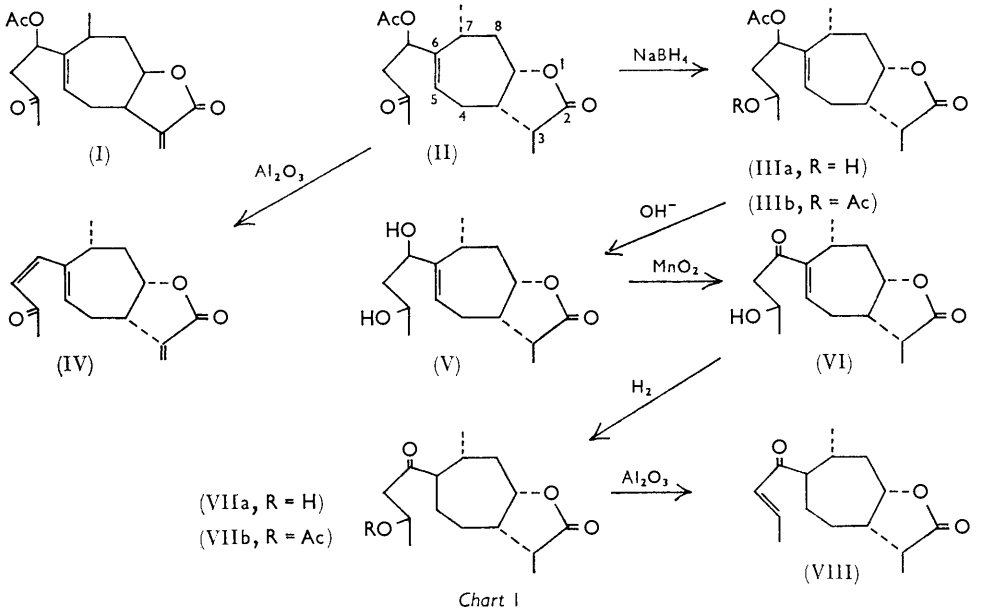


Chart I

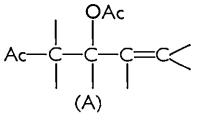
For the γ-lactone function, the following data are shown. In the n.m.r. spectrum, xanthumin (II) showed two vinyl protons at τ 3·75 (doublet, J = 2·8 c./sec.) and τ 4·45 (doublet, J = 2·8 c./sec.), which disappeared in its dihydrohydroxy-derivative (IIIa)

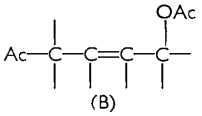
[1] Part X, H. Minato, M. Ishikawa, and T. Nagasaki, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 717.
[2] T. A. Geissman, P. G. Deuel, E. K. Bonde, and F. A. Addicott, *J. Amer. Chem. Soc.*, 1954, **76**, 685.
[3] T. A. Geissman and P. G. Deuel, *Chem. and Ind.*, 1957, 328.
[4] T. A. Geissman, *J. Org. Chem.*, 1962, **27**, 2692.
[5] L. Dolejš, V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1958, **23**, 504.
[6] J. Tóth, S. Holly, L. Ferenczy, and Ö. Kovács, *Rev. Chim. Acad. Rep. Populaire Roumaine*, 1962, **7**, 1339.

obtained by reduction of (II) with sodium borohydride. Compound (IIIa) absorbed at 1766 cm.$^{-1}$ (γ-lactonic C=O) in the infrared and at 206 mμ (ε 5500) in the ultraviolet spectrum; xanthumin therefore possesses an αβ-unsaturated γ-lactone function. From the n.m.r. data and the fact that xanthumin afforded the saturated lactone (IIIa) by reduction with sodium borohydride,[7,8] it was elucidated that xanthumin (II) has an exocyclic methylene-αβ-unsaturated γ-lactone grouping. As xanthumin furthermore shows a vinyl proton signal at τ 4·15 (quartet, J = 8·0, 6·4 c./sec.), it has one trisubstituted ethylenic double bond, and consequently is a monocyclic sesquiterpene having a γ-lactone function.

On alumina chromatography, xanthumin (II) afforded an oily lactone (IV), which no longer showed frequencies due to acetoxyl grouping and showed a band at 1668 cm.$^{-1}$ (>C=C–C=O) in the infrared and a maximum at 279 mμ (ε 14,200) [2,4-dinitrophenylhydrazone, m. p. 158—159°, $\lambda_{max.}$ 390 mμ (ε 36,500)] in the ultraviolet spectrum. It is reasonable to suppose that xanthumin (II) was converted into the dienone derivative (IV) as a result of elimination of its acetoxyl group on treatment with alumina.

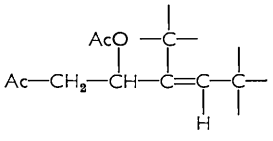
In order to confirm the relationship between the double bond and the acetoxyl group in (II), (IIIa) was hydrolysed with potassium carbonate in methanol to give an oily lactone (V), which was oxidised to a ketone (VI) with manganese dioxide. This ketone (VI) is an αβ-unsaturated ketone, since it has $\lambda_{max.}$ 234 mμ (ε 10,200) and $\nu_{max.}$ 1665 cm.$^{-1}$ (>C=C–C=O). Since the ketonic group in xanthumin (II) is isolated from the double bond, it must be obtained in (VI) by manganese dioxide oxidation of the hydroxyl group newly derived from hydrolysis of the acetoxyl group in (II). Therefore, the acetoxyl group of xanthumin (II) should be situated at the allylic position of the ethylenic double bond, and xanthumin has the partial structure represented by (A) or (B).





