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ON THE STEREOISOMERS OF SOME ENMEIN DERIVATIVES

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This communication deals with the synthesis of possible four epimers 4, 5, 8, and 10 from enmein(1) and the assignment of their structure and absolute configuration.

The ketolactone ester 3 was derived from enmein(1), a diterpenoid bitter major principle of the leaves of Isodon species, *via* compound 2 through the known route.[1]

While compound 3, on treatment with $NaBH_4$ in methanol containing some water, afforded a *trans*-β-alcohol 4, m.p.157.5-158°, it gave only a *cis*-α-alcohol 5, m.p. 134-135°, on reduction with $LiAl(t\text{-}BuO)_3H$ in anhydrous tetrahydrofuran. The latter on treatment with 0.03 *M*. $NaHCO_3$ in a mixture of methanol and water (4:1) was epimerized into 4. Both alcohols 4 and 5 on chromic acid oxidation gave the same ketone 3, which means that the configuration of the C-16 methyl group is the same in both compounds. Now, the X-ray analysis carried out by Coggan and Sim on the bromoacetate*[2] of the compound 4 confirmed that compound 4 has the absolute configuration shown in the Chart I. The bromoacetate crystallizes in the orthorhombic system, space group $P2_12_12_1$. There are four

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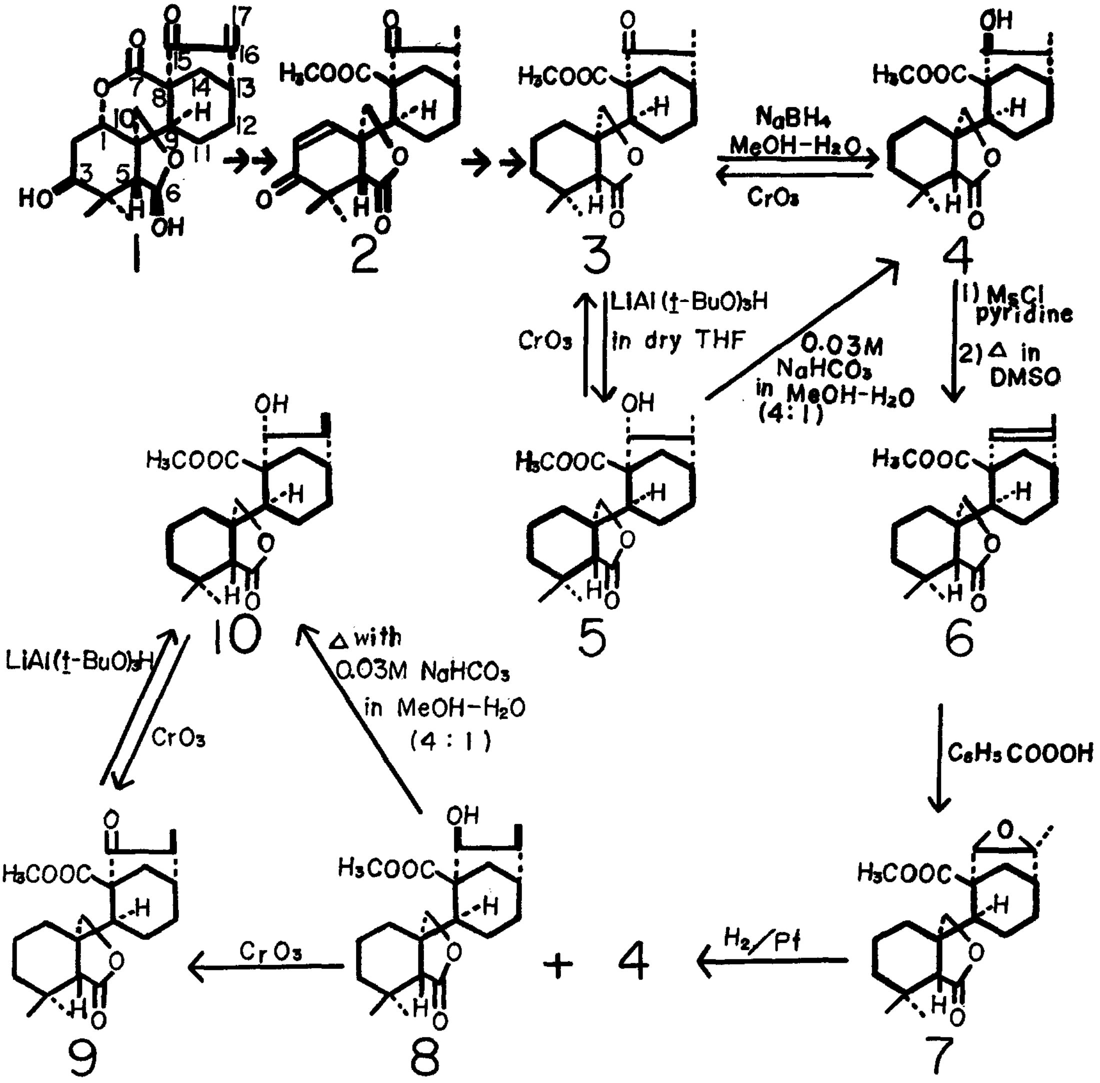
*[2] The bromoacetate on weak alkaline hydrolysis (5% K_2CO_3 in $MeOH\text{-}H_2O$) was reconverted into 4.


