Tetrahedron, 1961, Vol. 12, pp. 269 to 276. Pergamon Press, Inc. Printed in Northern Ireland

NATURAL FURAN DERIVATIVES—VIII[1]

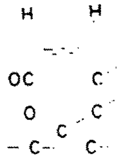
RELATIONSHIP BETWEEN THE FURAN RING AND SIX AND SEVEN-MEMBERED LACTONE RINGS IN OBACUNONE

T. MATSUURA, T. KAMIKAWA and T. KUBOTA
Institute of Polytechnics, Osaka City University, Minamiogimachi, Kitaku, Osaka, Japan

(*Received* 12 *October* 1960)

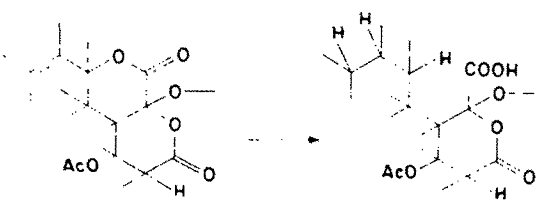
Abstract—The presence of a α,β-epoxy-(β-furyl)-δ-lactone group in obacunone was suggested, from the catalytic reduction and conversion to desoxy compound of the dilactone (V), one of the oxidation products of obacunone with potassium permanganate. The stability of saturated, seven-membered lactone ring in obacunone derivatives was discussed. Degradation of the masked hydroxyl group is tertiary and is bonded to isopropyl group. Formula Ie was proposed for the partial structure of obacunone.

IN the preceding paper of this series,[1] two of the authors (T. Ka. and T. Ku.) indicated the presence of an α,β-unsaturated, seven-membered lactone group (Ia) in obacunone.



I a

Obacunone possesses another lactone, which is known to be a six-membered lactone from its infra-red absorption and its facile relactonization.[2] Dean and Geissman[2] obtained methyl hydrogen octahydro-obacunoninate (II) by catalytic reduction of obacunone (I) followed by treatment with methanol. These workers also obtained



III IV

hexahydronomilinic acid (IV) by catalytic reduction of nomilin* (III). From extremely low values of p*Ka* of these two acids, presence of an oxide linkage was

---

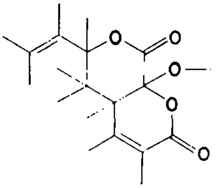
* Nomilin was found to be an acetoxy-dihydro-obacunone, a compound with an acetoxyl group in β-position of the α,β-unsaturated lactone in obacuhone.[3,4]

[1] Part VII: T. Kamikawa and T. Kubota, *Tetrahedron* **12**, 262 (1961).

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

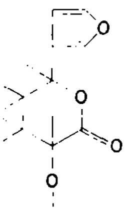
[3] O. H. Emerson, *J. Amer. Chem. Soc.* **73**, 2621 (1951).

assumed in the α-position of the carbonyl group in the six-membered lactone of obacunone and nomilin which undergoes hydrogenolysis. The conversion of III to IV was explained by assuming the following partial structural formulae.*



Ib

The dilactone[1] (V), $C_{24}H_{28}O_7$, one of the permanganate oxidation products of obacunone, retains the furan ring and six-membered lactone present in obacunone, and possesses a five-membered lactone ring newly formed by oxidation of the unsaturated, seven-membered lactone. Catalytic reduction of V results in saturation of the furan ring to give two products, a tetrahydro-dilactone (VI), $C_{24}H_{32}O_7$, and a monocarboxylic acid (VII), $C_{24}H_{34}O_7$. Infra-red spectra of VII (5·69 and 5·90 μ) and its methyl ester (5·70 μ) indicate the presence of a five-membered lactone in VII and this fact shows that the six-membered lactone in V had suffered hydrogenolysis by activation by the double bond† of the furan ring (β-furyl group[4]). Since the p*Ka* value of the acid (VII) is of a low order (Table 1), comparable to that of methyl hydrogen octahydro-obacunoninate (II), presence of an oxide linkage in the α-position of carboxyl group may be considered. Consequently, partial formula Ic would be given to the six-membered lactone in obacunone and the dilactone (V). This partial structure is also supported by the low p*Ka* value (indicates an oxygen linkage in α-position of the carboxyl group) of etio-obacunoic acid[5] (VIII), obtained by degradation of the furan ring in obacunone.