When the ketone (VI) was hydrogenated with 5% palladium–barium carbonate in ethanol, it afforded a ketone (VIIa) ($\nu_{max.}$ 1700 cm.$^{-1}$), the acetate (VIIb) of which was chromatographed on alumina to give a new αβ-unsaturated ketone (VIII), $\lambda_{max.}$ 225 mμ (ε 7900), $\nu_{max.}$ 1663 cm.$^{-1}$ (>C=C–C=O). As an αβ-unsaturated ketone system again is obtained by this operation and the eliminated acetoxyl group is derived from reduction of the ketonic group in (II), the acetoxyl group of xanthumin (II) should be at the β-position to its ketonic group, that is, xanthumin possesses the (A) system.

Ultraviolet spectra of (VI) and (VIII) ($\lambda_{max.}$ 234 and 225 mμ) showed that these ketones are a trisubstituted and a disubstituted αβ-unsaturated ketone, respectively. As the n.m.r spectrum of (II) furthermore showed a quartet signal (J = 8·1, 5·5 c./sec.) due to a proton attached to the carbon atom carrying the acetoxyl group at τ 4·85, there can only be two protons on carbon atoms adjacent to this carbon atom in (II). From these results, xanthumin has the following partial structure.



Compound (VI) afforded a dicarboxylic acid (IX) (di-*p*-bromophenacyl ester, m. p. 94—95°) by ozonolysis, followed by oxidation of its ozonide with potassium permanganate in acetic acid. By pyrolysis of the dicarboxylic acid (IX) with barium hydroxide, perhydrobenzofuran-2-one derivatives (Xa and Xb), m. p. 165—166° and m. p. 119—120°

[7] K. Takeda, H. Minato, and M. Ishikawa, *J.*, 1964, 4578.
[8] H. Minato, S. Nosaka, and I. Horibe, *J.*, 1964, 5503.

were obtained. In order to confirm the structure of compound (X), 3,6-dimethylperhydrobenzofuran-2,5-dione (X) was synthesised.

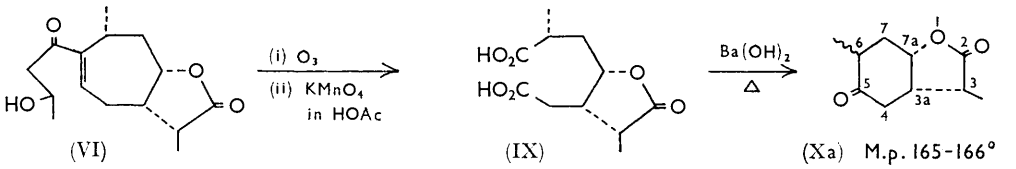


Chart 2

3-Methyl-4-methoxyphenol (XI) obtained from *o*-cresol by Baker and Brown's method [9] afforded a ketone (XIII) on hydrogenation with Raney nickel, followed by oxidation of (XII) with chromium trioxide. When the enamine of the ketone (XIII) was treated with ethyl α-bromopropionate, it gave a keto-ester (XIV), which was hydrolysed to give a keto-acid (XV), m. p. 122—123°.

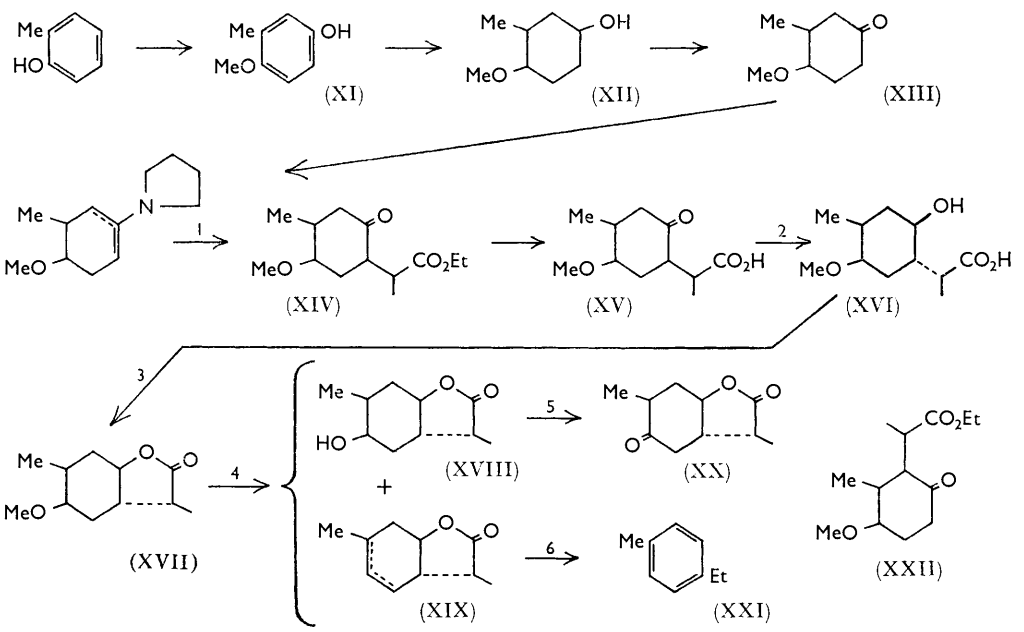


Chart 3

Reagents: 1, MeCHBr·CO_2Et; 2, Li–liq NH_3–MeOH; 3, H^+; 4, HI; 5, CrO_3; 6, Pd–C, $-H_2$

