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ESTABLISHMENT OF THE CORRELATION OF OBACUNONE AND LIMONIN[1]

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ARIGONI, Barton, Corey, Jeger, and collaborators established the complete structure I for limonin. They also proposed the formula II as the plausible and biogenetically attractive one for obacunone.[2] Kubota, Kamikawa, Tokoroyama, and Matsuura proposed the partial structure III on the basis of the degradation reaction of obacunone.[1,3-6] Recently, the partial structure IV for obacunone has been provided by Barton and collaborators. These workers have also suggested the stereochemical structure V by assuming that obacunone is related, stereochemically as well as constitutionally, to

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[1] For previous work see: T.Matsuura, T.Kamikawa and T.Kubota, Tetrahedron 12, 269 (1961).

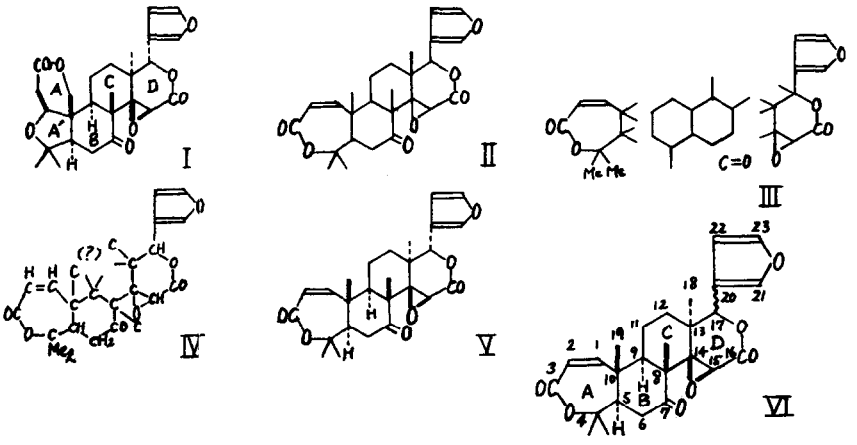
[2] D.Arigoni, D.H.R.Barton, E.J.Corey, O.Jeger and collaborators, Experimentia 16, 41 (1960).

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

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

[6] T.Kamikawa and T.Kubota, Tetrahedron 12, 262 (1961).



limonin.[7] We now wish to report that the stereochemical structure VI has been established for obacunone by the correlation of obacunone and limonin via a degradation product and by the incidental chemical evidences.

When obacunoic acid (VII) was treated with barium hydroxide for a shorter time than in process of the preparation of isoobacunoic acid (VIII: R=H) from obacunoic acid, it afforded a new isomer of obacunoic acid, epi-isoobacunoic acid (IX: R=H), $C_{26}H_{32}O_8$,* m.p. 270-271° dec. (λ_{max}^{EtOH} 209 mμ (ε 5900); ν_{max}** 3200, 1738, 1712, 1700 cm^{-1}), which lacked the α,β-unsaturated acid group and also the hydroxyl group like isoobacunoic acid. Epi-isoobacunoic acid could be converted to isoobacunoic acid on treatment with barium hydroxide for a longer time. This result and the other properties of epi-isoobacunoic acid show that this acid is an epimer of

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* All analytical data were satisfactory to the calculated values.

