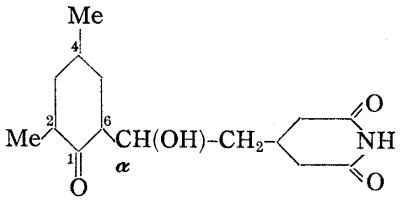
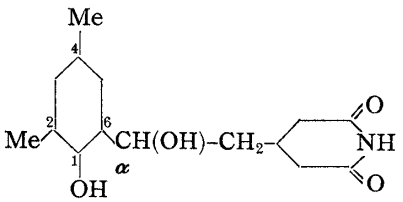
UDC 547.824.02 : 615.779.931

Further Studies on the Absolute Configuration of Naramycin-A (Cycloheximide) and its Isomeric Naramycin-B

The writer previously reported[1,2] that Naramycin-A (identified with cycloheximide) (I) was assumed to have (4S:6S)-configuration and its stereoisomeric Naramycin-B (II), (4S:6R)-configuration. Now the writer wishes to report on the absolute configuration of α-carbon which is equal in both antibiotics.



Plane structure of Naramycins



Plane structure of dihydrogenated Naramycins

In compounds like Naramycin and its dihydrogenated compound which have two bulky moieties such as cyclohexyl and glutarimide in the molecule, the molecule itself tends to stabilize itself by locating these moieties linearly as far as possible, and the free rotation between 6- and α-carbons is thought to be restricted to some extent.

Based on the above assumption and considering the fact that α-hydroxy-β-(1,6-dioxo-4-piperidyl)ethyl group in the molecule is oriented equatorially in both antibiotics,[1] spatial correlation between α- and 1-OH in dihydrogenated cycloheximide would be illustrated as shown in Table I.

Table I. Spatial Correlation between α- and 1-Hydroxyl Groups in Dihydrogenated Cycloheximide

Case No.	Absolute configuration at 6-carbon	Absolute configuration at α-carbon	Spatial relation between α- and 1-hydroxyl groups	
			1-OH (eq.)	1-OH (ax.)
1	S	S	*cis*-like[a]	*trans*-like[b]
2	S	R	*trans*-like	*cis*-like
3	R	S	*trans*-like	*cis*-like
4	R	R	*cis*-like	*trans*-like

a) Spatially, both OH groups exist very closely without rotation between α- and 6-carbons.
b) Both OH groups come close only after rotation between α- and 6-carbons.

Table I suggests that the absolute configuration of α-carbon is assumable, if the absolute configuration of 6-carbon, the conformation of 1-OH, and spatial relation between 1-OH and α-OH in dihydrogenated cycloheximide were confirmed. Following experiments were carried out on Naramycin-A.

Dihydrocycloheximide (Dihydroactidione)[3] (III), m.p. 131.5~132°[4]; $[\alpha]_D^{17}$ +13.2°[5] (c=1.0), which is obtained on reduction of (I) with Adams' PtO_2 in glacial AcOH (yield,

1) T. Okuda, M. Suzuki, Y. Egawa, K. Ashino : This Bulletin, **6**, 328(1958).
2) T. Okuda : *Ibid.*, **6**, 711(1958).
3) E.C. Kornfeld, R.G. Jones, T.V. Parke : J. Am. Chem. Soc., **71**, 150(1949).
4) All m.p.s are not corrected. Kornfeld, *et al.* (*loc. cit.*) records m.p. 133~134°(Fisher-John's m.p. block and corrected). Authentic sample derived from Actidione (Upjohn) melts at 132~132.5°, which showed no m.p. depression on admixture with this sample.
5) All $[\alpha]_D$ values were measured in MeOH.

