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NATURAL FURAN DERIVATIVES—VII[1]

THE PRESENCE OF A SEVEN-MEMBERED α,β-UNSATURATED LACTONE IN OBACUNONE

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Abstract—Oxidation of obacunone with potassium permanganate afforded three neutral substances containing a furan ring; a glycol, $C_{26}H_{32}O_9$, a hydroxy-dilactone, $C_{25}H_{30}O_8$, and a dilactone, $C_{24}H_{28}O_7$. Obacunoic acid was isomerized to iso-obacunoic acid. From these experimental results and from various reactions of etio-obacunoic acid, the presence of a seven-membered, α,β-unsaturated lactone system (Ia) in obacunone was indicated.

IN Part V of this series,[2] it was shown that three double bonds, in the furan ring and α,β-unsaturated lactone, are present in obacunone. The unsaturated lactone of obacunone can be oxidized under mild condition, without affecting the furan ring. Oxidation of obacunone (I) with potassium permanganate in a mixture (9:1) of acetone and water affords three neutral substances; a glycol (II), $C_{26}H_{32}O_9$, a hydroxy-dilactone* (III), $C_{25}H_{30}O_8$, and a dilactone (IV), $C_{24}H_{28}O_7$. These three substances show absorptions of a furan ring at 3·20 and 11·44 μ in their infra-red spectra and show that they all retain the furan ring.

Treatment of the glycol (II) with acetic anhydride and pyridine affords a diacetate (no absorption of a hydroxyl group in its infra-red spectrum) while its oxidation with lead tetra-acetate or periodic acid results in consumption of one equivalent of the oxidant, which shows that the double bond in the α,β-unsaturated lactone of obacunone had been oxidized into a vicinal glycol. Further oxidation of the glycol (II) with potassium permanganate gives IV.

The hydroxy-dilactone (III) forms a monoacetate (no absorption of hydroxyl group in its infra-red spectrum) and a mono-2,4-dinitrophenyl-hydrazone. Alkaline hydrolysis of III results in consumption of two equivalents of alkali and acidification of the hydrolysate regenerates III. Presence of one hydroxyl, two six-membered lactones, and one carbonyl in the hydroxy-dilactone is borne out, besides the above experimental results, by the presence of absorptions at 2·98, 5·73 and 5·80 μ in its infra-red spectrum.

The dilactone (IV) consumes two equivalents of alkali in alkaline hydrolysis and is recovered on acidification of its hydrolysate. The infra-red spectrum of IV with absorptions at 5·67, 5·77 and 5·87 μ indicates the presence of a newly formed γ-lactone, δ-lactone originally present in obacunone, and a ketone. This ketone has a

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* This substance was designated to "substance A" in Part VI.[1]

[1] Part VI: T. Kubota, T. Matsuura, T. Kamikawa and T. Tokoroyama, *Tetrahedron Letters* No. 8, 1 (1960).

[2] T. Tokoroyama, T. Kamikawa and T. Kubota, *Bull. Chem. Soc. Japan* **34**, 131 (1961).

poor reactivity and does not form an oxime or a semicarbazone under conditions identical with that used for obacunone.

The α,β-unsaturated lactone in obacunone undergoes irreversible fission of the ring by the action of alkali and forms obacunoic acid (V).[3–5] This acid (V) somewhat resists permanganate oxidation but oxidation under drastic condition affords the foregoing dilactone (IV). Obacunoic acid has an absorption maximum at 210 mμ (ε 11,600) in its ultra-violet spectrum. As indicated in Table 1, this absorption is an overlapped maxima of the furan ring and α,β-unsaturated carboxylic acid. The absorption maximum of 210 mμ suggests that obacunoic acid is a β-monosubstituted α,β-unsaturated acid.[6]

TABLE 1

	λ_{max}	ε
Obacunoic acid	210	11,600
Marrubiin[7]	208	5,600
	212	5,600
	216	5,000
Limonin[8]	208	6,300
Iso-obacunoic acid	210	6,600