When the keto-acid (XV) was reduced with lithium–methanol in liquid ammonia to give the equatorial hydroxyl derivative, a hydroxy-acid (XVI), m. p. 119—121°, was obtained quantitatively. This acid afforded an oily lactone (XVII), which was converted into a hydroxy-lactone (XVIII) and an unsaturated compound (XIX) on treatment with hydriodic acid. On dehydrogenation of compound (XIX), it gave only *p*-ethyltoluene (XXI) as benzene derivative; therefore the condensation product by the enamine method was not compound (XXII) but (XIV).

Oxidation of (XVIII) with chromium trioxide gave a keto-lactone (XX), m. p. 118—

[9] W. Baker and N. C. Brown, *J.*, 1948, 2303.

119°, which showed a signal due to the axial-like proton on C-7a at τ 5·71 (octet, 11·0, 9·8, 3·5 c./sec.) in the n.m.r. spectrum. This fact and the following *cis*-lactone synthesis lead to the conclusion that the keto-lactone (XX) is a *trans*-lactone. As neither the natural keto-lactone (Xa) nor (Xb) was identical with the *trans*-lactone (XX), we intended to synthesise the *cis*-lactone.

On heating (XV) in acetic anhydride containing sodium acetate, we obtained an oily unsaturated lactone, a mixture of (XXIII) and (XXIV), which was hydrogenated with Raney nickel to give an oily saturated lactone (XXV). It was seen from the infrared and the n.m.r. spectra that this lactone (XXV) was contaminated with the *trans*-lactone (XVII). When the lactone (XXV) was treated with hydriodic acid, it gave an oily mixture of hydroxy-lactones and an unsaturated compound (XXVII), which afforded an oily hydroxy-lactone (XXVI) and the *trans*-hydroxy-lactone (XVIII) by alumina and preparative thin-layer chromatography. The hydroxy-lactone (XXVI) was oxidised with chromium trioxide to give a keto-lactone (XXVIIIa), m. p. 133—134°, which showed a signal due to the equatorial-like proton on C-7a at τ 5·13 (quintet, J = 3·4 c./sec.). This

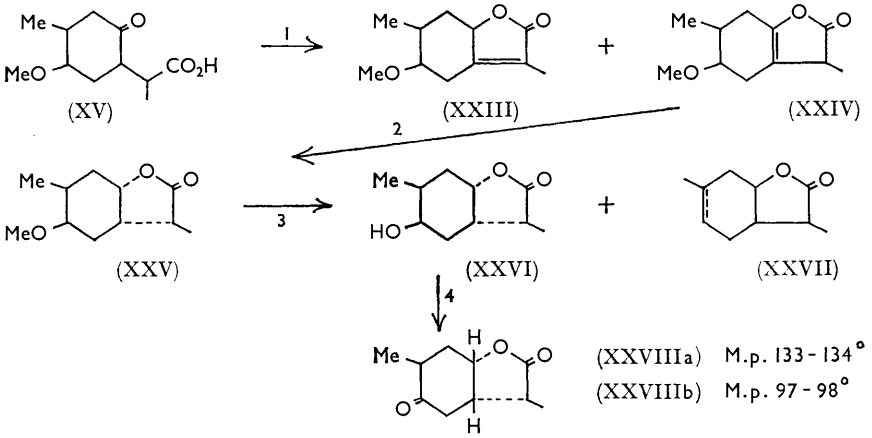
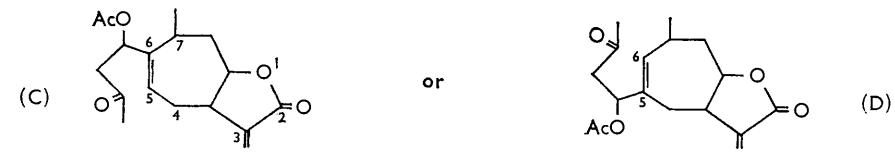


Chart 4

Reagents: 1, Ac_2O–$MeCO_2Na$; 2, H_2–Raney Ni; 3, HI; 4, CrO_3

3,6-dimethylperhydrobenzofuran-2,5-dione (XXVIIIa) therefore is a *cis*-lactone, and was shown to be identical with the natural product (Xa), m. p. 165—166°, by infrared and n.m.r. spectra. From this result, either formula (C) or (D) represents the structure of xanthumin (II).



As already mentioned, the vinyl proton of xanthumin (except the vinyl protons in the $\alpha\beta$-unsaturated γ-lactone system) was shown at τ 4·15 as a quartet (J = 8·0 and 6·4 c./sec.). If xanthumin is represented by formula (D), the proton signal at C-6 is not seen since the quartet has such large coupling constants. But if we assume that the vinyl proton of xanthumin is the one at C-5 in formula (C) and split by two protons at C-4, the observed signal pattern satisfies this assumption. However, the following route should be discussed in connection with the formation of the *cis*-lactone (Xa). If the lactone (Xa) is obtained

by this route, xanthumin is represented by formula (XXIX) and the compound corresponding to compound (VIIa) is (XXX).

