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ON THE CHEMICAL CONSTITUTION OF OBACUNONE

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SINCE the isolation of obacunone $C_{26}H_{30}O_7$(I), a bitter principle of Rutaceae, from Phelledendron amurense, Rupr. by Murayma and Takata[1] in 1928, it has been investigated by many workers.[1-5] Kaku and Ri[2] showed that (I) possessed two lactones (one, α-β-unsaturated) and a keto group. Later Kubota and Tokoroyama[4] proved that one of the two remaining oxygens belonged to a furan ring and suggested that the other could be assigned to an ether linkage. In 1958, Dean and Geissman[5] proposed a partial structure (IA) for obacunone based on the results of spectral studies. In continuation of our earlier studies, we should now like to record some observations which lead to the assignment of another partial structure (IB) to this substance.

(i) The number of double bonds in abacunone (Scheme 1 and Fig. 1)

As a result of ozonization of obacunone hydrochloride (II) three carbons were lost giving ethioobacunoic acid hydrochloride (III) $C_{23}H_{29}O_8Cl$,

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[1] Y. Murayama and J. Takata, J.Pharm.Soc.Japan 47, 1037 (1928).

[2] T. Kaku, C. Cho and T. Orita, J.Pharm.Soc.Japan 52, 594 (1932).

[3] O.H. Emerson, J.Amer.Chem.Soc. 70, 545 (1948); 73, 2621 (1951); 74, 688 (1952).

[4] T. Kubota and T. Tokoroyama, Chem. & Ind. 298 (1957).

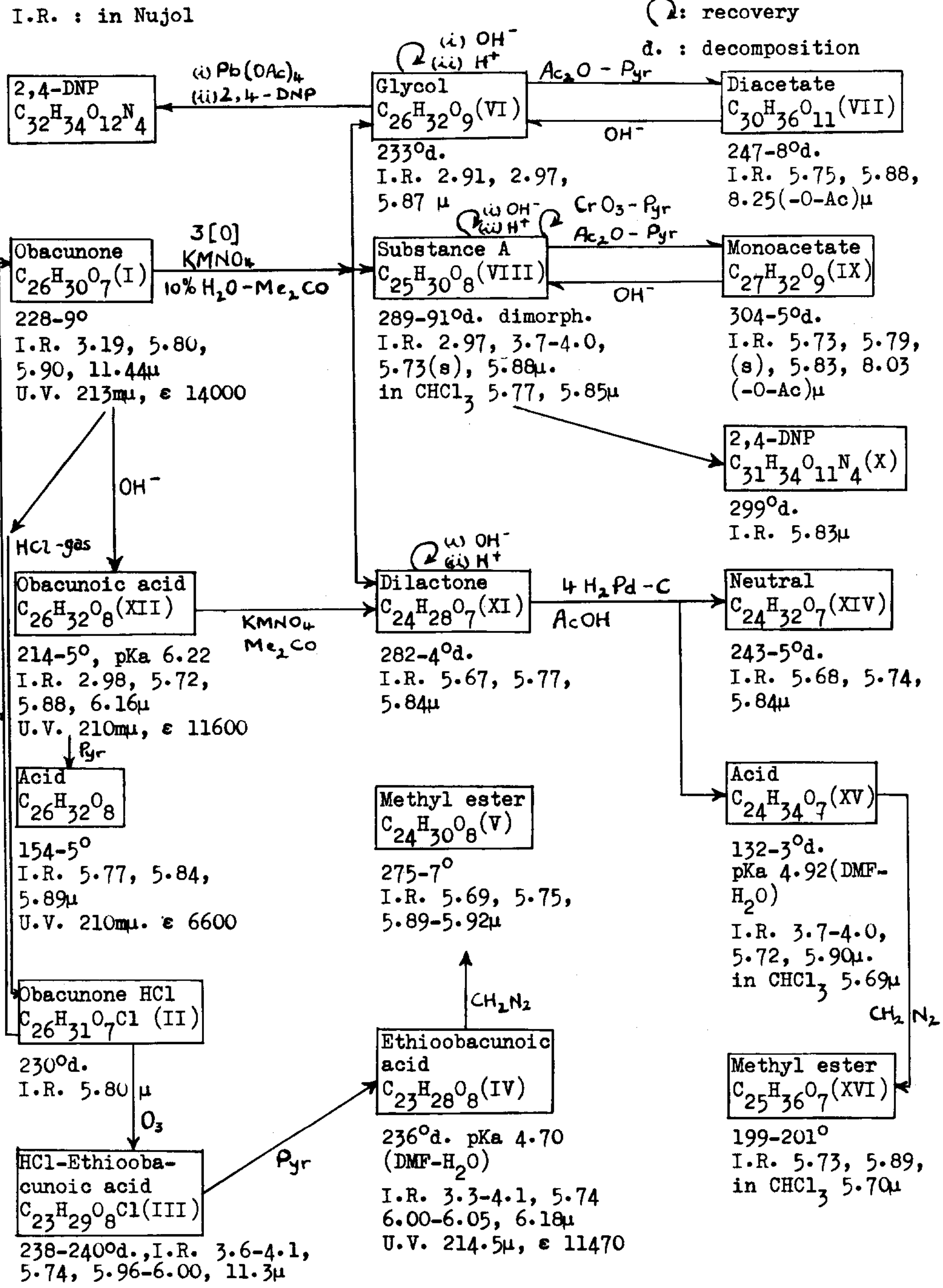
[5] F.M. Dean and T.A. Geissman, J.Org.Chem. 23, 596 (1958).