The hydroxyl group in obacunoic acid resists oxidation with chromium trioxide under various conditions and is therefore considered to be tertiary. By heating obacunoic acid with acetic anhydride and sodium acetate, Kaku and Li[3] obtained an acid of m.p. 154–156°, and Emerson[4] isolated an acid of m.p. 145°. The latter acid was recognized from its analytical values to be acetyl-obacunoic acid. Re-examination of this reaction afforded an acid (VI) of m.p. 154–155°, an isomer of obacunoic acid, and was named iso-obacunoic acid. Infra-red spectrum of iso-obacunoic acid lacks the absorption of a double bond conjugated with the carboxyl at 6·16 μ, present in obacunoic acid, and that of hydroxyl. Its ultra-violet spectrum indicates only the absorption of a furan ring (Table 1).

Iso-obacunoic acid is also obtained by hydrolysis of the amorphous methyl ester obtained by application of diazomethane to obacunoic acid or its methyl ester for a long period of time. It is also obtained by long heating of obacunone or obacunoic acid with alkali.*

The oxidative degradation of obacunone and formation of iso-obacunoic acid can be explained, as shown below, by considering the presence of a seven-membered unsaturated lactone grouping (Ia) in obacunone (I). Partial structures IIa, IIIa, IVa, Va, and VIa will therefore be given respectively for the glycol (II), hydroxy-dilactone (III), dilactone (IV), obacunoic acid (V), and iso-obacunoic acid (VI).

The presence of a seven-membered α,β-unsaturated lactone (Ia) is also supported from various reactions of etio-obacunoic acid[2] (VII), $C_{23}H_{28}O_8$, obtained by degradation of the furan ring in obacunone. Oxidation of methyl etio-obacunoate[2] (VIII) with potassium permanganate in boiling acetone affords oxalic acid and a dilactone

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* Reaction of obacunone with alkali will be reported in a forthcoming paper.

[3] T. Kaku and P. Li, *J. Pharm. Soc. Japan* **55**, 1153 (1935).

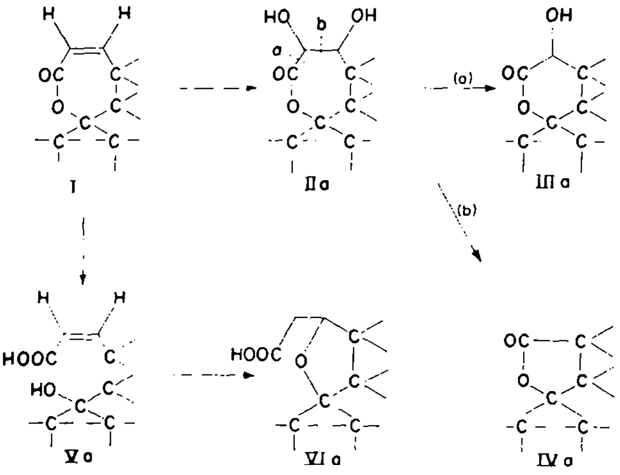
[4] O. L. Emerson, *J. Amer. Chem. Soc.* **70**, 545 (1948); **73**, 2621 (1951).

[5] F. M. Dean and T. A. Geissman, *J. Org. Chem.* **23**, 596 (1958).