** All infra-red spectra were taken in Nujol.

7 D.H.R.Barton, S.K.Pradham, S.Sternbell and J.F.Templeton, J.Chem.Soc. 255 (1961).

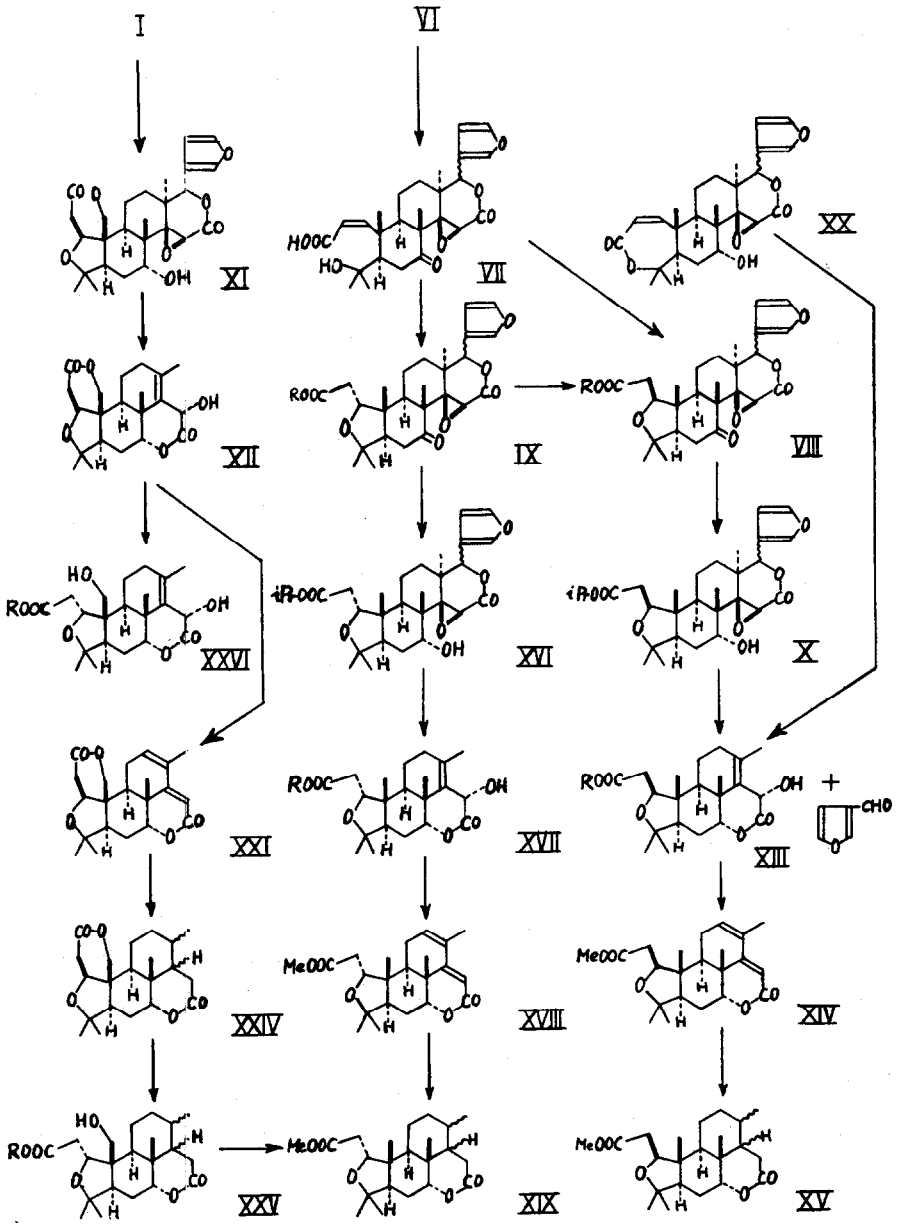
isoobacunoic acid at the C_1-position.

Meerwein-Ponndorf reduction of methyl isoobacunoate (VIII; R=CH_3), $C_{27}H_{34}O_8 \cdot CH_3CO_2H$, m.p. 116-119°, afforded isopropyl isoobacunolate (X), $C_{29}H_{40}O_8$, m.p. 236-237°, as the major product. Treatment of X with sodium hydroxide under the condition needed to transform limonol (XI) to meroliminol (XII)[8] gave meroobacunolic acid (XIII; R=H), $C_{21}H_{30}O_6 \cdot CH_3OH$, m.p. 195-196° ($\nu_{max}$ 3400-3360, 2720-2400, 1723, 1710, 1663 cm^{-1}), characterized as the monomethyl ester, $C_{22}H_{32}O_6$, m.p. 194-195° (λ_{max}^{EtOH} 226.5 mμ (ε 2950); λ_{min}^{EtOH} 218 mμ (ε 2740); ν_{max} 3400, 1732 cm^{-1}), and monoacetate, $C_{23}H_{32}O_7 \cdot CH_3OH$, m.p. 140-142° dec. Methyl meroobacunolate (XIII; R=CH_3) was dehydrated with phosphorous oxychloride and pyridine to give methyl anydromeroobacunolate (XIV), $C_{22}H_{30}O_5$, m.p. 174-175° (λ_{max}^{EtOH} 277 mμ (ε 13,400); ν_{max} 1730, 1713, 1645, 1612, 818 cm^{-1}), which, on catalytic hydrogenation, gave methyl tetrahydroanhydromeroobacunolate (XV), $C_{22}H_{34}O_5$, m.p. 104-105° (ν_{max} 1730, 1717 cm^{-1}).

