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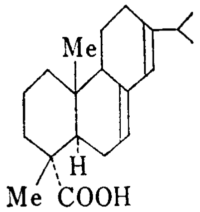
Synthesis of Four Possible Isomers of 4β,10-Dimethyl-1,2,3,4,5,10-hexahydrofluorene-4,6-dicarboxylic Acid Derivatives[1]

In the present decade, skeleton transformation of resin acid, *e.g.* abietic acid (I), to fluorene compounds regarded as basic skeleton of gibberellin, have attracted our interest. A few attempts were already achieved in English[2a] and our laboratories.[2b]

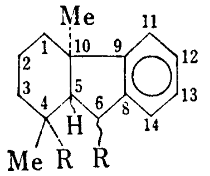
Now, a synthesis of four possible stereoisomers of 4β,10-dimethyl-1,2,3,4,5,10-hexahydrofluorene-4,6-dicarboxylic acid derivatives (acid (II), (III), (IV), (V); ester (VI), (VII), (VIII), (IX)) having a closed structure to gibberellin A_{12}(X), will be described.

Fluorene anhydride (XI), previously synthesized from abietic acid (I),[2a] was treated by catalytic hydrogenation (Pd-C, AcOH) and successive alkaline hydrolysis. From the reaction mixture, stereoisomeric acids (II), $C_{17}H_{20}O_4$, oil, τ: 8.90(C_{10}-Me), 8.77 (C_4-Me) and (III), $C_{17}H_{20}O_4$, mp 222—224°, τ: 8.76(C_{10}-Me), 8.53(C_4-Me) in addition to the hydrolyzed starting anhydride (XII) can be separated by recrystallization.

The corresponding methyl esters (VI), $C_{19}H_{24}O_4$, oil, τ: 8.81 (C_{10}, C_4-Me), and (VII), $C_{19}H_{24}O_4$, mp 130—132°, τ: 8.89 (C_{10}-Me), 8.57 (C_4-Me), were readily epimerized at C_6-position by sodium methanolate treatment to give isomeric esters (VIII), $C_{19}H_{24}O_4$, mp 110—114.5°, τ: 8.82 (C_{10}-Me), 8.72 (C_4-Me) and (IX), $C_{19}H_{24}O_4$, mp 124—126°, τ: 9.13 (C_{10}-Me), 8.80 (C_4-Me), respectively. In order to confirm that a structural change except for the epimerization of

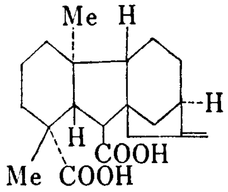


I

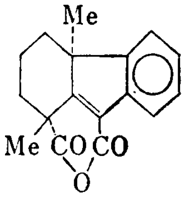


R=COOH
- II : αC_5-H, βC_6-COOH
- III : βC_5-H, αC_6-COOH
- IV : αC_5-H, αC_6-COOH
- V : βC_5-H, βC_6-COOH

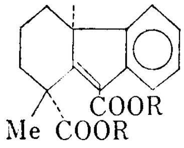
R=COOMe
- VI : αC_5-H, βC_6-COOMe
- VII : βC_5-H, αC_6-COOMe
- VIII : αC_5-H, αC_6-COOMe
- IX : βC_5-H, βC_6-COOMe



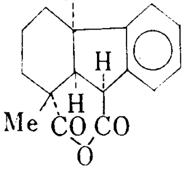
X



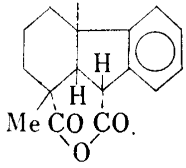
XI



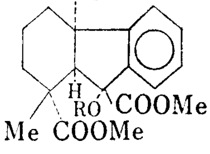
XII : R=H
XIII : R=Me



XIV



XV



XVI : R=H
XVII : R=Ac

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[1] A part of this work was presented at the 89th Annual Meeting of the Pharmaceutical Society of Japan at Nagoya, April 1969 (Meeting Abstracts, p. 239). New compounds indicated by molecular formula gave satisfactory analytical values and were homogeneous on gas-liquid chromatography. NMR spectra were measured at 60 Mc in $CDCl_3$ *vs.* Me_4Si as internal reference.

[2] *a*) J.F. Grove and B.J. Riley, *J. Chem. Soc.*, **1961, 1105**; *b*) A. Tahara, *Chem. Pharm. Bull.* (Tokyo), **9**, 252 (1961); A. Tahara and O. Hoshino, *ibid.*, **9**, 655 (1961); *idem*, *Tetrahedron Letters*, **1966**, 3825, 5031; A. Tahara, O. Hoshino and T. Ohsawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 54, 64, 68 (1969).

C_6-configuration did not occur under the alkaline condition, the stable diesters (VIII) and (IX) were converted to the known fluorene derivative (XIII)[2a] by bromination (NBS) and successive dehydrobromination. Alkaline hydrolysis of diesters (VIII) and IX afforded the corresponding diacids (IV), $C_{17}H_{20}O_4$, mp 142—150°, τ: 8.65 (C_{10}, C_4-Me) and (V), $C_{17}H_{20}O_4$, mp 223—225°, τ: 9.02 (C_{10}-Me), 8.67 (C_4-Me), which were esterified again to give the original diesters, respectively.

For structural elucidation of the four kinds of the stereoisomers, the obvious evidences were adduced as follows:

i) A pair of diacids (II) and (III) were obtained together from unsaturated anhydride (XI), as previously described, and were also converted to the respective anhydrides (XIV), $C_{17}H_{18}O_3$, mp 120.5—122° and (XV), $C_{17}H_{18}O_3$, mp 161—164°, by boiling with acetic anhydride. The anhydrides were readily hydrolyzed to the original diacids, respectively. Conversely, the other pair of diacids (IV) and (V) could not formed the anhydride bridge under the same condition. Molecular model clearly indicates that only structure shown as (II) or (III) can be formed the anhydride ring. Furthermore, the fact that acids (II) and (III) have *cis* C_5-H/C_6-H configuration and have quasi axial C_6-COOH group, can be consistently explained by mode of catalytic hydrogenation (XI→II+III) and alkaline epimerization respectively.

ii) Since hydrogenolysis (Pd-C, AcOH, H_2SO_4) of hydroxy diester (XVI) having a reliable structure,[2] afforded diesters (VI) and (VIII), both of the diesters should have the same *cis* A/B ring fusion as XVI. Accordingly, a pair of the other esters (VII) and (IX) should have *trans* A/B ring fusion.

iii) Chemical shifts due to C_5-H of the isomeric four diesters ((VI): 6.77, (VIII): 6.53 and (VII): 7.72, (IX): 7.62 τ) can be distinguished as two classes, which are caused by stereoisomerism of A/B ring fusion. The values of the former group (VI and VIII) belong in those of the diesters ((XVI): 6.47 and (VXII): 6.67 τ) having reliable *cis* A/B ring fusion.[3]

iv) On the basis of structural model of the diesters as assigned above, coupling constants between C_5-H and C_6-H ((VI): $J=7.5$ cps, $\Phi=30°$, (VII): $J=6.7$ cps, $\Phi=35°$, (VIII): $J=12.0$ cps, $\Phi=150°$, (IX): $J=13.3$ cps, $\Phi=155°$) were calculated by substitution of measured dihedral angle to the Williamson and Johnson's modified equation.[4] The values can not contradict the observed coupling constants ($J=$(VI): 9.0 cps, (VII): 8.5 cps, (VIII): 11.0 cps, (IX): 11.5 cps).

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3) Analysis of chemical shifts due to C_4- and C_{10}-Me are consistent with the conclusion and will be reported in detail later.

4) K.L. Williamson, W.S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961).