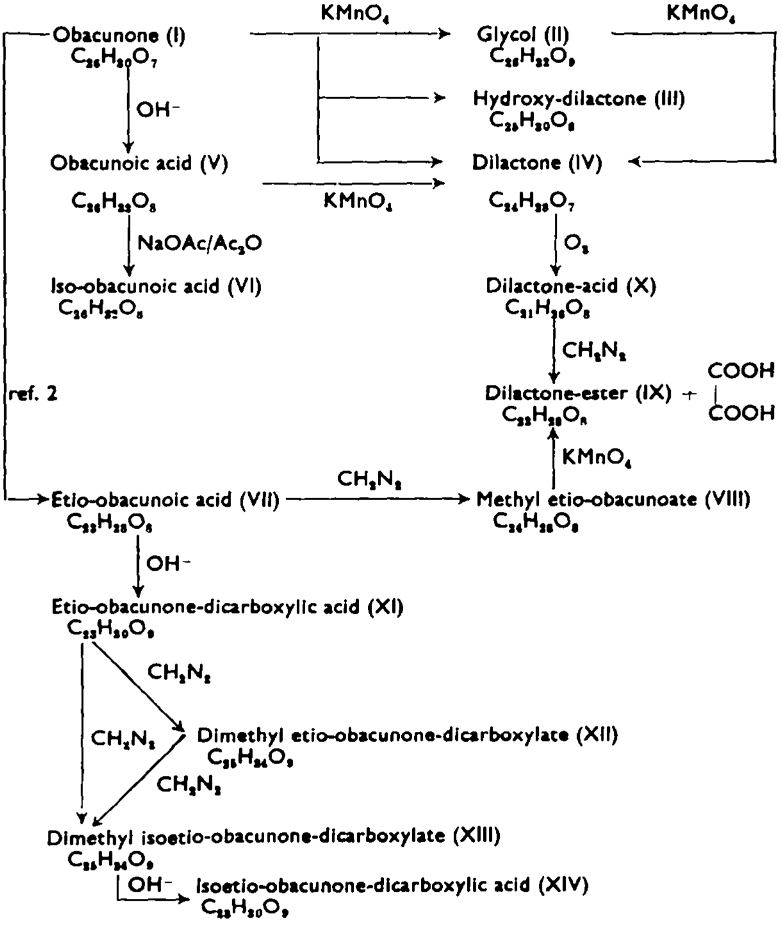
[6] A. T. Nielsen, *J. Org. Chem.* **22**, 1539 (1957).

[7] W. Cocker, B. E. Cross, S. R. Duff, J. T. Edward and T. F. Holley, *J. Chem. Soc.* 2540 (1953).

[8] T. Tokoroyama, *J. Chem. Soc. Japan* **79**, 316 (1958).



ester (IX), $C_{22}H_{28}O_8$, as the main products. Infra-red spectrum of IX shows absorptions at 5·68 (γ-lactone) and 5·75 μ(δ-lactone and ester). The ester (IX) was identical with the dilactone ester obtained by methylation of dilactone acid (X), $C_{21}H_{26}O_8$,



which was formed by ozonolysis of the dilactone (IV). This indicates the presence of Ia grouping in etio-obacunoic acid (VII) and IVa grouping in the dilactone ester (IX).

Etio-obacunone-dicarboxylic acid (XI),[2] $C_{23}H_{30}O_9$, obtained by mild alkaline hydrolysis of etio-obacunoic acid, and its dimethyl ester (XII), when allowed to stand with diazomethane over a long period time, form a dimethyl ester (XIII), $C_{25}H_{34}O_9$, named dimethyl isoetio-obacunone-dicarboxylate, which no longer exhibits infra-red absorptions of a hydroxyl group and of double bond conjugated to carboxyl group and can be hydrolysed to isoetio-obacunone-dicarboxylic acid (XIV), $C_{23}H_{30}O_9$. This indicates the presence of VIa grouping in isoetio-obacunone-dicarboxylic acid (XIV), as in iso-obacunoic acid (VI).

The glycol (II) is recovered on alkaline hydrolysis followed by acidification of its hydrolysate. This abnormal reaction in which the seven-membered saturated lactone ring undergoes reversible ring fission is rather interesting. Such stability of this lactone ring, in spite of the irreversible fission of saturated seven-membered lactone ring in other compounds of obacunone series,* is probably due to the fact that the two vicinal hydroxyl groups take the conformation by which they easily undergo relactonization by the steric effect of other groups in the molecule.

