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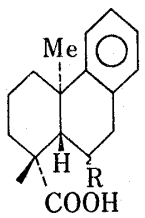
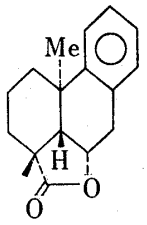
Lactonization of 6β-Hydroxy-tetrahydro- and -hexahydro-*enantio*-deoxypodocarpic Acid. Synthesis of 6α-Hydroxy-tetrahydro- and -hexahydro-*enantio*-deoxypodocarpic Acid[1)]

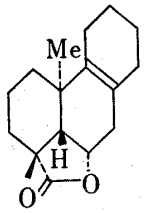
During our synthetic study of natural diterpenoids, an attractive phenomenon was observed. Namely, 6β-hydroxy-deoxy-*enantio*-podocarpic acid (I) was readily lactonized under acidic condition and the lactone (III) did not return to the original acid (I) by alkaline



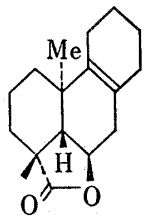
I: R=βOH
II: R=αOH



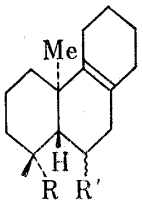
III



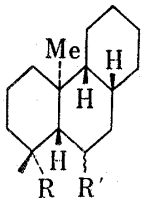
VI



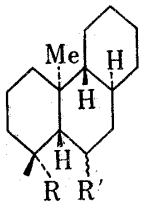
XIII



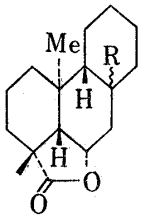
IV: R=COOH, R′=βOH
VIII: R=COOH, R′=αOH
X: R=COOMe, R′=αOH
XV: R=CH_2OH, R′=βOH
XVII: R=CH_2OH, R′=αOH
XXVI: R=COOMe, R′=βOH



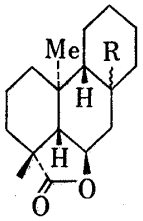
V: R=COOH, R′=βOH
IX: R=COOH, R′=αOH
XI: R=COOMe, R′=αOH
XVI: R=CH_2OH, R′=βOH
XVIII: R=CH_2OH, R′=αOH
XXVII: R=COOMe, R′=βOH



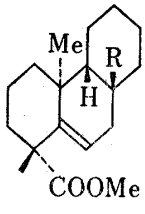
XIX: R=COOH, R′=βOH
XXII: R=COOH, R′=αOH
XXIII: R=COOMe, R′=αOH
XXIV: R=CH_2OH, R′=βOH
XXV: R=CH_2OH, R′=αOH
XXVIII: R=COOMe, R′=βOH



VII: R=βH
XXI: R=αH



XIV: R=βH
XX: R=αH



XII

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

hydrolysis, but was converted to a new isomeric hydroxy acid (II).[2] Since this type epimerization at the lactone formation is unprecedented,[3] now the problem is furthermore investigated.

Hydrogenated compounds of (I)[2] have been firstly used as subject of this purpose. 6β-Hydroxy-tetrahydro- (IV) and an isomer (V) (*cis* B/C-ring fusion) of 6β-hydroxy-hexahydro-acid[4] were readily lactonized with the interesting epimerization at C_6-position to give the respective lactone (VI), $C_{17}H_{24}O_2$, mp 85—87°, ν_{max}^{KBr} cm^{-1}: 1761, τ 9.04 (C_{10}-Me), 8.73 (C_4-Me), and (VII), $C_{17}H_{26}O_2$, mp 159.5—161°. ν_{max}^{KBr} cm^{-1}: 1762, τ 9.12 (C_{10}-Me), 8.72 (C_4-Me), under acidic condition (reflux, 10% HCl aq. *t*-BuOH[5]). Alkaline hydrolysis (reflux, KOH–MeOH–H_2O) of the lactones (VI) and (VII) afforded the other isomeric 6α-hydroxy acids (VIII), $C_{17}H_{26}O_3$, mp 206—207°, and (IX), $C_{17}H_{28}O_3$, mp 187—188°, respectively, which were relactonized to the corresponding original lactones (VI) and (VII). 6α-Hydroxy esters (X), $C_{18}H_{28}O_3$, mp 91.5—93° and (XI), $C_{18}H_{30}O_3$, mp 110—111.5°, obtained (CH_2N_2) from the respective acids (VIII) and (IX), were easily lactonized by chromatography (Al_2O_3) to (VI) and (VII) and were also hydrolized (KOH–MeOH–H_2O) to the original acids VIII and IX respectively. It was confirmed by the following experiments that 6α-hydroxy series had same skeleton as the corresponding 6β-hydroxy compounds with the exception of C_6-configuration: i) The tetrahydro-acid (VIII) was obtained by reduction (Li–EtNH_2–*t*-AmOH) of the authentic 6α-hydroxy acid (II) and ii) the hexahydro-ester (XI) was dehydrated ($POCl_3$- or MsCl–Py.) to give $\Delta^{5,6}$-ester (XII) (*cis* B/C-ring fusion), $C_{18}H_{28}O_2$, mp 63—64°, as a sole product.[4]

