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STEREOCHEMISTRY OF THE SIDE CHAIN OF DAMMARANE TYPE TRITERPENES

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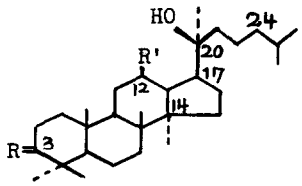
During the course of our chemical studies on the Ginseng saponins, it has been reported that on acid treatment, the dammarane type triterpenes having 12β and 20-hydroxyls, such as betulafolianetriol(I)(1), are rapidly equilibrated with their C-20 epimers(2). It has also been found that the side chain of the dammar-24-ene derivatives with 12β and 20-hydroxyls, such as betulafolienetriol(II)(1), are cyclized to yield a mixture of C-20 epimers of the compounds with 2,2,6-trimethyltetrahydropyran ring (type III) on acid treatment(2,3).

In order to elucidate the role of 12β-hydroxyl in the above mentioned epimerization of the C-20 tertiary hydroxyl, dammaran-20S-ol(IV)(1) was treated with boiling mineral acid in aqueous ethanol. In contrast to the case of the compounds having 12β-hydroxyl, the reaction mixture mainly consisted of a non-polar substance, whose Rf value in the thin layer chromatography on silica gel impregnated with silver nitrate was same as that of one of the dehydration products of IV with $POCl_3$ in pyridine(1). The thin layer chromatography also revealed the absence of the C-20 epimer of IV in this acid catalyzed reaction mixture. On treatment of IV even under the mild condition, p-toluenesulfonic acid in $CHCl_3$ at room temperature(2), the dehydration of C-20 hydroxyl was found to proceed still faster than its epimerization, though the formation of a small amount of the C-20 epimer of IV from IV was observed in this case.

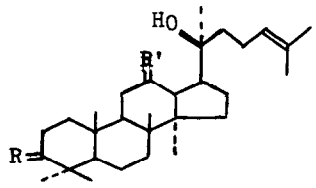
The remarkable difference of the reactivity between the compounds with and without 12β-hydroxyl was further demonstrated in the above mentioned acid catalyzed cyclization of the side chain. Dammar-24-en-20S-ol(V), m.p.59-61°, $/\alpha/_D^{12}$ +38.7°($CHCl_3$), prepared from II through its 3,12-diketone(VI), m.p.152-



I: R=  , R'=OH

IV: R=  , R'=H

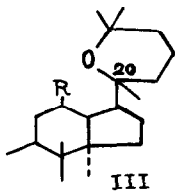
XII: R=  , R'=H



II: R=  , R'=

V: R=R'=

VI: R=R'= =O



III

153.5°, $/\alpha/_D^{10}$ -72.1°($CHCl_3$), was refluxed with dil.mineral acid in aqueous ethanol. The thin layer chromatography of the reaction mixture indicated that the compound having the trimethyltetrahydropyran ring(type III) was not produced and the main product of this reaction was a nonpolar substance with the same Rf value as that of one of the dehydration products of V with $POCl_3$ in pyridine.

The other anomalous chemical property of the side chain was encountered when betulafolienetriol(II) was reacted with N-bromosuccinimide. On the action of this reagent in CCl_4 at room temperature, II afforded a crystalline compound(VII), m.p.170-174°, $C_{30}H_{51}O_3Br$, $/\alpha/_D^{10}$ -10.3°($CHCl_3$), IR $\nu_{max}^{CCl_4}$ 3385(concentration independent) and 3635cm^{-1}, in a good yield. The NMR spectrum of VII in $CDCl_3$ showed no vinylic proton signal but exhibited a broad signal near τ 6.08(1H) along with the similar signals to those characteristic to the protons at C-3 and C-12 of II; tertiary methyl signals appeared at τ 9.18(3H), 9.14(3H), 9.10 (6H), 8.98(3H), 8.69(3H), 8.32(3H), and 8.28(3H). Treatment of VII with zinc dust in acetic acid at room temperature(4) reproduced II in a quantitative yield. It should be noted that VII was yielded from II even in the presence of the radical inhibitor, such as m-dinitrobenzene or hydroquinone. Formation of VII from II was also found by the action of N-bromosuccinimide in aqueous acetone as well as bromine in $CHCl_3$ along with a small amount of a by-product which seemed to be the C-24 epimer of VII because of the similarity of its NMR spectrum to that of VII. These evidences led to suggest that in this reaction, the normal allylic bromination with N-bromosuccinimide did not occur and the reaction would proceed stereospecifically by the ionic mechanism. On the basis of the above results, the structure A (excepting the configuration at C-24) was proposed for VII. The