EXPERIMENTAL

Permanganate oxidation of obacunone (I)

Obacunone (10 g) was dissolved in a mixture of acetone and water (9:1, 250 ml) and powdered potassium permanganate (5·6 g, 3 atom equivalents) added all at once under stirring and ice-cooling. The mixture was stirred at 20° until the permanganate was completely consumed. Manganese dioxide precipitated was filtered and washed with hot acetone 3 times. The filtrate and washing were combined and evaporated to a small volume under reduced press. Dilution with water precipitated a crystalline mass, which on digestion with chloroform was separated into the soluble part (A) and the insoluble part (B). The above aqueous filtrate was shaken with chloroform to remove the neutral material which was combined with (A). Acidification of the aqueous layer gave precipitates (C) which were filtered and dried (6·4 g).

Dilactone (IV). The soluble part (A) was washed with water, dried with anhydrous sodium sulphate and evaporated under reduced pressure. The residue (1·3 g) was dissolved in chloroform and passed through a column containing silicagel (39 g). Elution with chloroform–acetone (9:1) gave a crystalline solid which was recrystallized from acetone–water as leaflets or long prisms (484 mg), m.p. 282–284° (dec). $[\alpha]_D^{10}$ −39·3° (*c*, 0·981 in chloroform). I.R. spectrum (Nujol): 3·20 (furan), 5·67 (γ-lactone), 5·77 (δ-lactone), 5·84 (ketone), 11·44 μ (furan). $\lambda_{\max}^{EtOH}$ 208·5 mμ (ε 6,400). Saponification equivalent: 209. Calc. for two lactones: 214. (Found: C, 67·24; H, 6·59. Calc. for $C_{24}H_{28}O_7$: C, 67·27; H, 6·59%.)

Glycol (II). Recrystallizations of the insoluble part (B) from acetone–water gave prisms (1·2 g), m.p. 233° (dec). I.R. spectrum (Nujol): 2·91 and 2·97 (hydroxyl), 3·18 (furan), 5·77 (lactones and ketone), 11·44 μ (furan). (Found: C, 61·61; H, 6·87. Calc. for $C_{26}H_{32}O_9 \cdot H_2O$: C, 61·65; H, 6·77 %.) On titration with lead tetra-acetate and periodic acid, the glycol consumed respectively 0·9 and 0·8–1·0 mole of the reagent.

Hydroxy-dilactone (III). The precipitates (C) were recrystallized from methanol–ether as silky needles, m.p. 289–291° (dec). From the mother liquor separated dimorphic plates, m.p. 289–291° (dec), which could be converted to the original needles on recrystallization from methanol–ether. IR spectrum (nujol): 2·98 (hydroxyl), 5·73 (shoulder; lactones), 5·80 (ketone), 11·44 μ (furan). Saponification equivalent: 223. Calc. for two lactones: 229. (Found: C, 65·73; H, 6·61. Calc. for $C_{25}H_{30}O_8$: C, 65·49; H, 6·60%.)

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* Behaviour of the lactone ring in compounds with saturated seven-membered lactone derived from obacunone will be discussed in the following paper.

Diacetate of the glycol (II)

The glycol was acetylated with acetic anhydride and pyridine at room temp overnight. Recrystallization of the product from ethanol gave prisms, m.p. 247–248° (dec). I.R. spectrum (Nujol): 3·18 (furan), 5·77 (acetoxyls and lactones), 5·88 (ketone), 11·44 μ (furan). Acetyl number: 1·87. (Found: C, 63·02; H, 6·87. Calc. for $C_{30}H_{36}O_{11}$: C, 62·91; H, 6·34%.) The diacetate gave the parent glycol (II) on alkaline hydrolysis followed by acidification.

2,4-*Dinitrophenylhydrazine of the hydroxy-dilactone* (III)

The 2,4-dinitrophenylhydrazone prepared in the usual manner, was recrystallized from a mixture of ethyl acetate, ethanol and water as yellow needles, m.p. 294° (dec). (Found: C, 58·14; H, 5·25; N, 8·87. Calc. for $C_{31}H_{34}O_{11}N_4$: C, 58·29; H, 5·25; N, 8·77%.)