which, in turn, was dehydrochlorinated in pyridine to ethioobacunoic acid (IV), $C_{23}H_{28}O_8$. The spectral data of IV, [U.V. 214.5 mμ (ε 11,500), I.R. 6.18] indicated that the α,β-unsaturated lactone was regenerated and the furan ring destroyed on ozonization. Since the ester of III gave a negative test with tetranitromethane and has no appreciable absorption above 205 mμ, (ε_{210} 400), it must be a saturated substance. Obacunone (I), therefore, has no unsaturation other than the furan ring and the α,β-unsaturated lactone group.

(ii) The α,β-unsaturated 7-membered lactone ring in obasunone (Scheme 1 and Fig. 1)

The following three compounds were obtained when obacunone (I) was oxidized with potassium permanganate in acetone solution: (a) A glycol (VI), $C_{26}H_{32}O_9$ [diacetate (VII) $C_{30}H_{36}O_{11}$; lead tetraacetate value, 0.9; periodate value, 1.6], (b) A substance A (VIII), $C_{25}H_{30}O_8$ [monoacetate (IX), $C_{27}H_{32}O_9$; mono-2,4-dinitrophenylhydrozone (X), $C_{31}H_{34}O_{11}N_4$], (c) A dilactone (XI), $C_{24}H_{28}O_7$. (VIII) and (XI) were also obtained by further oxidation of the glycol (VI) under the same conditions. The infra-red spectrum of VIII (2.98, 3.7-4.0, 5.73, 5.88 μ), showed that it contained two 6-membered lactones one of which is probably hydroxy-lactone. From the spectral data of XI (5.67 and 5.77 μ) it must also contain two lactone rings, one of which is the original 6-membered lactone and the other a newly formed 5-membered one. Hydrolysis of obacunone with dil. alkali gave obacunoic acid (XII), $C_{26}H_{32}O_8$, the I.R. absorption of which clearly indicated the presence of an hydroxyl, a maximum of this compound (U.V. 210 mμ (ε 11,600)) suggested that it must be a β-monosubstituted-α,β-unsaturated carboxylic acid. The hydroxyl group in XII was believed to be tertiary, since it resisted chromic

SCHEME 1



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oxide oxidation under various conditions. An attempted acetylation (by the pyridine or sodium acetate method), however, gave rise to an isomeric carboxylic acid (XIII), $C_{26}H_{32}O_8$. XIII was also obtained by merely boiling XII in pyridine. The infra-red spectrum of XIII showed no absorption bands corresponding to an hydroxyl, an acetyl or a double bond conjugated with a carboxyl group. In the ultra-violet spectrum the intensity of the maximum at 210 mμ had fallen to 6,600, almost half of the original value. These facts indicated the disappearance of α,β-unsaturation. The above date could be properly interpreted by assuming the presence of an α,β-unsaturated 7-membered lactone ring in obacunone.

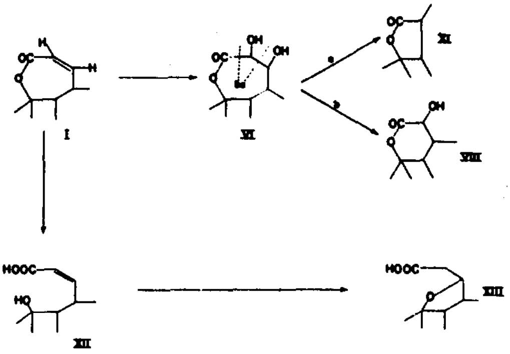


FIG. 1.