I c

Treatment of the dilactone (V) with hydriodic acid gives desoxydilactone (IX), $C_{24}H_{28}O_6$, whose ultra-violet spectrum shows absorption maximum at 214 mμ (ε 12,300). The difference curve with the absorption curve of the dilactone (V) (λ_{max} 208 mμ, ε 6140) shows absorption maximum at 218 mμ (ε 7200). This nature of ultra-violet absorption spectrum agrees well with that of the ultra-violet spectra of

---

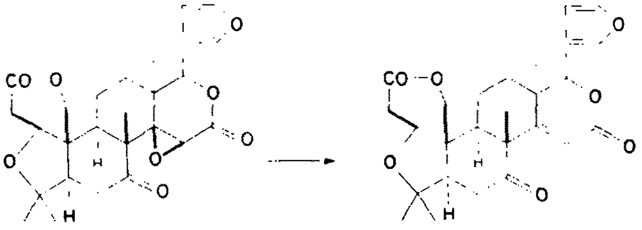
* These formulae suggest that obacunone would be represented by the formula Ib. Dean and Geissman stated that the double bond in III may be a part of the furan ring.

† Since obacunone has no double bond other than those in the furan ring and unsaturated lactone,[5] the double bonds in the dilactone (V) are only two in the furan ring.

[4] T. Kubota and T. Tokoroyama, *Chem. & Ind.* 1298 (1957). Also see T. Tokoroyama, *J. Chem. Soc. Japan* 79, 319 (1958).

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

limonin (X) and desoxy-limonin[6] (XI), formed by treatment of limonin with hydriodic acid. Formulae X and XI have been given for limonin and desoxy-limonin by Arigoni and others,[7] and it is concluded that an α,β-epoxy-δ-lactone group adjacent to the furan ring, as indicated by the formula V, is present in the dilactone.



X XI

Methyl hydrogen octahydro-obacunoninate (II), obtained by catalytic reduction of obacunone (I) followed by treatment with methanol, is also obtained by catalytic reduction of methyl obacunoate (XII).[2] This substance (II) is now formulated as $C_{27}H_{42}O_8$. This fact can be interpreted as hydrogenolysis of the six-membered lactone due to activation by the furan ring, in the first case, but the latter involves, in addition to the hydrogenolysis, methanolysis of the saturated seven-membered lactone. This instabilization of the saturated, seven-membered lactone is also observed in the reduction of compounds of etio-obacunoic acid series to be described below.