Methyl epi-isoobacunoate (IX; R=CH_3), a amorphous solid, was subjected to the above series of reactions. Meerwein-Ponndorf reduction afforded exclusively isopropyl epi-isoobacunolate (XVI), $C_{29}H_{40}O_8$, m.p. 187-188° (ν_{max} 3500, 1730, 1165 cm^{-1}), which, on treatment with sodium hydroxide, gave an isomer of meroobacunolic acid, epi-meroobacunolic acid (XVII; R=H), $C_{21}H_{30}O_6 \cdot H_2O$, m.p. 243-244° ($\nu_{max}$ 3480, 2700-2500, 1738, 1720, 1675 cm^{-1}). This acid was characterized as the monomethyl ester, $C_{22}H_{32}O_6$, m.p. 145-147° (λ_{max}^{EtOH} 226.5 mμ (ε 2990); λ_{min}^{EtOH} 218 mμ (ε 2740); ν_{max} 3480, 1738, 1722 cm^{-1}), and monoacetate, $C_{23}H_{32}O_7 \cdot H_2O$, m.p. 224-226°.

Dehydration of methyl epi-meroobacunolate (XVII; R=CH_3) afforded methyl anhydro-epi-meroobacunolate (XVIII), m.p. 192-194° (λ_{max}^{EtOH} 276 mμ

[8] A.Melera, K.Schaffner, D.Arigoni and O.Jeger, Helv.Chim.Acta 40, 1427 (1957).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(ε 11,900); ν_{max} 1730, 1700, 1633, 1600, 790 cm^{-1}), which, on catalytic hydrogenation, gave methyl tetrahydroanhydro-epi-meroobacunolate (XIX), $C_{22}H_{34}O_5$, m.p. 193-194° [ν_{max} 1730, 1715 cm^{-1}, $[\alpha]_D$ + 30° (C, 0.90; EtOH)].

On the other hand, sodium brohydride reduction of obacunone afforded two isomeric alcohol, obacunol (XX), $C_{26}H_{32}O_7 \cdot C_2H_5OH$, m.p. 248-250° ($\nu_{max}$ 3640-3560, 1724, 1690, 1066 cm^{-1}), as the major product, and isoobacunol, $C_{26}H_{32}O_7 \cdot 2CH_3OH$, m.p. 134-137° dec. ($\nu_{max}$ 3640-3440, 1730, 1690, 1018, 1040 cm^{-1}), as the minor product. Obacunol was characterized as the monoacetate, $C_{28}H_{34}O_8$, $1/2CH_3OH$, m.p. 151-153° dec. (ν_{max} 1730, 1715, 1690, 1220 cm^{-1}), and on chromium trioxide oxidation gave obacunone. Isoobacunol was also characterized as the monoacetate, $C_{28}H_{34}O_8$, m.p. 212-214° (ν_{max} 1738, 1700, 1680, 1240, 1032 cm^{-1}). At present there is not sufficient data for the correlation among these two alcohols and α- and β-obacunol obtained by potassium borohydride reduction[9] of obacunone. Meroobacunolic acid (XIII; R=H) and furan-3-aldehyde, (2,4-dinitrophenylhydrazone, $C_{11}H_8O_5N_4$, m.p. 231-233°*) were isolated on treatment of obacunol (XX) with sodium hydroxide. Furthermore meroobacunolic acid and epimeroobacunolic acid were also obtained by the Meerwein-Ponndorf reduction of obacunone followed by alkali treatment of the amorphous reduction product

The ultra-violet spectra of the methyl esters of meroobacunolic acid and epi-meroobacunolic acid were superimposable on that of merolimonol (XII) and the absorption maxima of the anhydro derivatives of both methyl esters, XIV and XVIII, were also identical with that of anhydromerolimonol (XXI). From these results, we can now formulate meroobacunolic acid and epi-meroobacunolic acid as the partial structure XXII, consequently

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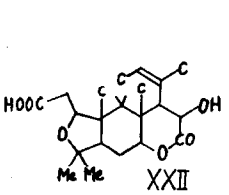
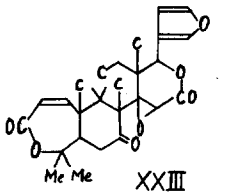
* The 2,4-dinitrophenylhydrazone was identical with an authentic sample which was kindly supplied by Dr. S.Kusumoto.

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

obacunone as the structure XXIII. The fact that IX and XVI are obtained as



XXII



XXIII

the major product of the Meerwein-Ponndorf reduction and the inspection of the C-O stretching band[10] of obacunol (XX) and its acetate led us to the conclusion that the C_7-hydroxyl groups of meroobacunolic acid and of epi-meroobacunolic acid have axial configuration and therefore XIII (R=H) and XVII (R=H) must be epimeric at the C_1-position.