This assumption received further support from the observation that obacunone and ethioobacunoic acid [iii(b) and iii(c)]: show extremely facile hydrolysis of the 7-membered lactone when the α.β-unsaturation is removed.

(iii) <u>The relationship between the furan, 6-membered and 7-membered lactone rings</u>

For the following reasons the three rings are placed as shown in I

(Fig. 2): namely, the furan ring is joined to the 6-membered lactone which has an ether linkage in the α-position to the carbonyl, while the 7-membered lactone is not directly linked to the other two rings.

(a) (Scheme 1 and Fig. 2). The previously described dilactone XI, one of whose lactones is 6-membered, inherited form the presurser, and the other 5-membered newly formed by oxidation, was hydrogenated in AcOH solution over Pd/C to give a neutral compound XIV, $C_{24}H_{32}O_7$, and a carboxylic acid XV, $C_{24}H_{34}O_7$. Bands corresponding to a furan ring were absent from the I.R. spectrum of XIV indicating the saturation of this ring. The infra-red spectra of XV (I.R. 5·72, 5·90 μ in Nujol; 5·69 μ in $CHCl_3$) and its ester XVI (I.R. 5·73, 5·89 μ in Nujol; 5·70 μ in $CHCl_3$) indicated that the 6-membered lactone present in the precurser, which was activated by the furan ring, had been hydrogenolysed but that the 5-membered lactone had survived.

(b) (Scheme 2 and Fig. 2). Methyl hydrogenoctahydroobacunoninate XVIII, $C_{27}H_{42}O_8$,[5] obtained by hydrogenation of methyl obacunoate (XVII) in

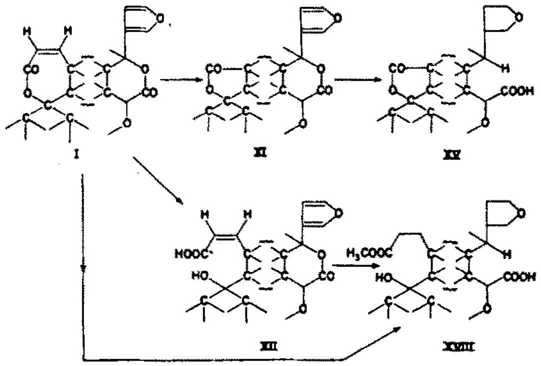
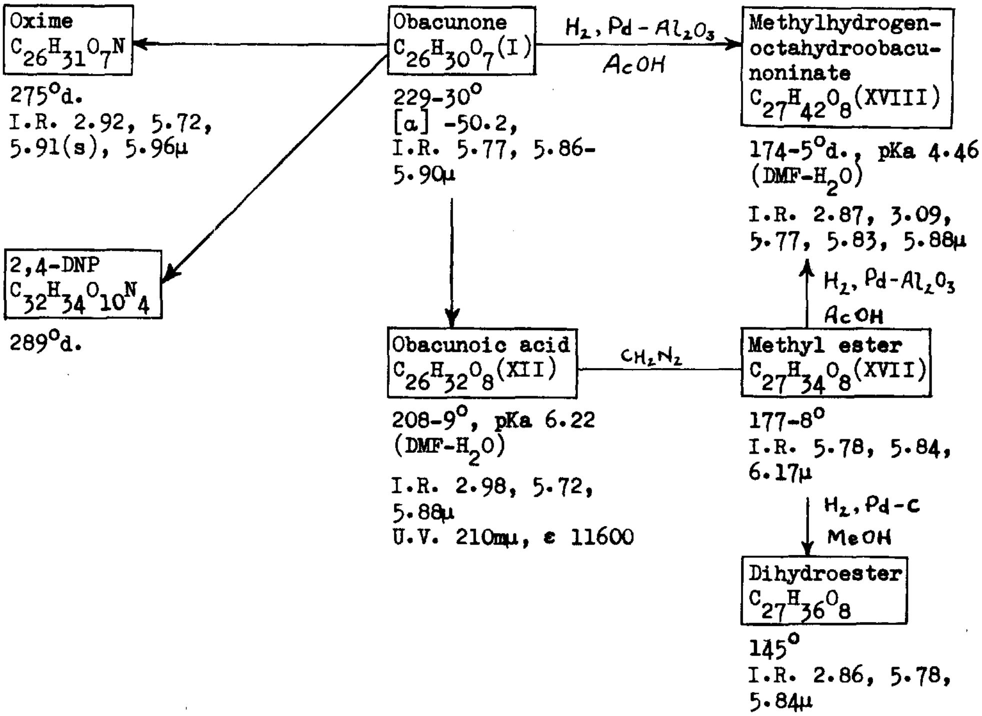


FIG. 2.