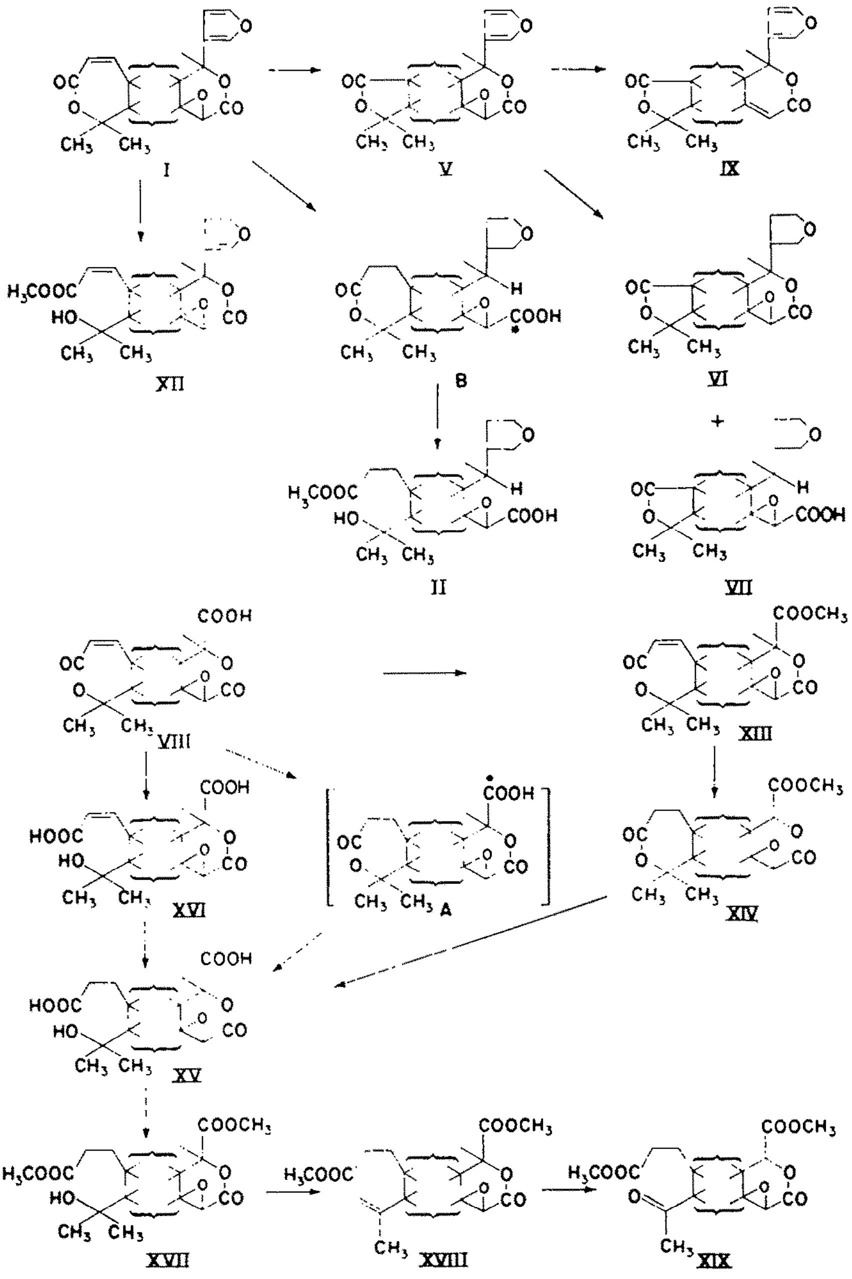
Catalytic reduction of methyl etio-obacunoate (XIII) merely gives methyl dihydroetio-obacunoate (XIV),[5] but that of etio-obacunoic acid (VIII) itself results in absorption of one mole of hydrogen and recrystallization of the product from acetone–water mixture gives a saturated hydroxy-dicarboxylic acid (XV), $C_{23}H_{32}O_9$, named dihydroetio-obacunone-dicarboxylic acid. This acid (XV) possesses one hydroxyl group which resists acetylation and is titrated as a dicarboxylic acid lactone by alkali. The acid (XV) can be derived from etio-obacunoic acid by two different routes. The one is the catalytic reduction of etio-obacunone-dicarboxylic acid (XVI),[5] obtained by a mild saponification of etio-obacunoic acid, and the other is alkaline hydrolysis of methyl dihydroetio-obacunoate (XIV). Therefore, it is clear that XV was formed by hydrolysis of the seven-membered lactone ring in the dilactone acid (formula A) during recrystallization, formed as intermediate during reduction of etio-obacunoic acid (VIII). It is interesting that the saturated, seven-membered lactone has undergone hydrolysis in the case of the intermediate A, while methyl dihydroetio-obacunoate (XIV) can be recrystallized from acetone–water without hydrolysis of the lactone ring. In the formation of XV and II, the saturated, seven-membered lactone of the precursors, A and B, probably suffers hydrolysis or methanolysis to give XV and II by catalytic action of the carboxyl group (marked *) with a strong acidity. Naturally, compounds (for example, XIV) which do not have such a strong acid group in their molecule undergo irreversible ring fission by alkaline hydrolysis.*

---

* There is an exception of a reversible ring-fission of the saturated, seven-membered lactone in the glycol, $C_{26}H_{32}O_9$, one of the products of permanganate oxidation of obacunone.[1]

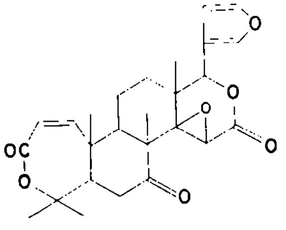
[6] T. A. Geissman and V. Tulagin, *J. Org. Chem.* **11**, 760 (1946).

[7] D. Arigoni, D. H. R. Barton, E. J. Corey, O. Jeger, L. Caglioti, Sukh Dev, P. G. Ferrini, E. R. Glazier, A. Melera, S. K. Pradhan, K. Schaffner, S. Sternhell, J. F. Templeton and S. Tobinaga, *Experientia* **16**, 41 (1960).

