Natural Furan Derivatives. V[1]. The Number of Double Bonds in Obacunone

By Takashi TOKOROYAMA, Tadao KAMIKAWA and Takashi KUBOTA

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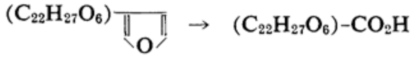
Obacunone ($C_{26}H_{30}O_7$) is known as the bitter principle contained in the plants of the *Rutaceae* family, together with limonin[2] and nomilin[3]. It has been studied by many investigators[3-6] since the beginning of this century. Casimirolid, isolated from *Casimiroa edulis* Lave et Lex, was recently proved to be identical with obacunone[7-10].

Studies made to date have revealed the presence of one ketone group and two lactone groups, one being opened reversibly and the other being an α,β-unsaturated lactone group which suffers irreversible fission. Of the remaining two oxygen atoms, one has been proved by Kubota and Tokoroyama[11] to be present in β-substituted furan ring and the other is considered to be present as an oxide bond from its inert nature.

Dean and Geissman[6] concluded from spectroscopic studies on obacunone and nomilin (acetoxydihydroobacunone with an acetoxyl group in the β-position of the unsaturated lactone group in obacunone)[3] and from the complicated behavior of these two compounds toward catalytic reduction* that obacunone had another double bond besides the three in the furan ring and the α,β-unsaturated lactone group, and that it is a monocarbocyclic compound. The present paper presents evidences that obacunone possesses only three double bonds.

Obacunone (I) easily undergoes the addition of one mole of hydrogen chloride to form obacunone hydrochloride (II)[6]. Since this compound does not show the characteristics of an α,β-unsaturated lactone and easily regenerates obacunone on being heated with pyridine, it is clear that the addition of hydrogen chloride has taken place at the double bond in the α,β-unsaturated lactone group[6].

Ozonolysis of obacunone hydrochloride at room temperature affords an acid, $C_{23}H_{28}O_8\cdot HCl$, by losing three carbon atoms. The acid has been named etioobacunoic acid hydrochloride (III) which is characterized as its methyl ester (IV), $C_{24}H_{30}O_8\cdot HCl$. III and IV do not show infrared absorption characteristics of the furan ring at 3.18, 6.66 and 11.42 μ[12]. Treatment of III with pyridine results in dehydrochlorination and a dilactone-carboxylic acid, etioobacunoic acid (V), $C_{23}H_{28}O_8$, is formed. Etioobacunoic acid shows the absorption of a double bond conjugated with a carboxyl group at 6.18 μ and an absorption maximum at 214.5 mμ (ε 11,500) indicating that the α,β-unsaturated lactone system has been regenrated as in the case of the conversion of obacunone hydrochloride to obacunone. It follows, therefore, that the change of obacunone to etioobacunoic acid may be indicated as follows:



I V

Hydrolysis of obacunone results in the irreversible fission of the unsaturated lactone ring and an unsaturated hydroxy acid, obacunoic acid (VIII), is formed[5]. Mild hydrolysis of etioobacunoic acid (V) also gives an unsaturated hydroxy-dicarboxylic acid $C_{23}H_{30}O_9$, which has been named etioobacunone-dicarboxylic acid (IX) and shows absorptions at 2.96 (hydroxyl) and 6.18 μ (conjugated double bond). Careful methylation of IX with diazomethane affords a dimethyl ester (X) corresponding to methyl obacunoate[5].

Methyl etioobacunoate hydrochloride (IV) gives no coloration with tetranitromethane.

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1) Part IV: T. Tokoroyama, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **79**, 319 (1958).

2) D. Arigoni et al., *Experientia*, **16**, 41 (1960).

3) O. H. Emerson, *J. Am. Chem. Soc.*, **70**, 545 (1948); **73**, 2621 (1951).

4) Y. Murayama and J. Takata, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), **47**, 1037 (1928).

5) a) T. Kaku, C. Cho and T. Orita, ibid., **52**, 594 (1932). b) T. Kaku and P. Ri, ibid., **55**, 1153 (1935).

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

7) F. B. Power and T. Callan, *J. Chem. Soc.*, **99**, 2004 (1911).

8) A. Aebi, *Helv. Chim. Acta*, **39**, 1495 (1956).