Monoacetate of the hydroxy-dilactone (III)

The hydroxy-dilactone was acetylated with acetic anhydride and pyridine at room temp overnight. Recrystallization of the product from acetone gave prisms, m.p. 304–305° (dec). I.R. spectrum (Nujol): 5·73 (acetoxyl and lactones), 5·83 (ketone). Acetyl number: 0·97. (Found: 64·84; H, 6·40. Calc. for $C_{27}H_{32}O_9$: C, 64·79; H, 6·44%.) The monoacetate gave the parent hydroxy-dilactone (III) on alkaline hydrolysis followed by acidification.

Permanganate oxidation of the glycol (II)

To a stirred solution of the glycol (1 g) in acetone (80 ml) was added powdered potassium permanganate (0·8 g) and after standing overnight, water (10 ml) was added. The mixture was treated as described in the permanganate oxidation of obacunone and divided into the 3 fractions: chloroform-soluble fraction (A), chloroform-insoluble fraction (B) and water-soluble fraction (C). The fraction (A) was evaporated and the residue (247 mg) chromatographed through a column containing silica gel (9 g). Elution with chloroform-acetone (9:1) gave crystalline mass which was recrystallized from acetone-water as leaflets (40 mg), m.p. 282–284° (dec), pure and mixed with dilactone (IV). The infra-red spectrum was identical with that of the dilactone (IV).

The fraction (B) was recrystallized from acetone-water as prisms (61 mg), m.p. 233° (dec), pure and mixed with the glycol (II).

The fraction (C) was acidified and the resulting precipitates (397 mg) were recrystallized from dilute methanol. Only a minute amount of plates, m.p. 263° (dec), was obtained, which was not further investigated.

Lead tetra-acetate oxidation of the glycol (II)

To a stirred solution of the glycol (500 mg) in glacial acetic acid (20 ml) was added a solution of lead tetra-acetate (400 mg) in glacial acetic acid (5 ml). After the mixture was heated at 60° for 1 hr, the solvent was removed under reduced press. The residue was dissolved in ethanol and mixed with a solution of 2,4-dinitrophenylhydrazine in ethanol containing sulphuric acid. Recrystallization of the precipitates from a mixture of ethyl acetate, ethanol and water gave yellow needles, m.p. 255° (dec). I.R. spectrum (Nujol): 5·76, 5·83, 5·88, 6·20, 6·34 μ. (Found: C, 57·46; H, 5·03; N, 8·43. Calc. for $C_{32}H_{34}O_{12}N_4$: C, 57·64; H, 5·14; N, 8·40%.)

Obacunoic acid (V)

Obacunoic acid was prepared according to the method of Kaku and Li[3] and recrystallized from acetone-water and then from ethanol as needles, m.p. 214–215°. I.R. spectrum (Nujol): 2·98 (hydroxyl), 3·6–4·0 (carboxylic acid), 5·72 (δ-lactone), 5·88 (ketone and α,β-unsaturated carboxylic acid), 6·16 (conjugated double bond), 11·45 μ (furan). λ_{max}^{EtOH} 210 mμ (ε 11,600).

Methyl obacunoate

Methyl obacunoate was prepared by a slight modification of the method of Kaku and Li[3]. Excess of diazomethane, soon after the addition, should be removed by evaporation under reduced pressure or by decomposition with the addition of acetic acid, in order to obtain the methyl ester in high yield. Recrystallization from ethanol gave plates, m.p. 175–176°. I.R. spectrum (nujol): 5·78 (δ-lactone), 5·84 (ketone and α,β-unsaturated ester), 6·17 μ (conjugated double bond).