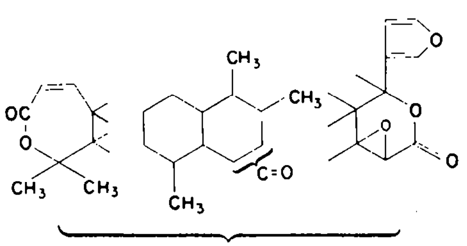


The tertiary nature of the masked hydroxyl group in the unsaturated, seven-membered lactone in obacunone was assumed from the resistance of obacunoic acid to oxidation by chromium trioxide.[1] The methyl ester (XVII) of dihydroetio-obacunone-dicarboxylic acid (XV) is not acetylated by treatment with acetic anhydride and pyridine at room temperature but is easily dehydrated by treatment with acetic anhydride and potassium hydrogen sulphate or with phosphoryl chloride and pyridine to form an anhydro-compound (XVIII), $C_{25}H_{34}O_8$, which shows absorption of terminal methylene at 11·23 μ in its infra-red spectrum and forms formaldehyde and a norketone (XIX), $C_{24}H_{32}O_9$, by ozonolysis.[*] The norketone is positive to the iodoform reaction, indicating that a methyl ketone group had newly been formed. From these experimental results, it may be concluded that the masked hydroxyl group in the unsaturated, seven-membered lactone in obacunone is tertiary and is bonded to iso-propyl group.

There are no experimental evidences to show that the two lactone rings in obacunone are directly bonded through common carbon atoms (cf. formula Ib), as assumed by Dean and Geissman.[2] It seems more appropriate to assumed, therefore, that the two lactone groups are present separately in the obacunone molecule, as indicated in the formula I



I d



I e

Lithium aluminium hydride reduction of methyl etio-obacunoate (XIII) and dehydrogenation of its amorphous product with selenium affords 1,2,5-trimethylnaphthalene. This seems to suggest that the two carbocyclic rings in obacunone are present as hydronaphthalene. Recently, Arigoni and others[7] proposed the formula Id as the plausible and biogenetically attractive one for obacunone by deduction from the structure X of limonin, which is considered to be closely related to obacunone.

From the experimental results obtained to date, partial structure of Ie is presented for obacunone.

TABLE 1. p*Ka* VALUES

	In dimethylformamide-H_2O (1:1)	In H_2O
Acetic acid	6·52	—
Benzoic acid	6·12	—
Obacunoic acid	6·15	—
Acid (VII)	4·90	—
Methyl hydrogen octahydro-obacunoninate (II)	4·46	2·9[8]
Hexahydrolimonic acid	—	2·7[9]
Etioobacunoic acid (VIII)	4·90	—

---

[*] In a communication,[8] formation of acetone and a compound of $C_{22}H_{28}O_9$ was reported but it was later found that acetone had been derived from impurities in a solvent and the latter compound was due to erroneous analytical calculation.

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

[9] A. Melera, K. Schaffner, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **40**, 1420 (1957).

EXPERIMENTAL

Measurement of p*Ka values.* The p*Ka* values of compounds listed in Table 1 were measured in dimethylformamide–water (1:1), according to the method of Parke and Davis.[10]

Methyl hydrogen octahydro-obacunoninate (II)

This compound was prepared according to the method of Dean and Geissman.[2] Methyl obacunoate[1] (0·5 g) was dissolved in acetic acid (20 ml) and shaken in an atmosphere of hydrogen in the presence of 1% palladium-on-alumina[11] (0·5 g). Absorption of 88·6 ml (3·6 moles) of hydrogen was observed (18 hr). The catalyst was filtered and the filtrate was evaporated under reduced press. The residue was dissolved in chloroform and shaken with bicarbonate solution. Acidification of the bicarbonate solution with dil HCl gave precipitates which were recrystallized twice from dil methanol as needles, m.p. 174–175° (dec) (164 mg). Infra-red spectrum (nujol): 2·87, 3·09, 3·6–4·0, 5·77, 5·83, 5·88 μ. (Found: C, 65·62; H, 8·67. Calc. for $C_{27}H_{42}O_8$: C, 65·56; H, 8·56%.)