82.5%), gives theoretical amount of the boric acid-complex (IV), m.p. 174.5~175°; $[\alpha]_D^{17}$ +14.0°(c=1.0) (*Anal.* Calcd. for $C_{15}H_{24}O_5NB$: C, 58.25; H, 7.76; N, 4.53; B, 3.51. Found: C, 58.54; H, 7.73; N, 5.01; B, 3.23) by recrystallization of (III) in 30% acetone containing excess of H_3BO_3. (IV) is also obtained by reduction of (I) with $NaBH_4$ in hydr. MeOH by inverse addition method[6] at −5° (yield, 81%). (III) and (IV) give the same Dihydroactidionic acid[3] (V) by alkaline hydrolysis, and give the same new product (VI),[7] m.p. 137~138°; $[\alpha]_D^{25}$ +2.9°(c=0.5) (*Anal.* Calcd. for $C_{18}H_{30}O_5NB$: C, 61.53; H, 8.55; N, 3.99. Found : C, 61.91; H, 8.61; N, 4.15) by the action of BF_3-ether complex in acetone (yield, 85% from each material). By tosylation in cold pyridine, (III) gives a diol-monotosylate (VII), m.p. 140.5~141.5°; $[\alpha]_D^{25}$ +48.5°(c=1.0) (*Anal.* Calcd. for $C_{22}H_{31}O_6NS$: C, 60.27; H, 7.08; N, 3.20; S, 7.30. Found : C, 60.22; H, 7.11; N, 3.32; S, 7.30) in 76% yield. (VII) shows ν_{C-OH} 1040 cm^{-1}(Nujol) in its infrared spectrum. O-Tosylcycloheximide (VIII), m.p. 100.5~101.5°(*Anal.* Calcd. for $C_{22}H_{29}O_6NS$: C, 60.69; H, 6.67; N, 3.22. Found : C, 60.64; H, 6.68; N, 3.13), which is obtained by treating (I) with tosyl chloride in ice-cold pyridine (yield, 66.5%), gives the above-mentioned (VII) by means of four kinds of reduction procedures, viz. (1) with Adams' PtO_2 in AcOH (yield, av. 60%), (2) with $NaBH_4$ in hydr. MeOH (yield, 72%), (3) with $LiAlH_4$ in tetrahydrofuran (yield, 73%), and (4) with $LiAlH$-(*tert*-$BuO)_3$ in tetrahydrofuran (yield, 79%). Cycloheximide acetate (IX) gives Kornfeld's Dihydroactidione monoacetate (X),[3] m.p. 165°; $[\alpha]_D^{19}$ +29.0°(c=1.0), I.R. ν_{OH} 3390~3322 cm^{-1}, ν_{NH} 3226 cm^{-1}(Nujol), on reduction with Adams' PtO_2 in glacial AcOH and gives a new isomer (XI), m.p. 177~178°; $[\alpha]_D^{19}$ +34.3°(c=2.0); I.R. ν_{OH} 3509 cm^{-1}, ν_{NH} 3175 cm^{-1} (Nujol) (*Anal.* Calcd. for $C_{17}H_{27}O_5N$: C, 62.75; H, 8.37; N, 4.31. Found : C, 62.71; H, 8.15; N, 4.31) by reduction with $NaBH_4$, as well as by $LiAlH$(*tert*-$BuO)_3$ (yield, 20% and 86%, respectively). By alkaline hydrolysis (XI) gives the above-mentioned Dihydroactidionic acid (V), whereas (X) forms an isomeric compound (XII), m.p. 173~173.5°; mixed m.p. with (VII) (m.p. 174~175°), 159~163° (*Anal.* Calcd. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found : C, 63.69; H, 8.55). The above reactions are summarized in Chart 1. Experimental details will be published later.

Allow the writer to give some stereochemical considerations on the above reactions. It is regretful that Naramycins are so sensitive to alkali and mineral acid that the usual conformational analysis including isomerization studies is unavailable in the case of Naramycins. Therefore, stereochemistry of Naramycins was deduced only from the above reduction procedures.

1) The configurations of 1-OH which is present in (III), (IV), (VII), and (XI) are the same but differ from that of 1-OH in (X).

2) Reduction over PtO_2 in acid solution tends to give an axial OH in unhindered cyclohexanone and an equatorial OH in hindered ketone.[8,9] $LiAlH_4$ as well as $LiAlH$-(*tert*-$BuO)_3$[10] tends to give an equatorial OH in unhindered cyclohexanone. Therefore, when reduction with PtO_2 or $LiAlH_4$ (or $LiAlH$(*tert*-$BuO)_3$) gives different stereoisomers it seems proper to think that PtO_2-reduction gives an axial-OH isomer and $LiAlH_4$ (or $LiAlH$(*tert*-$BuO)_3$) gives an equatorial-OH isomer. Thus, it is assumable that (X) has 1-axial OH and (XI) has 1-equatorial OH.