1
2
3
4
5
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8
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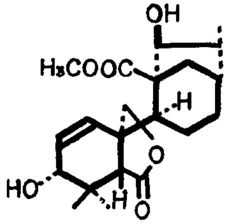
10
NaBH4 MeOH-H2O
CrO3
LiAl(t-BuO)3H in dry THF
CrO3
0.03M NaHCO3 in MeOH-H2O (4:1)
1) MsCl pyridine 2) Δ in DMSO
C6H5COOOH
H2/Pt
+ 4
CrO3
Δ with 0.03M NaHCO3 in MeOH-H2O (4 : 1)
LiAl(t-BuO)3H
CrO3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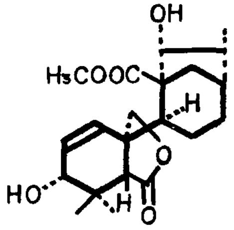
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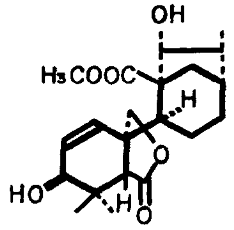
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molecules of $C_{23}H_{33}O_6Br$ in the unit cell, and $\underline{a}$ = 8.40, $\underline{b}$ = 12.29, $\underline{c}$ = 22.02 Å, $\underline{D}_m$ = 1.43, $\underline{D}_c$ = 1.42 g. cm.$^{-3}$. The position of the bromine atom was derived from a Patterson synthesis, and the carbon and oxygen atoms were located in three-dimensional electron-density distributions. The absolute configuration of the molecule was determined by Bijvoet's anomalous-dispersion method.[2]

These epimeric alcohols, $\underline{4}$ and $\underline{5}$, have been obtained by Professor Okamoto et al.[3] through the $NaBH_4$ reduction*[3] of $\underline{3}$ and separated by the chromatography on silica-gel column. Their assignments of structure and stereochemistry to these epimers were proved to be correct.

Subsequently, the alcohol $\underline{4}$ was converted into the methanesulphonate[3] and the latter was heated at 150-160° for 3 hours in dimethylsulphoxide[4] to yield an unsaturated product $\underline{6}$.[3] Epoxidation of $\underline{6}$ with perbenzoic acid in a mixture of chloroform and benzene(4:1) gave $\underline{7}$, m.p. 172-173°, which on hydrogenolysis using Adams' catalyst in acetic acid yielded $\underline{4}$ and a new cis-alcohol $\underline{8}$ in a ratio of 4 : 3. Compound $\underline{8}$ was a crystalline alcohol, m.p. 141-142°, whose N.M.R.*[4] spectrum exhibited a doublet signal(J = 8.5 c.p.s.) assignable to C-15-$\underline{H}$ at $\delta^{benzene}$ 3.73 ppm. The fact that alcohol $\underline{4}$ was obtained in the foregoing hydrogenolysis clarified the β-configuration of the epoxide ring in compound $\underline{7}$ and allowed[5] a reasonable assignment of cis-β-alcohol configuration to $\underline{8}$.

Alcohol $\underline{8}$ on chromic acid oxidation gave a ketone $\underline{9}$, which on treatment with LiAl(t-BuO)$_3$H in anhydrous tetrahydrofuran afforded the fourth epimer, the trans-alcohol $\underline{10}$, m.p. 125-126°, whose N.M.R. spectrum showed a doublet (J = 4.5 c.p.s.) assignable to C-15-$\underline{H}$ at δ^{CDCl_3}3.53 ppm. An epimerization from $\underline{8}$ to $\underline{10}$ proceeded under the same conditions as in the case of $\underline{5}$ to $\underline{4}$, although it was necessary to heat the mixture. The alcohol $\underline{10}$ was reconverted into ketone $\underline{9}$ by chromic acid oxidation.

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*[3] We are grateful to Professor T. Okamoto and Dr. K. Shudo, University of Tokyo, for valuable discussions.

*[4] The N.M.R. spectra were taken on a Varian A-60 spectrometer using TMS as an internal standard.

Finally, 2 on treatment with $NaBH_4$ in tetrahydrofuran containing some water gave only a diol 11[I.R.($CHCl_3$): 3550, 1755, and 1724 cm.$^{-1}$, N.M.R.: 3.44(1H, doublet, J = 4.5 c.p.s., C-15-H), 3.97(1H, doublets of doublet, J = 1.5 and 2.0 c.p.s., C-3-H)], while it on treatment with LiAl(*t*-BuO)$_3$H in absolute tetrahydrofuran gave only epimeric diol, 12[I.R.($CHCl_3$): 3600, 1760, and 1725 cm.$^{-1}$, N.M.R. : 3.79(1H, doublet, J = 11.0 c.p.s., C-15-H), 3.99(1H, doublets of doublet, J = 1.0 and 2.5 c.p.s., C-3-H)] and 13, m.p. 164-167°[I.R.($CHCl_3$): 3500, 1765, and 1715 cm.$^{-1}$, N.M.R.: 2.82(1H, doublet, J = 5.0 c.p.s., C-15-H), 3.53(1H, doublet, J = 6.0 c.p.s., C-3-H), 4.04(1H, doublets of doublet, J = 5.0 and 10.0 c.p.s., C-15-H)] in a ratio of 1 : 3.4. These compounds were also converted into their diacetates, and their structure assignments were reconfirmed to be correct. The alcohols 11, 12, and 13, on chromic acid oxidation, reformed ketone 2. Moreover, the epimerization of 12 to 11 occurred under the same condition as in the case of epimerization of 5 to 4.

All of the foregoing epimerization may proceed through a retroaldol-type transition state and recyclization. In order to release the unfavourable *cis* eclipsed interaction between C-15 hydroxy and C-16 methyl groups, a rotation of the C-15 substituent around the C-C bond of C-15 and C-16 must take place during this process to afford a *trans* product in each case. It is noteworthy that the C-15 β-hydroxy group was epimerized into the thermodynamically less favourable α-orientation in the case of 8 to 10, even though the rate was slower.

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Satisfactory analyses and/or mass spectra were obtained for all new compounds described.