When compound (VIIa) was oxidised with trifluoroperacetic acid, followed by hydrolysis of (XXXI) and oxidation of (XXXII) with chromium trioxide, it afforded a keto-lactone (XXXIII) (2,4-dinitrophenylhydrazone, m. p. 171°), which showed infrared frequencies at 1765 cm.$^{-1}$ (γ-lactonic C=O) and 1714 cm.$^{-1}$ corresponding to the six- or seven-membered ring ketone. As a five-membered ring ketone ought to be obtained by these operations with compound (XXX), the formula (XXIX) must be abandoned for xanthumin. Therefore xanthumin was established to have structure (II).

Although *cis*-lactone (Xa), m. p. 165—166°, was recovered from the starting material by reflux in 3% potassium hydroxide–methanol, it gave an equilibrium mixture (*ca.* 1 : 1) of itself and (Xb), m. p. 119—120°, on treatment with 3% hydrochloric acid–methanol. The lactone (Xb) afforded (Xa) quantitatively on treatment with alkali. These facts were similarly observed on the synthesised *cis*-lactone (XXVIIIa), m. p. 133—134°. The lactone (XXVIIIa) afforded an equilibrium mixture (*ca.* 1 : 1) of itself and (XXVIIIb), m. p. 97—98°, on treatment with acid, and (XXVIIIb) was also converted into (XXVIIIa) by alkali. The lactone (XXVIIIb) so obtained was shown to be identical with the natural product (Xb) by infrared and n.m.r. spectra.

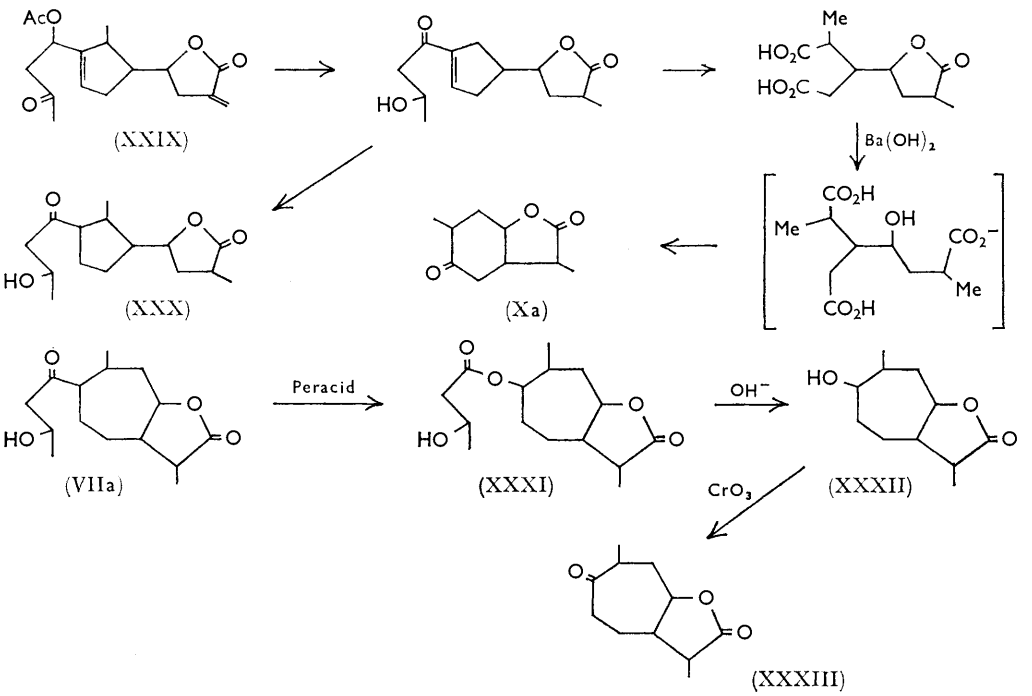
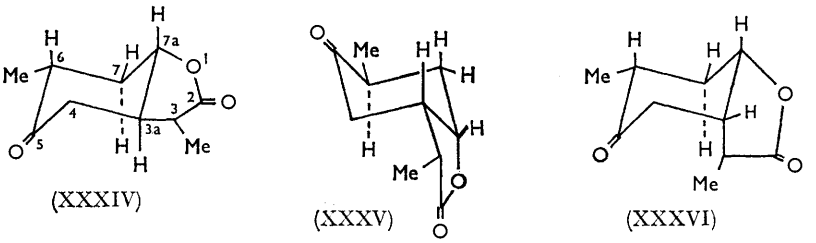


Chart 5

The lactone (Xb) showed a signal due to the axial-like proton on C-7a at τ 5·12 (multiplet, $W_{\frac{1}{2}} = 25$ c./sec.*) in the n.m.r. spectrum. These chemical and n.m.r. data suggest that (Xb) is also a *cis*-lactone and its cyclohexane ring is in a flapping chair form in (Xa). This interpretation is also supported by optical rotatory dispersion: lactone (Xa) or (Xb) possessed a negative ($a = -28{\cdot}4$) or a positive ($a = +27{\cdot}4$) Cotton effect, respectively.

* A proton which has a such large coupling constant should possess a proton *trans*-diaxially oriented to itself at the adjacent carbon atom; that is, this proton has an axial character.