AcOH solution over Pd-Al_2O_3, was also formed by hydrogenation of obacunone itself in the same way, followed by crystallization from methanol. These facts can be interpreted as hydrogenolysis of the 6-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 7-membered lactone [see also iii(c)].

SCHEME 2



The unusually high acidity (Table 1) of the carboxylic acids XV and XVIII suggests that there may be an electron-withdrawing group (probably an ether group) located on the α-carbon atom to the carboxyl group which was generated during hydrogenolysis.

TABLE 1. pKa Values of Carboxylic Acids in 50% DMF-H_2O

CH_3COOH	6.52
C_6H_5COOH	6.12
obacunoic acid (XII)	6.22
acid (XV)	4.90
acid (XVIII)	4.46
acid (XVIII)	2.9*
hexahydrolimonic acid	2.7*
ethioobacunoic acid (IV)	4.67

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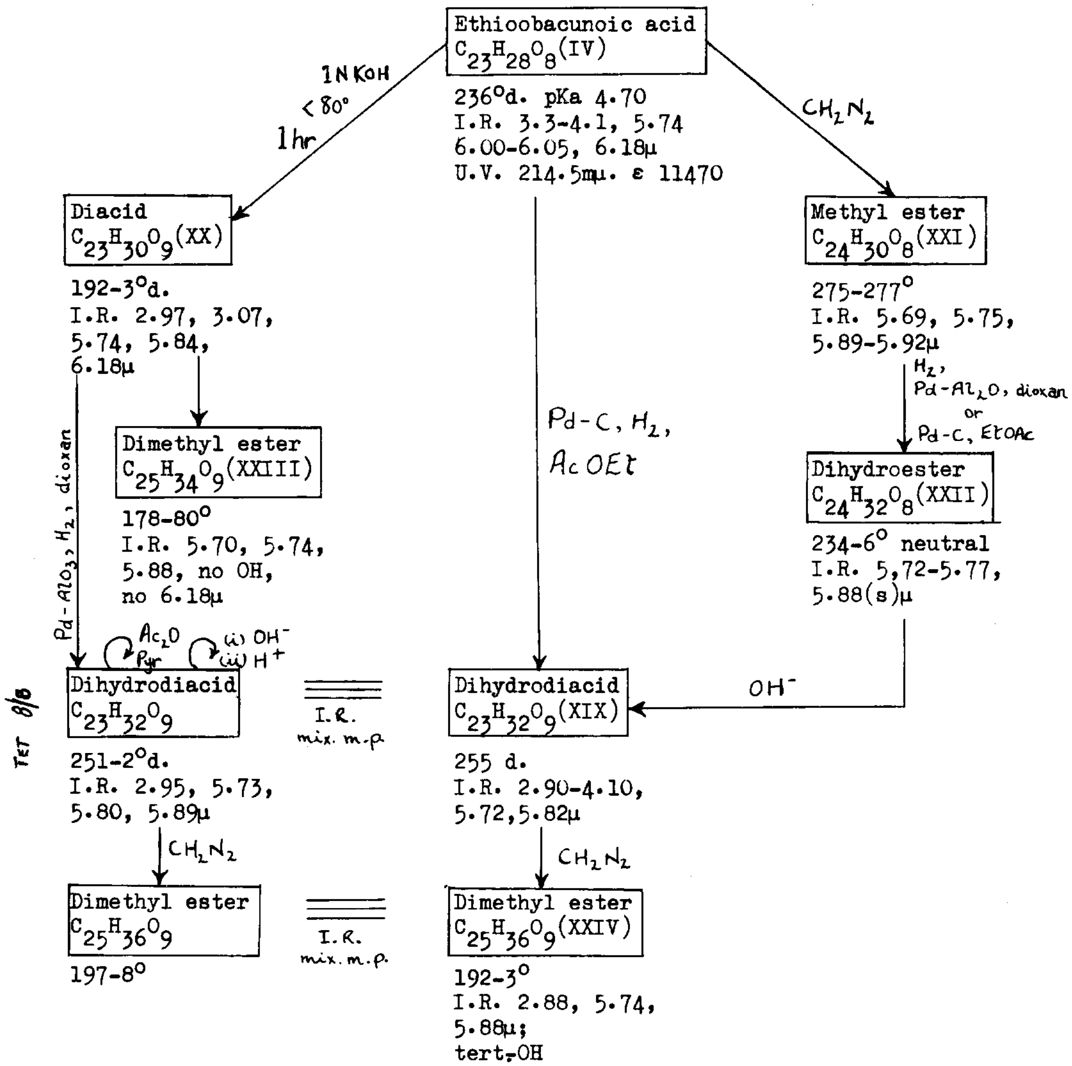
* in H_2O