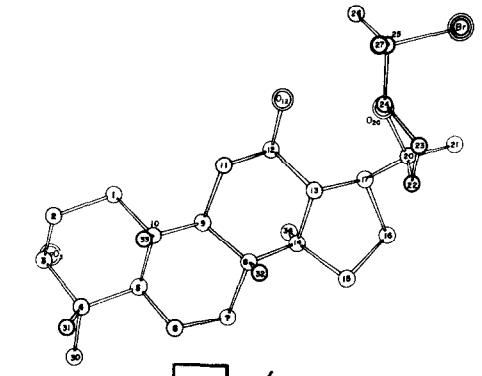
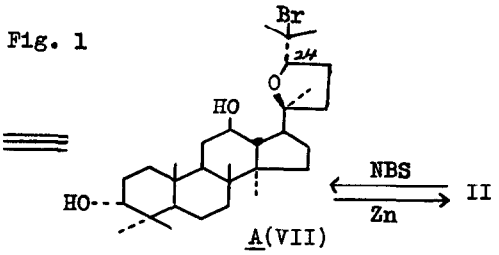
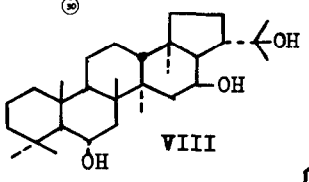
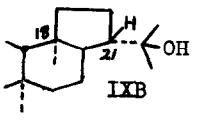
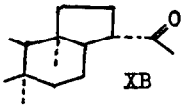


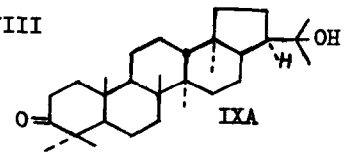
Fig. 1

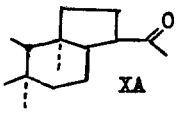


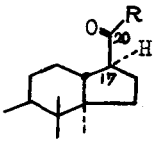












a: R=CH_3

b: R=C_6H_{13}

final elucidation of the structure of VII including the stereochemistry was achieved by its X-ray crystallographic analysis (see Fig. 1).

The crystals of VII were orthorhombic, colorless needles elongated along c-axis(from a mixture of benzene and acetone). The lattice constants and space group determeined from precession photographs using CuKα radiation were, a=19.00, b=20.47, c=7.03Å, $P2_12_12_1$ with four molecules in the unit cell. Three-dimensional diffraction data were recorded on multiple film equi-inclination Weissenberg photographs taken with CuKα radiation of the layers zero through fifth about each of the axis b and c. A total of 1358 independent observed structure factors were derived by visual estimation of the intensities using calibrated intensity scales. The structure was solved by the heavy atom method with the use of several repeated cycles of Fourier and difference Fourier syntheses coupled with the structure factor calculations. Refinement of the structural parameters was made by the block-matrix least-squares calculations to an R value of 0.17, in which anisotropic thermal vibrations of the bromine atoms were allowed for.

Recently, the structure of leucotylin(VIII), the metabolite of lichens, has

been established by X-ray chrystallographic analysis of its derivative(5). In connection with this study,Yosioka et al. reported that the stereochemistry of hydroxyhopanone should be amended to 21-αH structure(IXA)(5). The previous assignment of the configuration at C-21 of hydroxyhopanone(21-βH, IXB) was based on the consideration that the ready inversion of 21-H of the norketone(X) derived from hydroxyhopanone was due to the 1,3-cis steric interaction between the α-methyl ketone at C-21 and the α-methyl at C-18(XB)(6). According to the new formulation of hydroxyhopanone by Yosioka et al., this unstable norketone(X) should be represented by XA(the methyl ketone at C-21/the methyl at C-18:trans). Since the configuration at C-17 of dammarane type triterpenes(the side chain at C-17/the α-methyl at C-14: trans) has been proved by the similar reason to that of the case of hydroxyhopanone i.e. the stability of the 20-keto derivatives(XIa, b) prepared from 3-O-acetyldammaranediol-II(XII), one might expect that the configuration at C-17 of dammarane type triterpenes would be also revised to 17-βH structure. However, our present result of X-ray crystallographic analysis of VII conclusively supports the former proposal of the stereochemistry of dammarane type triterpenes (17-αH)(7).

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