Iso-obacunoic acid (VI)

(a) Obacunoic acid (1 g) and anhydrous sodium acetate (1 g) was refluxed in acetic anhydride (30 ml) for 1 hr, according to the method of Kaku and Li[3]. After cooling the mixture was poured into ice-water and allowed to stand overnight. The viscous material solidified on scatching was filtered and treated with benzene. The benzene insoluble solid was filtered and recrystallized from chloroform–benzene as fine needles (400 mg), m.p. 155–157°. I.R. spectrum (Nujol): 3·18 (furan), 3·6–4·0 (carboxylic acid), 5·77 (δ-lactone), 5·84 (carboxylic acid), 5·89 μ (ketone). λ_{max}^{EtOH} 210 mμ (ε 6,600). Saponification equivalent: 241. Calc. for monobasic acid lactone: 236. (Found: C, 65·86; H, 6·78. Calc. for $C_{26}H_{32}O_8$: C, 66·08; H, 6·8%.)

(b) Obacunoic acid dissolved in acetone was mixed with an ether solution of a large excess of diazomethane, and the mixture allowed to stand for 2 days. Evaporation of the solvent left an amorphous solid which failed to crystallize. The amorphous methyl ester was hydrolysed with 1 N NaOH on the water-bath. Acidification with dil HCl gave a solid which recrystallized from chloroform–benzene as fine needles, m.p. 150–152°, pure and mixed with an authentic sample of iso-obacunoic acid.

Permanganate oxidation of obacunoic acid (V)

To a solution of obacunoic acid (2 g) in acetone (100 ml), was added in portions under refluxing powdered potassium permanganate (4 g). After refluxing for 1 hr the mixture was cooled and acidified with dil HCl, and manganese dioxide decomposed with sulphur dioxide. The clear solution was evaporated under reduced press and the crystals separated were filtered and treated with chloroform. Recrystallization of the chloroform-insoluble crystals from acetone–water gave needles (1·1 g), m.p. 197–198°, pure and mixed with an authentic sample of obacunoic acid. The chloroform-soluble part was evaporated and the residue recrystallized from acetone–water as leaflets (97 mg), m.p. 278–279° (dec), pure and mixed with an authentic sample of dilactone (IV). The infra-red spectrum was identical with that of the dilactone (IV).

Attempted oxidation of the hydroxyl group of obacunoic acid

(a) *With chromium trioxide-pyridine.* A solution of obacunoic acid (1 g) in pyridine (20 ml) was added to a mixture of chromium trioxide (0·6 g) in pyridine (6 g) below 20°, and the mixture allowed to stand at room temp overnight. The reaction mixture was diluted with water (50 ml) and extracted with chloroform. The chloroform layer was washed with dil HCl and then with water, dried and evaporated. Recrystallization of the residue from ethanol gave needles (439 mg), m.p. 204–206° (dec), pure and mixed an authentic sample of obacunoic acid. The infra-red spectrum was identical with that of obacunoic acid.

(b) *With chromium trioxide–acetone–sulphuric acid.* To a solution of obacunoic acid (236 mg) in acetone (12 ml) was added 1·38 ml of chromium trioxide solution, prepared from chromium trioxide (270 mg), sulphuric acid (0·3 ml) and water (9·7 ml), under ice-cooling. After 4 hr standing, the mixture was diluted with water. Resulting precipitates were filtered and recrystallized from acetone–water to give obacunoic acid (200 mg), m.p. 206–207°.

Ozonolysis of the dilactone (IV)

Ozonized oxygen was passed through a solution of the dilactone (1·5 g) in methylene chloride (70 ml) for 3 hr under ice-cooling. The opaque solution was poured into a large volume of water.

After standing at room temp for 2 days, the organic layer was separated, dried and evaporated. The residue was dissolved in chloroform and shaken with aqueous sodium bicarbonate solution. The bicarbonate solution was acidified with dil HCl and extracted with ether. Evaporation of the ether solution left the dilactone-acid as a gum which did not crystallize in this stage. The crude dilactone-acid (X) was dissolved in acetone and methylated with an excess of diazomethane in ether. The dilactone-ester (IX) was recrystallized from methanol as needles (280 mg), m.p. 219–221°. I.R. spectrum (Nujol): 5·68 (γ-lactone), 5·75 (δ-lactone and ester), 5·84 μ (ketone). (Found: C, 62·60; H, 6·72. Calc. for $C_{22}H_{28}O_8$: C, 62·84; H, 6·71%.)