(c) (Scheme 3 and Fig. 3). Ethioobacunoic acid (IV) absorbed 1 mole

SCHEME 3



of hydrogen in AcOH solution over Pd/C to give the dihydro-dicarboxylic acid XIX $C_{23}H_{32}O_9$. This compound had an hydroxyl group which resisted acetylation, and showed tribasisity under normal titration conditions. The same compound XIX was also obtained by two different methods. (1) Treatment of IV with 1 N KOH solution to give an unsaturated dicarboxylic acid XX, $C_{23}H_{30}O_9$, which on sequent hydrogenation over Pd-Al_2O_3, yielded XIX. (2) Under the same hydrogenation the methyl ester of IV (XXI, $C_{24}H_{30}O_8$) gave a neutral dihydro-ester XXII, $C_{24}H_{32}O_8$, which was, in turn, hydrolysed to give XIX. Apparently the reduction of ethioobacunoic acid (IV) to the dihydrodicarboxylic acid XIX involves only the saturation of an α,β-unsaturated 7-membered lactone and subsequent facile hydrolysis of the resulting saturated lactone, but not the hydrogenolysis of the 6-membered lactone. The stability of the 6-membered lactone in this case was attributed to the lack of furan ring activation.

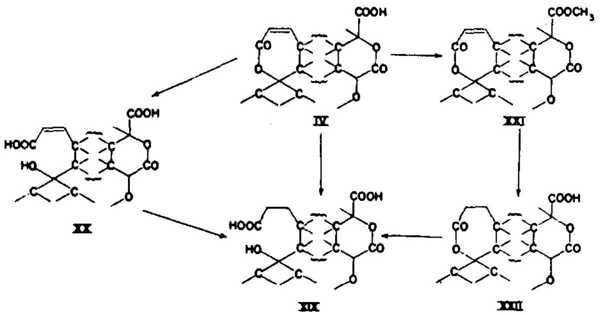


FIG. 3.

The low pKa value (see Table 1) of ethioobacunoic acid (IV) also lends support to the assignment of a carboxyl group, as indicated in IV.

The tertiary character of the hydroxyl group present in dihydrodicarboxylic acid XIX, obtained from the opening of the 7-membered lactone, in obacunoic acid (XII) and XX was indicated by the following observations. (1) With acetic anhydride in pyridine XIX gave unchanged starting material, and XII gave rise to a new tetrahydrofuran group (XIII) instead of an acetate. (2) An attempted methylation of XX with CH_2N_2 gave a dimethyl ester with simultaneous loss of the hydroxyl band in the I.R. absorption. (3) The resistance of XII to oxidation with chromic acid.

And the evidence that this tertiary hydroxyl group in XIX is attached to CMe_2 group was presented by the following experiments: when the dimethyl ester (XXIV) was treated by phosphoroxychloride in pyridine or potassium hydrogensulfate in acetic anhydride, the dehydro-dimethylester (XXV),

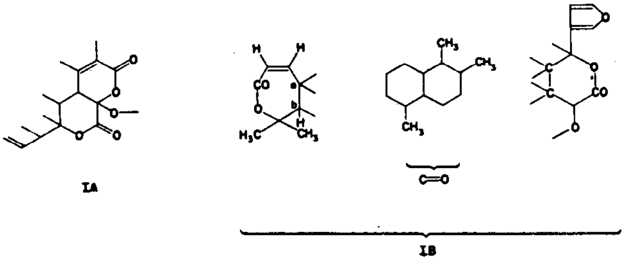


FIG. 4.

$C_{25}H_{34}O_8$, m.p. 149-151°C was obtained. With ozone XXV gave acetone (identified as 2,4-dinitrophenylhydrozone) and neutral crystalline compound m.p. 144-146°C.

The above results can be summarized as IB. Since the 7-membered lactone ring could be formed from the A-ring of lanostanone by Arigoni-type oxidation,[6] it might be thought that two carbon atoms (a and b in IB) of 7-membered lactone ring belong to the hydronaphthalene ring.

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[6] D. Arigoni, D.H.R. Barton, R. Bernaseoni, C. Djerassi, J.S. Mills and R. Wolf, <u>Proc. Chem. Soc.</u> 306 (1959).