On the basis of the octant rule, as conformation (XXXV) should have a negative dispersion curve while conformation (XXXVI) should have a positive dispersion curve, it is concluded that the lactone (Xa) or (Xb) is represented by formula (XXXV) or (XXXVI), respectively.



(XXXIV) (XXXV) (XXXVI)

Chart 6

If the methyl group at C-6 in (Xa) or (Xb) has an axial character, this methyl group and the γ-lactone function are found in octants having the same sign in the octant diagram, and the lactone (Xa) or (Xb) should possess the larger value [10] (>67) for the amplitude. The small values for the amplitudes of (Xa), −28·4, and (Xb), +27·4, therefore indicate that the methyl groups at C-6 in both lactones occupy the equatorial orientation as shown in formulæ (XXXV) and (XXXVI).

As application of the Hudson–Klyne lactone rule [11] to the lactone (Xa) establishes the absolute configurations of these lactones (Xa and Xb), we measured $[M]_D$ of the lactone (Xa) and its potassium salt. The Δ value is −24·6°, which showed that the absolute configuration at C-7a in (Xa) should belong to the L-series. Consequently the C-3a and -7a substituents in (Xa and b) possess α-configurations and the lactones (Xa and b) should be respresented by formulæ (XXXV) and (XXXVI), respectively, except for the configurations of the methyl groups on C-3.

In regard to the configuration of the methyl group at C-7 in xanthumin (II), we have no solid evidence. However, as mentioned earlier, the lactones (Xa and Xb) were obtained by pyrolysis of the dicarboxylic acid (IX) with barium hydroxide, and the lactone (Xb) was quantitatively isomerised to (Xa) on treatment with alkali. If xanthumin (II) possesses the methyl group on C-7 at the β-configuration, it is probable that the pyrolysis product consists of the lactone (Xa), which has the methyl group in the same configuration and is more stable than (Xb) to alkali. As we obtained almost the same amounts of the two lactones, it may reasonably be concluded that the methyl group at C-7 in xanthumin possesses the α-orientation and the absolute configuration of xanthumin is represented by formula (II), except for the configuration of the acetoxyl group in the side-chain.

Lastly, the difference between xanthinin * (I) and xanthumin (II) must be described. Although the plane structures of both compounds are completely identical, xanthinin differs from xanthumin in melting point (125—126°) and infrared spectrum. Moreover, as the di-*p*-bromophenacyl ester of the dicarboxylic acid (IX) from xanthumin (II), m. p. 94—95°, also differs from the corresponding derivative from xanthinin, m. p. 116°, xanthumin (II) must be a stereoisomer on the skeleton of xanthinin (I).

Experimental

N.m.r. spectra were taken in deuterated chloroform solutions with a Varian A-60 n.m.r. spectrometer. Ultraviolet spectra were taken in 95% ethanol and, unless otherwise stated,

* The authors are very grateful to Professor V. Herout for a sample of this compound.

[10] C. Beard, C. Djerassi, J. Sicher, F. Šipoš, and M. Tichý, *Tetrahedron*, 1963, **19**, 919.
[11] W. Klyne, *Chem. and Ind.*, 1954, 1198; V. Šykora and M. Romaňuk, *Coll. Czech. Chem. Comm.*, 1957, **22**, 1909.

rotations and infrared spectra were taken in dioxan and chloroform, respectively. M. p.s were measured on a Kofler block and corrected.

Isolation of Xanthumin (II) *from the Plant.*—The dried and sliced aerial part of the plant (7·0 kg.) was extracted with acetone (40 l. × 3) at room temperature giving a dark green paste (300 g.). The residue was extracted with light petroleum, leaving the insoluble paste (84·5 g.), which was again extracted with ether. The ether extract was crystallised from ether to give *xanthumin* (II, 13·4 g.) and a dark green oil (35·0 g.). This oil was extracted with water (5 l.) with stirring at room temperature for 40 hr., and the water layer was extracted with ether. The extract (14·2 g.) was crystallised from ether to give *xanthumin* (2·3 g.). Xanthumin (II), colourless plates, m. p. 100·5—101° (from ether–chloroform), $[\alpha]_D^{23}$ −48·2° (±2°) (*c* 1·059), $\lambda_{max.}$ 207·5 mμ (ε 14,300), $\nu_{max.}$ 1756 and 1735 cm.$^{-1}$, $\nu_{max.}$ (Nujol) 1765, 1754, 1732, 1721 cm.$^{-1}$ (Found: C, 66·55; H, 7·1%; *M*, 326. $C_{17}H_{22}O_5$ requires C, 66·65; H, 7·25%; *M* 306·4).

Conversion of (II) *into* (IV).—A solution of xanthumin (II, 70 mg.) in benzene (7 ml.) was passed through a neutral alumina column (Woelm, Activity II) giving the *product* (IV) as a colourless viscous oil (58 mg.), $\lambda_{max.}$ 279 mμ (ε 14,200), $\nu_{max.}$ 1760, 1668, 1594 cm.$^{-1}$; *2,4-dinitrophenylhydrazone*, dark red prisms, m. p. 158—159° (from ethanol–chloroform), $\lambda_{max.}$ 390 mμ (ε 36,500) (Found: C, 59·3; H, 5·3; N, 13·15%. $C_{21}H_{22}O_6N_4$ requires C, 59·15; H, 5·2; N, 13·15%).