In contrast to the epimerized lactones, it is noticeable that unepimerized lactones (XIII), $C_{17}H_{24}O_2$,[6] ν_{max}^{KBr} cm^{-1}: 1770, τ 8.97 (C_{10}-Me), 8.74 (C_4-Me), and (XIV), $C_{17}H_{26}O_2$, ν_{max}^{KBr} cm^{-1}: 1766, τ 8.89 (C_{10}-Me), 8.74 (C_4-Me), were formed from the corresponding 6β-hydroxy-acids (IV) and (V) under the following conditions: i) 200—210°, 1 hr, ii) reflux, *p*-TsOH in benzene and iii) DCC–Py. The lactones (XIII) and (XIV) were so unstable that they could not be purified and could be easily epimerized to the respective stable lactones (VI) and (VII) by the further treatment: i) 250—270°, *ca.* 5—8 hr, ii) Al_2O_3. In order to settle to which isomeric series (β- or α-hydroxy compound)do the lactones (VI and VII) and (XIII and XIV) belong, both the kinds of lactones were reduced ($LiAlH_4$) to give α-hydroxy alcohols (XVII), $C_{17}H_{28}O_2$, mp 141—143°, and (XVIII), $C_{17}H_{30}O_2$, mp 208—209.5° and β-hydroxy alcohols (XV), $C_{17}H_{28}O_2$, mp 138—139° and (XVI), $C_{17}H_{30}O_2$, mp 152.5—155°, respectively. The four kinds of the hydroxy alcohols were produced ($LiAlH_4$) from the corresponding esters (X), (XI), (XXVI) and (XXVII)[4] having the secure C_6-configuration. Accordingly, the epimerization was proved to be occured in the process of the acidic lactonization of β-hydroxy acids (IV and V) and of treatment of unstable lactones (XIII and XIV).

In comparison with the facile epimerization of the aforementioned 6β-hydroxy compounds, the other hexahydro-isomer (XIX) (*trans* B/C-ring fusion) assumed a different attitude to the lactonization. The acid (XIX) was hardly lactonized to only recover the starting acid, but it could be converted to unepimerized lactone (XX), $C_{17}H_{26}O_2$, mp 98—99.5°, ν_{max}^{KBr}

2) A. Tahara and K. Hirao, *Chem. Pharm. Bull.* (Tokyo), **12**, 984, 1121 (1964); A. Tahara, K. Hirao and Y. Hamazaki, *Tetrahedron*, **21**, 2133 (1965).

3) *cf. a)* D.H.A. Barton, *J. Org. Chem.*, **15**, 466 (1950); H. Ishikawa, *Yakugakuzasshi*, **76**, 504 (1956); G. Lucius, *Chem. Ber.*, **93**, 2663 (1960); E.J. Corey and R.R. Sauers, *J. Am. Chem. Soc.*, **81**, 1739 (1959); H.H. Appel, J.D. Connolly, K.H. Overton and R.P. Bond, *J. Chem. Soc.*, **1960**, 4685; H. Ogura and M. Yanagita, *Inter. Symp. on the Chem. of Nat. Prod.*, 1964, Kyoto, Abstract p. 31. *b)* A.A. Patchett and B. Witkop, *J. Am. Chem. Soc.*, **79**, 185 (1957); J. Meinwald and J.K. Crandall, *ibid.*, **88**, 1292 (1966); J. Meinwald, J.C. Shelton, G.L. Buchanan and A. Courtin, *J. Org. Chem.*, **33**, 99 (1968); K. Wiesner and I. Jinkovsky, *Tetrahedron Letters*, **1967**, 2077.