3) It is said[9] that reduction with $LiAlH_4$ should be product development controlled and yield an equatorial OH whereas $NaBH_4$ should be rather steric approach controlled. $LiAlH$(*tert*-$BuO)_3$ is said to be more strongly product development controlled.[10] The

6) E.B. Reid, J.R. Siegel : J. Chem. Soc., **1954**, 530.
7) This compound is thought to be a kind of boric acid-complex in which (IV) combines or associates with 1 mole of acetone unit.
8) D.H.R. Barton : J. Chem. Soc., **1953**, 1027.
9) W.G. Dauben, G.J. Fonden, D.S. Noyce : J. Am. Chem. Soc., **78**, 2579(1956); W.G. Dauben, E. J. Blanz, J. Jiu, R.A. Micheli : *Ibid.*, **78**, 3752(1956).
10) O.H. Wheeler, J.L. Mateos : Chem. & Ind.(London), **1957**, 395.

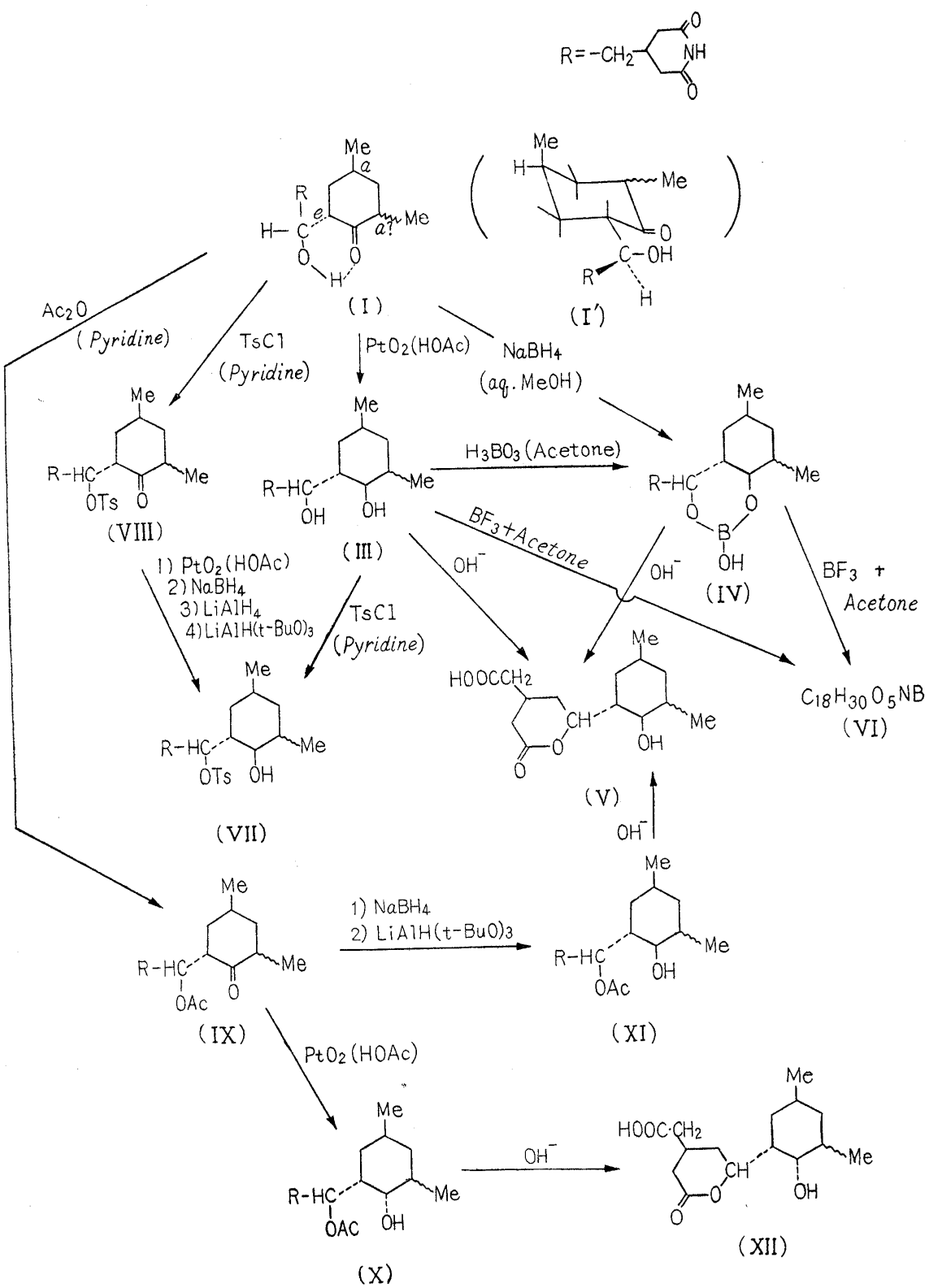


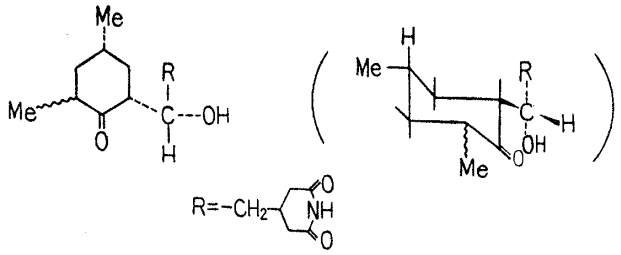
Chart 1.

fact that $LiAlH_4$ and $LiAlH(tert\text{-}BuO)_3$ were able to reduce (Ⅷ) and (Ⅸ) in a fair yield, while $NaBH_4$ reduced (Ⅷ) in a fair yield but (Ⅸ) in poor yield suggests that some unfavorable hindrance for the approach of $NaBH_4$ appeared in (Ⅸ). This hindrance is probably responsible for the different behavior of PtO_2 in reducing (Ⅷ) and (Ⅸ). Thus, this observation supports the above assumption that reduction with $LiAlH_4$ (or $LiAlH(tert\text{-}BuO)_3$) gave 1-equatorial OH.

4) It is observed from the infrared spectra of two dihydrocycloheximide monoacetates that (Ⅹ) has a more symmetric structure than (Ⅺ), that is, the spatial relation of two hydroxyl groups is closer in (Ⅺ) than in (Ⅹ). This phenomenon is similar to that found in the infrared spectra of Naramycin-B and -A. Besides these observations on the infrared spectra, the following experiment supports chemically the above-mentioned spatial