After failures of several attempts to inter-relate obacunone and limonin, we have succeeded in the derivation of limonin to methyl tetrahydroanhydro-epi-meroobacunolate (XIX). Tetrahydroanhydromerolimonol (XXIV) obtained from merolimonol (XII) *via* anhydromerolimonol (XXI) according to the method of Melera *et al.*,[8] was hydrolysed with barium hydroxide under drastic conditions to give a lactonic hydroxy-acid (XXV; R=R'=H), $C_{21}H_{32}O_6$, m.p. 265° dec. (ν_{max} 3470, 3180-2450, 1730, 1700 cm^{-1}). In this acid the lactone ring A was opened irreversibly and we assigned the structure XXV (R=R'=H), having the acetic acid side-chain with α-configuration at the C_1-position, comparable to the acid XXVI (R=H)[2] obtained from merolimonol. In our experiment, the acid (XXVI;R=H) was obtained as a crystalline form, $C_{21}H_{30}O_7 \cdot 1.5H_2O$, m.p. 243-244° dec., which was characterized as the monomethyl ester (XXVI; R=CH_3), $C_{22}H_{32}O_7$, m.p. 228-230°.

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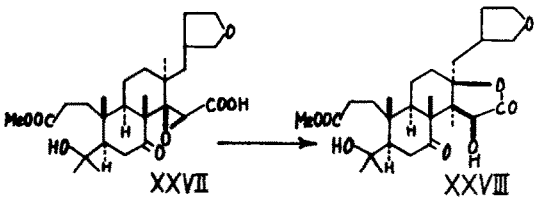
[10] E.A.Braude and E.S.Waight in W.Klyne, Progress in Stereochemistry Vol. I, p. 166. Butterworths,London (1954).

The lactonic hydroxy-acid (XXV; R=R'=H) was converted to the monomethyl ester (XXV; R=CH_3, R'=H), $C_{22}H_{34}O_6$, m.p. 205° (ν_{max} 3530, 1733, 1715 cm^{-1}). After several attempts to remove the hydroxyl group of this ester had been failed, the ester was converted to the mesylate (XXV; R=CH_3, R'=CH_3SO_2), $C_{23}H_{36}O_8S$, m.p. 209-210° (ν_{max} 1733, 1353, 1173, 983 cm^{-1}). Treatment of the mesylate with sodium iodide at 180° afforded an acidic product which, on methylation with diazomethan followed by treatment with zinc and acetic acid, gave a crystalline product, m.p. 194-195°, ($[\alpha]_D$ + 33° (C, 1.09; EtOH)). This product was identical with methyl tetrahydroanhydro-epi-meroobacunolate (XIX) as shown by comparison of infra-red spectrum (in both Nujol and chloroform) and in the mixture melting point determination. Anomalous formation of the acidic product in this reaction can be explained by the known type of hydrolysis of esters with metal halides.[11]

The derivation of XIX from limonin has regorously established the structure II for obacunone and also the same configurations at C_5-, C_8-, C_9- and C_{10}-positions as in limonin. Among four remaining asymmetric carbon atoms, the configurations at the C_{13}-, C_{14}- and C_{15}-positions have been deduced as follows. Barton and collaborators[7] found that treatment of methyl hydrogen octahydroobacunoninate (XXVII) with acid afforded the acidic product (XXVIII), analogous to the product of the acid-catalysed rearrangement of hexahydrolominic acid, and concluded that the CD ring



XXVII XXVIII

[11] F.Elsinger, J.Schreiber and A.Eschenmoser, Helv.Chim.Acta 43, 113 (1960) and cited references.

fusion of obacunone must be trans.[12] Furthermore, we can conclude that the 14, 15-epoxy group in obacunone probably has the β-configuration, since the back side attack of the 7-α-hydroxyl group to the C_{14}-position of the epoxy group of isopropyl epi-isoobacunolate (XVI) is required in the transformation of XVI to epi-meroobacunolic acid (XVII; R=H), comparable to the transformation of limonol (XI) to merolimonol (XII).[2,12]

We can now conclusively formulate obacunone as the sterochemical structure VI. Although the stereochemistry of the C_{17}-position can not be rigidly designated by chemical evidences, we assume that the β-furyl group has the α-configuration as shown in the structure V. We hope to provide a final solution to this problem in a further communication.

Our result indicates that the side-chains at the C_1-position of isoobacunoic acid (VIII; R=H) and epi-isoobacunoic acid (IX; R=H) have, respectively the β- and α-configuration. It is concluded that, in a series of obacunone derivatives, the β- epimer of the C_1-side-chain is more stable than the α-epimer, contrary to the limonin series [e.g. merolimonol (XII) ⟶ the acid (XXVI)].

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[12] A.D. Cross, Quart.Rev. 14, 326 (1960).