Dimethyl octahydro-obacunoninate

Methyl hydrogen octahydro-obacunoninate dissolved in methanol was methylated with an excess of diazomethane in ether. The solvent was evaporated and the residue recrystallized twice from dil methanol as needles, m.p. 94–97°. Infra-red spectrum (nujol): 5·68, 5·83 μ. (Found: C, 61·84; H, 8·84. Calc. for $C_{28}H_{44}O_8 \cdot 2H_2O$: C, 61·74; H, 8·88%) Dean and Geissman[2] reported that dimethyl octahydro-obacunoninate was obtained as a clear glass.

Catalytic reduction of the dilactone (V)

The dilactone (500 mg) dissolved in acetic acid (50 ml) was shaken in an atmosphere of hydrogen in the presence of 10% palladium-charcoal (250 mg). The mixture was shaken several times in air in order to activate the catalyst, in the course of the hydrogenation. Slow absorption of about 3 moles hydrogen ceased after 29 hr. The catalyst was filtered and the solvent evaporated under reduced press. The gummy residue was treated with a mixture of chloroform and aqueous bicarbonate solution.

The bicarbonate solution was acidified with dil HCl and the resulting precipitates filtered. Recrystallization from dil methanol gave VII as needles (220 mg), m.p. 132–133° (dec), which after being dried at 80°/1 mm sintered at 138° and melted at 140° with bubbling. This compound showed a pale blue color with acetic anhydride and sulphuric acid in chloroform. Negative reactions resulted with Ehrlich's and Brady's reagents. Infra-red spectrum (nujol): 2·87 (hydrate), 3·70–4·00 (carboxylic acid), 5·72 (γ-lactone; 5·69 μ in chloroform), 5·90 μ (carboxylic acid and ketone). (Found: C, 64·13; H, 8·10. Calc. for $C_{24}H_{34}O_7 \cdot H_2O$: C, 63·70; H, 8·10%.)

The acid (VII) was methylated with an ether solution of diazomethane. Recrystallization from methanol gave the methyl ester as needles, m.p. 199–202°. Infra-red spectrum (Nujol): 5·73 (5·69 μ in chloroform), 5·89 μ. (Found: C, 67·34; H, 8·20. Calc. for $C_{25}H_{36}O_7$: C, 66·94; H, 8·09%.)

The above chloroform solution was evaporated and recrystallization of the residue from dil methanol gave the tetrahydro-dilactone (VI) as needles (36 mg), m.p. 243–245° (dec). Infra-red spectrum (nujol): 5·68 (γ-lactone), 5·74 (δ-lactone), 5·84 μ (ketone). (Found: C, 65·98; H, 7·70. Calc. for $C_{24}H_{32}O_7$: C, 66·65; H, 7·46%.)

Desoxy-dilactone (IX)

A mixture of the dilactone (V, 0·5 g), freshly distilled hydriodic acid (0·6 g) and glacial acetic acid (30 ml) was heated at 80° for 4 hr. The reaction mixture was concentrated to a small volume (ca. 10 ml) and allowed to stand overnight after the addition of aqueous bisulphite solution. The separated precipitates were filtered, dried, dissolved in chloroform and chromatographed through a column containing silicagel (15 g). Elution with chloroform–acetone (9:1) yielded a crystalline mass which was crystallized from acetone–water as needles (175 mg), m.p. 306–307° (dec). On further recrystallizations from the same solvent the m.p. was raised to 339–340°. Infra-red spectrum (Nujol): 5·69 (γ-lactone), 5·88 μ (α,β-unsaturated δ-lactone and ketone). Ultra-violet spectrum: λ_{max}^{EtOH} 214 mμ

---

[10] T. V. Parke and W. W. Davis, *Analyt. Chem.* **26**, 642 (1954).

[11] A. C. Johnson, *Chem. Abstr.* **39**, 2001 (1945).

(ε 12,300); in difference curve with the absorption curve of the dilactone (V), λ_{max}^{EtOH} 218 mμ (ε 7,200). (Found: C, 69·98; H, 6·95. Calc for $C_{24}H_{28}O_6$: C, 69·88; H, 6·84%.)