Reduction of (II) *with Sodium Borohydride.*—A solution of xanthumin (II, 1·0 g.) and sodium borohydride (124 mg.) in methanol (10 ml.) was left for 2 hr. at room temperature. To this solution was added 2N-sulphuric acid (2 ml.); it was then extracted with ether. The extract was washed with 2N-sodium carbonate, dried (Na_2SO_4), and evaporated, leaving the *product* (IIIa) as a colourless viscous oil (1·0 g.), $\nu_{max.}$ 3720, 3560, 1766, 1729 cm.$^{-1}$, which was acetylated with acetic anhydride–pyridine to give the *acetate* (IIIb) as a colourless oil, b. p. 150—155°/0·1 mm. (bath temp.), $\lambda_{max.}$ 206 mμ (ε 5500), $\nu_{max.}$ 1763, 1730 cm.$^{-1}$ (Found: C, 64·75; H, 8·05%. $C_{19}H_{28}O_6$ requires C, 64·75; H, 8·0%).

Hydrolysis of (IIIa).—A solution of (IIIa) (502 mg.) in 10% potassium carbonate–methanol (7 ml.) was refluxed for 1 hr., then evaporated. The residue was dissolved in water and extracted with ether. The aqueous layer was acidified with 2N-hydrochloric acid and extracted with ether giving the *dihydroxylactone* (V, 422 mg.), a colourless viscous oil, $\nu_{max.}$ 3730, 3560, 1766 cm.$^{-1}$.

Oxidation of (V) *with Manganese Dioxide.*—A mixture of (V) (500 mg.) and manganese dioxide (2·5 g.) in benzene (25 ml.) was shaken for 13·5 hr. at room temperature, and filtered. The filtrate was evaporated leaving a colourless viscous oil (388 mg.), which was chromatographed on alumina to give the *product* (VI, 265 mg.), a colourless viscous oil, b. p. 160—165°/0·1 mm. (bath temp.), $[\alpha]_D^{24}$ −23·9° (±3°) (*c* 0·5647), $\lambda_{max.}$ 234 mμ (ε 10,200), $\nu_{max.}$ 3560, 1766, 1665 cm.$^{-1}$ (Found: C, 67·8; H, 8·35%. $C_{15}H_{22}O_4$ requires C, 67·65; H, 8·35%) and the starting material (V, 84 mg.).

Hydrogenation of (VI) *with* 5% *Palladium–Barium Carbonate.*—5% Palladium–barium carbonate (200 mg.) was added to a solution of (VI) (275 mg.) in ethanol (15 ml.) and hydrogenated at room temperature and atmospheric pressure. The mixture was filtered, and the filtrate evaporated. The residue was dissolved in ether, washed with water, dried (Na_2SO_4), and evaporated, leaving a colourless viscous oil (275 mg.), which was chromatographed on alumina to give the *product* (VIIa, 201 mg.) as a colourless viscous oil, b. p. 155—160°/0·1 mm. (bath temp.), $[\alpha]_D^{24}$ +26·2° (±2°) (*c* 1·109), $\nu_{max.}$ 3546, 1765, 1700 cm.$^{-1}$ (Found: C, 66·9; H, 9·1%. $C_{15}H_{24}O_4$ requires C, 67·15; H, 9·0%).

Dehydration of (VIIa).—Compound (VIIa) was acetylated in the usual manner to give the acetate (VIIb). The acetate (VIIb, 107 mg.) was dissolved in light petroleum (10 ml.) and passed through a neutral alumina column giving the *product* (VIII, 65 mg.) as a colourless oil, b. p. 140—150°/1·5 mm. (bath temp.), $\lambda_{max.}$ 225 mμ (ε 7850), $\nu_{max.}$ 1760, 1695, 1663, 1626 cm.$^{-1}$ (Found: C, 71·55; H, 8·7%. $C_{15}H_{22}O_3$ requires C, 71·95; H, 8·85%).

Oxidation of (VI) *to Dicarboxylic Acid* (IX).—A solution of (VI) (1·0 g.) in ethyl acetate (25 ml.) was ozonised under the usual conditions to give the ozonide, a yellow very viscous oil (1·12 g.). The ozonide was dissolved in 50% acetic acid (20 ml.) and oxidised by addition of powdered potassium permanganate (1·5 g.) with stirring in an ice-bath, and then stirred for 1 hr. at room temperature. To this solution was added aqueous sodium hydrogen sulphite to decompose manganese dioxide; the colourless solution was then acidified with 2N-sulphuric acid and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated, leaving the *product* (IX) as a light yellow viscous oil (764 mg., 91·5% yield);

dimethyl ester, a colourless oil, b. p. 145—150°/0·1 mm. (bath temp.), $[\alpha]_D^{24}$ +83·6° (±2°) (*c* 1·106), $\nu_{max.}$ 1773, 1738 cm.$^{-1}$ (Found: C, 57·15; H, 7·6%. $C_{13}H_{20}O_6$ requires C, 57·35; H, 7·4%); di-*p*-bromophenacyl ester, colourless prisms, m. p. 94—95° (from ether–benzene) (Found: C, 51·45; H, 4·2; Br, 25·55%. $C_{27}H_{26}Br_2O_8$ requires C, 50·8; H, 4·1; Br, 25·05%).