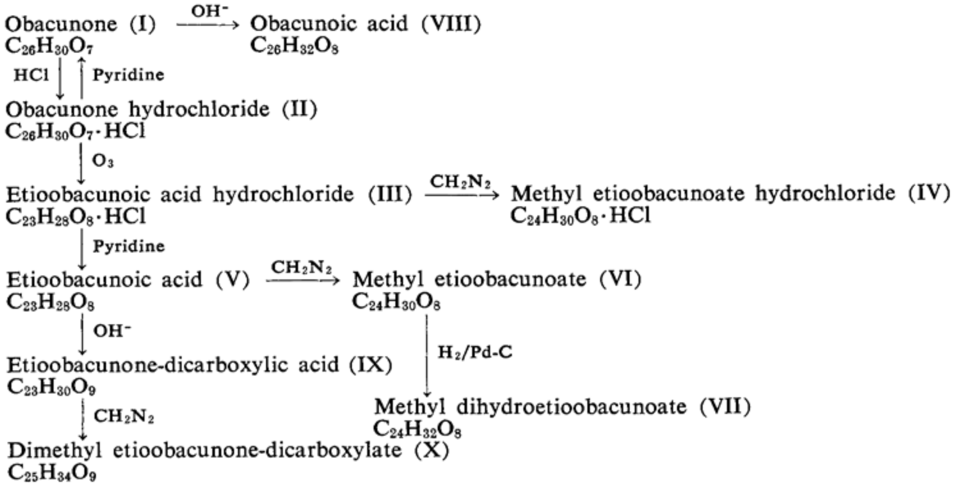
9) F. A. Kincl, J. Romo, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, **1956**, 4163.

10) F. Sondheimer et al., *J. Org. Chem.*, **23**, 762 (1958); **24**, 870 (1959).

11) T. Kubota and T. Tokoroyama, *Chem. & Ind.* **1957**, 1298. See also Ref. 1.

* Catalytic reduction of obacunone and its allied compounds will be reported in subsequent papers.

12) T. Kubota, *Tetrahedron*, **4**, 68 (1958); M. Yamaguchi, *Japan Analyst* (*Bunseki Kagaku*), **7**, 211 (1958).



Also its ultraviolet absorptions are weak in intensity, being end absorptions at 207 mμ (ε 520) and at 210 mμ (ε 400). If acid III should retain a double bond of poor reactivity with ozone and with tetranitromethane and thus a double bond of a tetrasubstituted ethylene, compound IV should show an absorption maximum of strong intensity of several thousands in ε at around 205 mμ[13]. Catalytic reduction of methyl etioobacunoate (VI) results in absorption of one mole of hydrogen to form methyl dihydroetioobacunoate (VII), which does not color with tetranitromethane and shows an end absorption of low intensity at 205 mμ (ε 850). Consequently, it follows that IV and VII are completely saturated and therefore it is concluded that obacunone possesses three double bonds, two in the furan ring and one in the α,β-unsaturated lactone group, and that it possesses a bicarbocyclic ring.

Experimental

Etioobacunoic Acid Hydrochloride (III).—Obacunone hydrochloride (2.0 g.), which was prepared according to the method of Dean and Geissman[6], was dissolved in methylene chloride (50 ml.) and ozonized until the solution was saturated with ozone. The mixture was poured into water (50 ml.) and allowed to stand for several days with occasional swirling. The separated crystals were filtered and recrystallized from acetone-water as needles (1.1 g.), m. p. 238~240°C (decomp.). Infrared absorption (Nujol): 3.6~4.1 (carboxylic group), 5.74 (lactone goups), 5.96~6.00 μ (ketone and carboxylic groups).

Found: C, 58.61; H, 6.43. Calcd. for $C_{23}H_{29}\cdot O_8Cl$: C, 58.91; H, 6.23%.

Methyl Etioobacunoate Hydrochloride (IV).—A solution of etioobacunoic acid hydrochloride in acetone was methylated with an ether solution of diazomethane. Repeated recrystallization of the product from acetone-water gave needles, m. p. 202°C (decomp.). Infrared absorption (Nujol): 5.74~5.77 (lactone and ester groups), 5.83 μ (ketone group).

Found: C, 59.53; H, 6.61. Calcd. for $C_{24}H_{31}\cdot O_8Cl$: C, 59.68; H, 6.47%.

Etioobacunoic Acid (V). — Etioobacunoic acid hydrochlorid (150 mg.) was dissolved in pyridine (2 ml.) and the solution refluxed for 1 hr. After removal of the solvent under reduced pressure, the residue was dissolved in water and the solution was acidified with dilute sulfuric acid. Recrystallization of the resulting precipitates (132 mg.) from acetone-water gave needles, m. p. 236°C (decomp.). Infrared absorption (Nujol): 3.3~4.1 (carboxylic group), 5.74 (lactone groups), 6.00~6.05 (carboxylic group, ketone and α,β-unsaturated lactone group), 6.18 μ (conjugated double bond).