Desoxylimonin (XI)[*]

A modification of the procedure of Geissman and Tulagin[6] was used for the preparation of desoxylimonin. Limonin (1·0 g) was heated at 60° in a mixture of acetic acid (15 ml) and hydriodic acid (15 ml) for 4 hr. The mixture was poured into water containing sodium bisulphite and extracted with chloroform. The chloroform layer was washed with water, bicarbonate solution and water, successively, dried and evaporated. Recrystallization of the residue from acetone–ethanol gave prisms, m.p. 332° (dec) (literature[6], m.p. 305° (dec)). Infra-red spectrum (Nujol): 5·75, 5·83 μ. Ultra-violet spectrum: λ_{max}^{EtOH} 215 mμ (ε 16,300); in difference curve with the absorption curve of limonin, λ_{max}^{EtOH} 218 mμ (ε 11,600). (Found: C, 68·84; H, 6·81. Calc. for $C_{26}H_{30}O_7$: C, 68·70; H, 6·65%.)

Dihydroetio-obacunone-dicarboxylic acid (XV)

(a) *From etio-obacunone-dicarboxylic acid* (XVI). Etio-obacunone-dicarboxylic acid[6] (0·5 g) dissolved in dioxane (30 ml) was shaken in atmosphere of hydrogen in the presence of 1% palladium-on-alumina[10] (0·5 g). Slow absorption of hydrogen ceased after 16 hr. The catalyst was filtered and the filtrate evaporated under reduced press. The residue was twice recrystallized from dioxane–water to give prisms (130 mg), m.p. 250–251° (dec). Infra-red spectrum (Nujol): 2·95 (hydroxyl), 5·73 (δ-lactone), 5·80 μ with a shoulder at 5·90 μ (carboxyls and ketone). Saponification equivalent: 153·7 (calc. for a dibasic acid: 150·6). (Found: C, 61·18; H, 7·39. Calc. for $C_{23}H_{32}O_9$: C, 61·05; H, 7·13%.)

(b) *From etio-obacunoic acid* (XII). Etio-obacunoic acid[6] (800 mg) dissolved in ethyl acetate (25 ml) was shaken in an atmosphere of hydrogen in the presence of 10% palladium-charcoal (200 mg). Absorption of 42·5 ml (0·93 mole) hydrogen was observed after about 2 hr. The catalyst was filtered and the filtrate evaporated under reduced press. Recrystallization of the residue from acetone–water gave the acid (XV) as prisms (473 mg), m.p. 237–238°, the m.p. was raised to 255° (dec) after several recrystallizations from the same solvent. The infra-red spectrum was identical with that of XV, obtained above.

(c) *From methyl dihydroetio-obacunoate* (XIV). Methyl dihydroetio-obacunoate[5] (178 mg) was heated on the water-bath in 0·1 N NaOH (25 ml) for 30 min. The mixture was evaporated to a small volume under reduced press and acidified (congo red) with dil HCl. The resulting crystals were collected and recrystallized from acetone–water to give prisms (0·13 g), m.p. 250–251° (dec), which were identified as XV by mixed m.p. and comparison of infra-red spectrum.

Dimethyl dihydroetio-obacunone-dicarboxylate (XVII)

Dihydroetio-obacunone-dicarboxylic acid (XV) was dissolved in dioxane and methylated with an excess of diazomethane in ether. The solvent was evaporated and the residue recrystallized from methanol to give prisms, m.p. 197–198°. (Practically quantitative yield.) Infra-red spectrum (Nujol): 2·88 (hydroxyl), 5·73 (δ-lactone and esters), 5·86 μ (ketone). (Found: C, 62·48; H, 7·63. Calc. for $C_{25}H_{36}O_9$: C, 62·48; H, 7·55%.)

Dimethyl anhydrodihydroetio-obacunone-dicarboxylate (XVIII)

(a) *With potassium hydrogen sulphate and acetic anhydride.* Dimethyl dihydroetio-obacunone-dicarboxylate (XVII, 1·10 g) and freshly fused potassium hydrogen sulphate (5 g) were refluxed in acetic anhydride (40 ml) for 15 min. The mixture was poured into ice-water and allowed to stand overnight. The resulting solid was filtered, dried, and recrystallized from methanol–water to give needles (0·9 g), m.p. 145–146° (sintered at about 80°). The m.p. was raised to 149–151° (sintered at about 90°) after recrystallization from the same solvent. Infra-red spectum (Nujol): 5·72 (δ-lactone and esters), 5·86 (ketone), 11·23 μ (terminal methylene). (Found: C, 64·75; H, 7·54. Calc. for $C_{25}H_{34}O_8$: C, 64·92; H, 7·41%.)