Pyrolysis of Dicarboxylic Acid (IX).—A mixture of (IX) (418 mg.) and barium hydroxide hydrate (27 mg.) was heated at 300—305° for 7 min., while carbon dioxide was violently generated. The residue was acidified with 2N-hydrochloric acid and extracted with chloroform. The extract was washed with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated, leaving a viscous oil (235 mg.), which was chromatographed on alumina to give a crystalline substance, m. p. 140—152° (50·4 mg.) and an oil containing crystals (152 mg.). The crystalline substance was fractionally recrystallised from ether–chloroform to give the *keto-lactone* (Xa), m. p. 165—166° (8 mg.); (Xb), m. p. 119—120° (10 mg.); and a mixture (32 mg.) of (Xa) and (Xb). (Xa), colourless needles (from ether–chloroform), had $[\alpha]_D^{25}$ +4·7° (±2°) (*c* 0·986 in methanol), $\nu_{max.}$ 1771, 1722 cm.$^{-1}$, o.r.d. $[\alpha]_{322}$ −584°, $[\alpha]_{318}$ −568°, $[\alpha]_{314}$ −627°, $[\alpha]_{274}$ +933°; c = 0·1865 in methanol; t = 27·5° (Found: C, 65·95; H, 7·85%. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·75%); potassium salt of (Xa), $[\alpha]_D^{25}$ +14·0° (±2°) (*c* 1·219 in methanol).

(Xb), colourless needles (from ether–chloroform), had $\nu_{max.}$ 1771, 1719 cm.$^{-1}$, o.r.d. $[\alpha]_{600}$ +85°, $[\alpha]_{308}$ +990°, $[\alpha]_{267}$ −517°; c = 0·1819 in methanol; t = 27·5° (Found: C, 66·3; H, 7·5%. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·75%)

3-*Methyl*-4-*methoxycyclohexanol* (XII).—A solution of (XI) (26 g.), obtained from *o*-cresol by Baker and Brown's method,[9] in ethanol (200 ml.) and W-2 Raney nickel (30 ml.) was shaken for 14 hr. at 160° under a hydrogen pressure of 70 atm. The catalyst and the solvent were removed, and the residue was distilled to give a colourless mobile oil (XII, 20 g.) b. p. 102—104°/20 mm.

3-*Methyl*-4-*methoxycyclohexanone* (XIII).—A solution of chromium trioxide (15 g.) in water (15 ml.) and acetic acid (70 ml.) was added dropwise to a solution of (XII, 20 g.) in acetic acid (80 ml.) with stirring for 1 hr. at 10—15° and stirred at 60—65° for 1 hr. The mixture was poured into saturated sodium sulphate solution (400 ml.), basified with 2N-sodium carbonate and extracted with ether. The extract was washed with saturated sodium sulphate, dried (Na_2SO_4), and evaporated leaving a yellow oil (19 g.), which was distilled to give a colourless mobile oil (XIII, 14 g.), b. p. 101—102°/22 mm., $\nu_{max.}^{film}$ 1716 cm.$^{-1}$; semicarbazone, colourless prisms (from ethanol), m. p. 184—186° (Found: C, 54·25; H, 8·7; N, 21·2%. $C_9H_{17}O_2N_3$ requires C, 54·25; H, 8·6; N, 21·1%).

Alkylation of 3-*Methyl*-4-*methoxycyclohexanone* (XIII).—A solution of (XIII, 10 g.) and pyrrolidine (15 g.) in dry benzene (70 ml.) was refluxed for 22 hr. with water-separator, and the solvent and an excess of pyrrolidine were removed to leave the enamine of (XIII) as a brown mobile oil (13·4 g.). A mixture of the enamine and ethyl α-bromopropionate (12·4 g.) in dry methanol (50 ml.) was refluxed for 17 hr. under nitrogen. To this solution was added water (20 ml.); it was then refluxed for 1·5 hr., and extracted with ether. The extract was washed with 2N-sodium carbonate and water, dried (Na_2SO_4), and evaporated, leaving a brown oil (12 g.) which was distilled to give a pale yellow oil (XIV, 7 g.), b. p. 158—161°/18 mm., $\nu_{max.}^{film}$ 1732, 1714 cm.$^{-1}$. The product (XIV) was hydrolysed with 10% potassium carbonate in methanol to give an oily acid (6·7 g.), which was crystallised from light petroleum–ether to give the *keto-acid* (XV), colourless prisms (1·78 g.), m. p. 122—123°, $\nu_{max.}$ 1714 cm.$^{-1}$ (Found: C, 61·9; H, 8·45%. $C_{11}H_{18}O_4$ requires C, 61·65; H, 8·45%).