4) A. Tahara, Y. Ohtsuka, N. Umino, K. Nagasawa and K. Hirao, *Chem. Pharm. Bull.* (Tokyo), **17**,1527 (1969).

5) *t*-BuOH was used in place of MeOH for prevention of the competitive esterification.

6) The product was oily compound, whose molecular formula was observed by mass-spectrometry.

cm^{-1}: 1773, τ 9.14 (C_{10}-Me), 8.74 (C_4-Me), by the treatment (reflux, *p*-TsOH in benzene). Unlike the other 6β lactones (XIII) and (XIV), the lactone (XX) was so stable that it could be recrystallized and could not be epimerized under the aforementioned thermal condition.

Consequently, synthesis of the 6α-hydroxy-hexahydro series (*trans* B/C-ring fusion) was performed by the other way. Catalytic hydrogenation (Pd–C, MeOH) of 6α-hydroxy-tetrahydro-ester (X) afforded oily product, which was chromatographed (Al_2O_3) to convert to a lactone (XXI) (*trans* B/C-ring fusion), $C_{17}H_{26}O_2$, mp 86—87°, ν_{max}^{KBr} cm^{-1}: 1758, τ 9.06 (C_{10}-Me), 8.73 (C_4-Me). The lactone (XXI) is distinguishable from the 6β lactone (XX) and the other isomeric lactones (XIV and VII) (*cis* B/C-ring fusion). Alkaline hydrolysis (KOH–EtOH–H_2O) of the lactone (XXI) gave the corresponding 6α-hydroxy acid (XXII), $C_{17}H_{28}O_3$, mp 227.5—228.5°, which was readily returned (reflux, 10% HCl aq. MeOH) to the original lactone (XXI) and was methylated (CH_2N_2) to the corresponding ester (XXIII), $C_{18}H_{30}O_3$, mp 142.5—144.5°. Further evidence on C_6-configuration of both the lactones (XX and XXI) was adduced by their reduction ($LiAlH_4$) to give the respective diol (XXIV), $C_{17}H_{30}O_2$, mp 141.5—143° and (XXV), $C_{17}H_{30}O_2$, mp 157.5—158.5°, which were also synthesized from the ester (XXVIII) and (XXIII) having reliable C_6-configuration, respectively.

In conclusion, it is clarified that the lactonization mode is very variable depending on the structure of B/C-ring fusion. A quantitative study on the epimerization is necessary and now is in progress.

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Structural Feature of *Pneumococcus* Type XIX Specific Polysaccharide[1)]

Some preliminary analytical data of *Pneumococcus* Type XIX specific polysaccharide have been given by Brown,[2)] Levine, *et al.*[3)] and Baddiley, *et al.*,[4)] little known about its components or that of some serological cross-reactivities of a type XIX antiserum.[5)]

The present communication is concerned with structural feature of a fragment which is considered to be a major unit in the polysaccharide.

Crude type specific material was fractionated by Cetavlon treatment,[6)] DEAE-cellulose column chromatography using borate,[7)] followed by gel-filtration (Sephadex G-100). During these treatments, particularly DEAE-cellulose treatment with sodium borate caused a remarkable fragmentation and serological activity of the material to the antiserum decreased.

1) A part of this work was presented at the Winter Meeting of the American Chemical Society, Phoenix, Ariz., January, 1966.
2) R. Brown, *J. Immunol.*, **37**, 445 (1939); *ibid.*, **47**, 7 (1943).
3) S. Levine, H.J.R. Stevenson and P.W. Kabler, *Arch. Biochem. Biophys.*, **45**, 65 (1953).
4) Z.A. Shabarova, J.G. Buchanan and J. Baddiley, *Biochim. Biophys. Acta*, **57**, 146 (1962).
5) M. Heidelberger, "Fortschritte der Organischer Naturstoffe," Vol. 18, Springer-Verlag in Vienna, 1960, p. 503.
6) J.E. Scott, *Chem. Ind.* (London), **1955**, 1568.
7) H. Neukon, H. Deuel, W.J. Heri and W. Kündig, *Helv. Chim. Acta*, **43**, 64 (1960).