(b) *With phosphorous oxychloride and pyridine.* The dimethyl ester (XVII, 100 mg) dissolved in pyridine (4 ml) was mixed with freshly distilled phosphorous oxychloride (0·3 ml) under ice-cooling.

---

[*] The authors are indebted to Dr. T. Tokoroyama for these experiments.

The mixture was then heated on the water-bath for 45 min. After the mixture was evaporated to a small volume, it was poured into ice-water. After several hour's standing the resulting solid was filtered, dried, and recrystallized from methanol-water to give needles (80 mg), m.p. 146–148°, which were identical with the anhydro-compound (XVIII) obtained above.

Ozonization of dimethyl anhydrodihydroetio-obacunone-dicarboxylate (XVIII)

A solution of the anhydro-compound (4·3 g) in chloroform (60 ml) was ozonized with ozonized oxygen under ice-cooling (5 hr). The mixture was heated with 200 ml water on the water-bath for 1 hr. The aqueous layer was divided into two parts of equal volume. The one part was allowed to stand with dimedone (0·6 g) in water (200 ml) overnight, then heated on the water-bath for 1 hr. The mixture separated silky needles (0·35 g), m.p. 186–188°, pure and mixed with an authentic sample of formdimedone. The other part of the aqueous layer was mixed with 2,4-dinitrophenylhydrazine solution in dil HCl. Orange precipitates were filtered, dried and recrystallized twice from ethyl acetate–ethanol to give orange needles (0·22 g), m.p. 163–165°, pure and mixed with an authentic sample of 2,4-dinitrophenylhydrazone of formaldehyde.

The chloroform layer was dried and evaporated. The residue was recrystallized from chloroform–ether to give the norketone (XIX) as leaflets (3·00 g), bubbled at 107° after sintering at about 90°. This compound showed a positive iodoform reaction and a positive Beilstein reaction. Infra-red spectrum (Nujol): 5·73 (esters and δ-lactone), 5·83 (ketone), 5·86 (ketone), near 13·2 μ (chloroform). (Found: C, 56·19; H, 6·44; Cl, 8·78. Calc. for $C_{24}H_{32}O_9 \cdot \frac{1}{2}CHCl_3$: C, 56·13; H, 6·25; Cl, 10·15%.)

This compound, after being dried at 110°/1 mm for 6 hr, was recrystallized from methanol to give plates, m.p. 152–154° (sintered at about 80°), which showed a negative Beilstein reaction. Infra-red spectrum (Nujol): 5·73 (esters and δ-lactone), 5·85 μ (ketones). (Found: C, 60·19; H, 7·21. Calc. for $C_{24}H_{32}O_9 \cdot CH_3OH$: C, 60·47; H, 7·31%.)

Selenium dehydrogenation of the lithium aluminium hydride reduction product of methyl etio-obacunoate (XIII)

Methyl etio-obacunoate (2·5 g) dissolved in anhydrous tetrahydrofuran (60 ml) was added dropwise to the refluxed mixture of lithium aluminium hydride (2 g) and tetrahydrofuran (30 ml). Refluxing was continued more 3 hr and the excess of the hydride was decomposed by the careful addition of ethyl acetate. The mixture was decomposed by the addition of saturated sodium sulphate solution and filtered. The filter cake was washed with hot ethyl acetate. The filtrate and washings were combined, dried and evaporated under reduced press to viscous material (1·45 g), whose infra-red spectrum did not show any carbonyl bands.

The reduction product (1·6 g) was mixed with selenium (4 g) and heated at 280–300° for 14 hr, then 320–340° for 6 hr. The reaction mixture was powdered and extracted with ether. The ether extract was evaporated to a dark brown liquid (90 mg), which was dissolved in pet. ether (5 ml) and passed through a column containing alumina (5 g). Elution with pet. ether yielded a yellow liquid (43 mg) which was dissolved in ethanol (1 ml) and added to a hot solution of picric acid (70 mg) in ethanol (1 ml). Spontaneous evaporation separated orange red needles which were washed with methanol, filtered and recrystallized from methanol to give needles, m.p. 125–130°. The mixed m.p. with 1,2,5-trimethylnaphthalene, m.p. 135°, which was prepared from manool by selenium dehydrogenation, was not depressed.