Methoxy-trans-*lactone* (XVII).—Lithium (1 g.) was added in small quantities to a solution of (XV, 500 mg.) in dioxan (5 ml.), liquid ammonia (100 ml.), and methanol (10 ml.) during 30 min. with stirring, and stirred for an additional 30 min., then ammonium chloride (5 g.) was added to this mixture. The residue obtained by evaporation of liquid ammonia was acidified with 4N-sulphuric acid and extracted with ether to give a hydroxy-acid (XVI, 500 mg.) as colourless prisms (from ether), m. p. 119—121°, which afforded the *methoxy*-trans-*lactone* (XVII), a colourless mobile oil (435 mg.), b. p. 130—135°/1·5 mm. (bath temp.), $\nu_{max.}^{film}$ 1782 cm.$^{-1}$ (Found: C, 66·6; H, 9·45%. $C_{11}H_{18}O_3$ requires C, 66·65; H, 9·15%).

trans-*Keto-lactone* (XX).—Methoxy-lactone (XVII, 435 mg.) was added to 56·7% hydriodic acid (2 ml.) and stirred for 2 hr. at 50—60°. The mixture was poured into ice–water, extracted with ether, washed with 2N-sodium carbonate, aqueous sodium thiosulphate, and water, dried (Na_2SO_4), and evaporated, leaving an orange viscous oil (347 mg.), which was chromatographed

on alumina to give an oil (XIX, 150 mg.) and an oily hydroxy-lactone (XVIII, 116 mg.), $\nu_{max.}^{film}$ 3522, 1768 cm.$^{-1}$. A solution of chromium trioxide (127 mg.) in water (1 ml.) and concentrated sulphuric acid (0·2 ml.) was added to a solution of (XVIII, 116 mg.) in acetone (2 ml.) in an ice-bath with stirring during 30 sec. and stirred for 10 min. at room temperature. The mixture was poured into ice–water and extracted with ether giving trans-*keto-lactone* (XX), colourless prisms (108 mg.) (from ether–chloroform), m. p. 118—119°, $\nu_{max.}$ 1781, 1718 cm.$^{-1}$ (Found: C, 65·9; H, 7·75%. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·75%).

Dehydrogenation of (XIX).—A mixture of (XIX, 720 mg.) and 10% Pd–charcoal (600 mg.) was heated at 320—330° for 1·5 hr. and extracted with light petroleum to give a pale yellow oil (175 mg.). The residue was chromatographed on alumina to give a colourless oil (XXI, 130 mg.), shown to be identical with *p*-ethyltoluene by infrared spectrum and gas chromatography.

Methoxy-cis-*lactone* (XXV) *from* (XV).—A mixture of (XV, 1 g.) and sodium acetate (40 mg.) in acetic anhydride (15 ml.) was refluxed for 3 hr. and the solvent was removed *in vacuo*. The residue was dissolved in ether, washed with water and 2N-sodium carbonate, dried (Na_2SO_4), and evaporated, leaving a brown oil (XXIII and XXIV) (960 mg.), $\nu_{max.}^{film}$ 1792 and 1748 cm.$^{-1}$. A solution of this residue in ethanol (30 ml.) and W-2 Raney nickel (2 g.) was shaken for 20 hr. at 130° under a hydrogen pressure of 120 atm. The catalyst and solvent were removed to leave a pale yellow oil (899 mg.). The residue was chromatographed on alumina and distilled to give the *methoxy*-cis-*lactone* (XXV), a colourless mobile oil (544 mg.), b. p. 120—125°/1·5 mm. (bath temp.), which was contaminated with (XVII) (Found: C, 66·8; H, 9·45%. $C_{11}H_{18}O_3$ requires C, 66·65; H, 9·15%).

cis-*Keto-lactone* (XXVIIIa).—Methoxy-lactone (XXV, 442 mg.) was added to 56·7% hydriodic acid (4 ml.) and stirred for 3 hr. at 50—60°. The mixture was poured into ice–water, extracted with ether, washed with aqueous sodium hydrogen carbonate, 10% sodium thiosulphate, and water, dried (Na_2SO_4), and evaporated, leaving a brown viscous oil (356 mg.), which was separated into an oil (XXVII, 69 mg.), (XVIII, 52 mg.) and an oily hydroxy-lactone (XXVI, 114 mg.), $\nu_{max.}$ 1764 cm.$^{-1}$, by preparative thin-layer chromatography (Merck, Kieselgel G). A solution of chromium trioxide (110 mg.) in water (1 ml.) and concentrated sulphuric acid (0·2 ml.) was added to a solution of (XXVI,100 mg.) in acetone (2 ml.) in an ice-bath with stirring, and stirred for 10 min. at room temperature. The mixture was poured into ice–water and extracted with ether giving a crystalline substance (90 mg.), which was recrystallised from chloroform–ether to give cis-*keto-lactone* (XXVIIIa), colourless prisms (43 mg.), m. p. 133—134°, $\nu_{max.}$ 1771, 1722 cm.$^{-1}$ (Found: C, 66·1; H, 7·8%. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·75%), identified with (Xa) by infrared and n.m.r. spectra.

Conversion of (XXVIIIa) *into* (XXVIIIb).—A solution of (XXVIIIa, 50 mg.) in 3% hydrochloric acid in methanol was refluxed for 1 hr. and the solvent was removed. The residue was dissolved in chloroform, washed with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated, leaving a crystalline substance (50 mg.), a mixture of (XXVIIIa and b) (*ca.* 1 : 1), which was fractionally recrystallised from ether–chloroform to give (XXVIIIa, 4 mg.) and (XXVIIIb, 3·7 mg.), colourless prisms, m. p. 97—98°, $\nu_{max.}$ 1771, 1719 cm.$^{-1}$ (Found: C, 66·2; H, 7·5%. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·75%), identified with (Xb) by infrared and n.m.r. spectra.

Conversion of (Xb) *into* (Xa).—A solution of (Xb, 5 mg.) in 3% potassium hydroxide in methanol (5 ml.) was refluxed for 30 min. and the solvent was removed to give (Xa, 5 mg.).

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