Found: C, 63.76; H, 6.80. Calcd. for $C_{23}H_{28}O_8$: C, 63.88; H, 6.53%.

Neutralization equivalent: 423 (Calcd. value 432.5). Saponification equivalent: 150 (Calcd. value: 144.2).

Methyl Etioobacunoate (VI). — A solution of etioobacunoic acid in a mixture of acetone and methanol was methylated with an excess of diazomethane in ether. Recrystallization of the product from acetone-water gave needles, m. p. 275~277°C, in a practically quantitative yield. Infrared absorption (Nujol): 5.69 (lactone group), 5.75 (ester group), 5.89~5.92 μ (ketone and α,β-unsaturated lactone groups).

Found: C, 64.52; H, 6.67. Calcd. for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77%.

Methyl Dihydroetioobacunoate (VII). — Methyl etioobacunoate (500 mg.) dissolved in a mixture of ethyl acetate (25 ml.) and dioxane (10 ml.) was shaken with hydrogen at 31°C in the presence of 10% palladium-charcoal (100 mg.). Absorption of 1 mol. (31 ml.) of hydrogen was completeted in $4\frac{1}{3}$ hr. After filtration of the catalyst, the solvent was evaporated under reduced pressure. Recrystallization of the residue from acetone-water or from ethanol gave prisms, m. p. 236~237°C. Infrared

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[13] P. Blauden, H. B. Henbest and G. W. Wood, *J. Chem. Soc.*, **1952**, 2737.

absorption (Nujol): 5.72∼5.88 μ (lactones, ester and ketone groups). Ultraviolet absorption: $\lambda_{205}^{\mathrm{EtOH}}$, ε 850; $\lambda_{210}^{\mathrm{EtOH}}$, ε 525.

Found: C, 63.81; H, 7.50. Calcd. for $C_{24}H_{32}O_8$: C, 64.27; H, 7.19%.

Saponification equivalent: 146 (Calcd. value: 149).

The dihydroester (VII) was also obtained by the hydrogenation of methyl etioobacunoate in the presence of palladium-alumina[14] in dioxane.

Etioobacunone-Dicarboxylic Acid (IX). — Etioobacunoic acid (2 g.) was dissolved in 1 N potassium hydroxide (20 ml.) and the solution heated below 80°C for 1 hr. After cooling the solution was acidified with 1 N hydrochloric acid (Congo Red). The separated crystals were collected and recrystallized twice from dilute methanol as needles (0.9 g.), m. p. 192∼193°C (decomp.). Infrared absorption (Nujol): 2.97 (hydroxyl group), 3.07 (hydroxyl group), 5.74 (lactone group), 5.84 (ketone and carboxylic groups), 6.18 μ (conjugated double bonds). Ultraviolet absorption: $\lambda_{205}^{\mathrm{EtOH}}$ ε 5,500; $\lambda_{210}^{\mathrm{EtOH}}$, ε 5,500.

Found: C, 61.24; H, 6.89. Calcd. for $C_{23}H_{30}O_9$: C, 61.32; H, 6.71%.

Dimethyl Etioobacunone-dicarboxylate (X).—To a solution of etioobacunone-dicarboxylic acid (IX) in methanol was added an ethereal solution of diazomethane in an amount less than the theoretical. Immediately after the addition of diazomethane, the solvent evaporated under reduced pressure. The residue was dissolved in chloroform and the solution was shaken with aqueous bicarbonate to remove an acidic material. The chloroform layer was washed with water, dried and evaporated. Recrystallization of the residue from acetone-water, then from ethanol, gave needles, m. p. 177∼178°C. Infrared absorption (Nujol): 2.81 (hydroxyl group), 5.73 (lactone and ester groups), 5.82 (α,β-unsaturated ester group), 5.88 (ketone group), 6.15 μ (conjugated double bond).

Found: C, 62.61; H, 7.43. Calcd. for $C_{25}H_{34}O_9$: C, 62.75; H, 7.16%.

Summary

Obacunone has only three double bonds in total, two in its furan ring and one in its α,β-unsaturated lactone group and, therefore, it possesses a bicarbocyclic ring.

Institute of Polytechnics
Osaka City University
Minamiogi-machi, Kita-ku, Osaka

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[14] A. C. Johnston, *Chem. Abstr.*, 39, 2001 (1945).