This methyl ester was hydrolysed with 1 N KOH below 80° for 1 hr. Acidification with 1 N HCl separated crystals which on recrystallization from acetone–water gave the dilactone-acid as needles, bubbled at 158°, then solidified and melted at 267–268°. I.R. spectrum (Nujol): 5·72–5·77, 5·84, 5·89 μ. (Found: C, 61·22; H, 6·48. Calc. for $C_{21}H_{26}O_8 \cdot \frac{1}{2}H_2O$: C, 60·72; H, 6·55%.)

Permanganate oxidation of methyl etio-obacunoate (VIII)*

To a boiling solution of methyl etio-obacunoate (2 g) in acetone (50 ml) was added in portions powdered potassium permanganate (4·5 g). The mixture was refluxed until the permanganate was consumed completely. Manganese dioxide was filtered and washed with hot acetone 3 times. The filtrate and washings were combined and evaporated to a small volume under reduced pressure and then shaken with a mixture of chloroform and dil HCl. The chloroform layer was shaken with aqueous sodium bicarbonate solution.

The chloroform layer was washed with water, dried and evaporated. Recrystallization of the residue from acetone–water gave needles (250 mg), m.p. 218–220°, which were identified as the dilactone-ester (IX) by mixed m.p. and infra-red spectrum.

The bicarbonate solution was acidified with dil HCl. The resulting precipitates were filtered, dried and recrystallized from acetone–water as prisms (50 mg), m.p. 254–255°. I.R. spectrum (Nujol): 2·89, 5·69, 5·80–5·84 μ. (Found: C, 61·45; H, 6·86. Calc. for $C_{21}H_{28}O_8$: C, 61·75; 6·19%.) This compound was not further investigated.

The above filtrate was continuously extracted with ether. Evaporation of the ether solution left needles (700 mg), m.p. 95–101°, which recrystallized from water as prisms, m.p. 101–104°, pure and mixed with an authentic sample of oxalic acid dihydrate.

Dimethyl isoetio-obacunone-dicarboxylate (XIII)

To a solution of etio-obacunone-dicarboxylic acid (XI)[2] in methanol was added an excess of diazomethane in ether solution and the mixture allowed to stand for a day in refrigerator. After evaporation of the solvent, the residue was recrystallized from methanol–water as prisms, m.p. 179–180°. I.R. spectrum (Nujol): 5·70, 5·74, 5·88 μ. Ultra-violet spectrum: λ_{204}^{EtOH} ε 890, λ_{210}^{EtOH} ε 560. (Found: C, 62·73; H, 7·31. Calc. for $C_{25}H_{34}O_9$: C, 62·75; H, 7·16%.)

Isoetio-obacunone-dicarboxylic acid (XIV).

Dimethyl isoetio-obacunone-dicarboxylate (0·5 g) was heated with 1 N NaOH (10 ml) at 80° for 1 hr. After cooling, the mixture was acidified with dil HCl (congo red) and allowed to stand overnight. Separated crystals (450 mg), m.p. 167–169° (dec) were recrystallized from acetone–water as prisms, m.p. 167–169° (dec). I.R. spectrum (Nujol): 2·83, 2·97, 5·73, 5·88 μ. Saponification equivalent: 159. Calc. for lactone dicarboxylic acid: 153. (Found: C, 60·02; H, 6·81. Calc. for $C_{23}H_{30}O_9 \cdot \frac{1}{2}H_2O$: C, 60·10; H, 6·80%.)

This acid, by the methylation with diazomethane, could be converted to the dimethyl ester (XII), m.p. 184–184·5°, whose infra-red spectrum was identical with that of the above dimethyl ester, m.p. 179–180°.

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