relation between two hydroxyl groups in (Ⅲ), viz., the fact that the formation of boric acid-complex from (Ⅲ) to (Ⅳ) was effected easily without accompanying a change in the values of optical rotation suggests that the α-OH is situated quite close (*cis*-likely) to the newly produced equatorial 1-OH.[11] Thus it is concluded that the case No. 1 in Table I would correspond to (Ⅲ). Consequently, the absolute configuration of α-carbon in Naramycin-A belongs to (S)-series. Therefore (I) is depicted as (I′).

From the hitherto reported information it is deducible that Naramycin-B has (4S:6R : αS)-configuration and would be represented by formula (Ⅱ).

(Ⅱ)



The direction of carbonyl group is said to be rather equatorial, so that the spatial distance between α-OH and C=O would be closer in (I) than in (Ⅱ). The configuration of 2-methyl group is uncertain, but the hitherto published and to be published data on chemical behavior of (I) and (Ⅱ) towards reducing agents[12] lead to the assumption that (I) has 2*a*,4*a*-conformation and (Ⅱ) has 2*e*,4*e*-conformation.

The infrared spectra of (I) shows the presence of intramolecular hydrogen bonding even in solid state, while that of (Ⅱ) shows that intermolecular association is rather predominant. These phenomena are explainable from the above information on spatial distance between α-OH and C=O and/or from the molecular asymmetry and symmetry of (I) and (Ⅱ), which are related to the conformation of 2- and 4-methyl groups.

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11) The writer experienced another type of boric acid-complex formation in which a remarkable change in optical rotation was observed.

12) (Ⅱ) tends to give a mixture of hydrogenated isomers on reduction.