Some Configurational Aspects on Naramycin-A (Cycloheximide) and its Stereoisomeric Antibiotic, Naramycin-B

It has been reported that Naramycin-A (identified with cycloheximide (Actidione)) and its isomeric Naramycin-B have the same configuration at the asymmetric carbons at 4- and α -positions.¹⁾ Now, the writer wishes to report some configurational informations which were deduced from the rotatory dispersion (R.D.) curves and infrared absorption spectra of these antibiotics, the measurement of the R.D. curves being run through the courtesy of Prof. C. Djerassi of the Wayne State University, U.S.A. Values found are as follows: Naramycin-A,²⁾ R.D. in MeOH ($c=0.016$): $[\alpha]_{700}^{80} -15^\circ$, $[\alpha]_{589} -8^\circ$, $[\alpha]_{400} -38^\circ$, $[\alpha]_{350} -80^\circ$, $[\alpha]_{325} -180^\circ$, $[\alpha]_{312.5} -310^\circ$ (trough), $[\alpha]_{295} -107^\circ$, $[\alpha]_{282.5}$ not measured. Naramycin-B, R.D. in MeOH ($c=0.084$): $[\alpha]_{700}^{80} 0^\circ$, $[\alpha]_{589} +40^\circ$, $[\alpha]_{400} +112.5^\circ$, $[\alpha]_{350} +250^\circ$, $[\alpha]_{325} +610^\circ$, $[\alpha]_{312.5} +815^\circ$ (peak), $[\alpha]_{295} +125^\circ$.

Fig. 1. Rotatory Dispersion Curves of Naramycin and its Related Compounds

As illustrated in Fig. 1, Naramycin-A exhibits a single, negative Cotton effect curve, while Naramycin-B gives a positive one. Eisenbraun, *et al.*³⁾ reported that *d*-2,4-*cis*-dimethylcyclohexanone (I), which is obtainable by the retro-aldolization of both antibiotics, has the (2R:4R)-configuration and gives the following $[\alpha]$ values: R.D. in MeOH ($c=0.097$), $[\alpha]_{589}^{25} +2.46^\circ$ (neat), $[\alpha]_{297.5} -278^\circ$ (trough), $[\alpha]_{275} -57^\circ$ (peak). In Fig. 1, the R.D. curve of (I) is also illustrated which is obtained by roughly plotting the above cited $[\alpha]$ values.

- 1) T. Okuda, M. Suzuki, Y. Egawa, K. Ashino: This Bulletin, **6**, 328(1958).
- 2) According to Prof. Djerassi's private communication, R.D. curve of Naramycin-A is identical with that of authentic Actidione, in which Actidione shows a peak at 282.5 mμ: $[\alpha]_{282.5} -20^\circ$ ($c=0.106$).
- 3) E. J. Eisenbraun, J. Osiecki, C. Djerassi: J. Am. Chem. Soc., **80**, 1261(1958).

The following considerations on these R.D. curves made it possible to assign (4S:6S)-configuration to Naramycin-A and (4S:6R)-configuration to Naramycin-B.

1) The R.D. curve of a compound which has more than two asymmetric centers generally represents the sum of all partial rotations mainly due to individual asymmetric centers in the molecule. For example, the R.D. curve of (I) is made up by superimposing negative Cotton effect curve due to (2R)-methyl group on negative plain curve due to (4R)-methyl group.⁴⁾ Thus, the R.D. curves of Naramycin-A and -B represent the sum of all partial rotations due to asymmetric carbons at 2-, 4-, 6-, and α -positions.

2) It is clear that the asymmetric carbon at 4-position displays only a plain curve by the distance factor.^{4,5)}

3) Among the remaining three asymmetric carbons, α -carbon would give the same sign of Cotton effect in both antibiotics, because the configuration of this carbon is equal in Naramycin-A and -B by the rule of shift.¹⁾

4) Cotton effect due to 2-methyl group would be too weak to cause any remarkable dispersion change, even if its configuration is different in Naramycin-A and -B.

5) Consequently, it seemed inevitable to conclude that the strongest factor which will determine the sign of Cotton effect is the absolute configuration at 6-position to which α -hydroxy- β -(2,6-dioxo-4-piperidinyl)ethyl group is attached.

This assumption is strongly supported by the fact⁶⁾ that 2 α (eq.)-methoxymethyl-*trans*-9-methyl-1-decalone gives a single, positive Cotton effect curve, as does its parent 2-unsubstituted decalone, and the 2 β (ax.)-isomer produces an inversion of the sign of Cotton effect.

The above consideration makes it possible to assume that these antibiotics have the configurations as depicted in formulae (II) and (III). The infrared spectra of these antibiotics suggest that the α -hydroxy- β -(2,6-dioxo-4-piperidinyl)ethyl group must be equatorially oriented to cyclohexanone ring in both antibiotics. Therefore, formula (II) would be more properly illustrated as inverted formula (II') so as to give the large substituent an equatorial conformation.⁷⁾ The conformation of 2-methyl group can not be determined only from the R.D. curve.

Further considerations should be made to determine which of these formulae, (II') and (III), corresponds to Naramycin-A and which to -B.

6) For the parent compounds of (II') and (III), it would be better to presume an imaginative(4S:6R)-4-methyl-6- $[\alpha$ -hydroxy- β -(2,6-dioxo-4-piperidinyl)ethyl]cyclohexanone (IV) and its (4S:6S)-isomer (V) rather than actual (I), because the contribution of α -hydroxy- β -(2,6-dioxo-4-piperidinyl)ethyl group on the sign of Cotton effect would be stronger than that of 2-methyl group. It is possible that (IV), which has an antipodal-like structure to (I), exhibits a positive Cotton effect curve and that (V), which has similar surroundings as (I) about a carbonyl function, gives a similar negative Cotton effect as (I).⁸⁾

4) According to Prof. Djerassi's finding (v.i.) the separation of the asymmetric center from the carbonyl function by two carbon atoms results in a plain dispersion curve. This is called "Distance Factor."

5) Private communication from Professor Djerassi.

6) C. Djerassi, O. Halpern, V. Halpern, B. Riniker: J. Am. Chem. Soc., **80**, 4001(1958).

7) This method of illustration agrees with that of Eisenbraun (*loc. cit.*) in which (2R:4R)-2,4-dimethylcyclohexanone is depicted as (I). It is thought that 2,4-diequatorial form is predominant.

8) These assignments are also possible by applying the Djerassi's " α -axial haloketone rule" to α -axial hydroxyalkyl group. The sign of Cotton effect shown by above-illustrated 2 β (ax.)-methoxymethyl-*trans*-9-methyl-1-decalone clearly obeys this rule. cf. C. Djerassi, W. Klyne: J. Am. Chem. Soc., **79**, 1506(1957); C. Djerassi, J. Osiecki, R. Riniker, B. Riniker: *Ibid.*, **80**, 1216(1958).

7) Consequently, Naramycin-A which displays a negative Cotton effect is thought to have a configuration similar to (V) and would be depicted as formula (II'). Thus, Naramycin-A has (4S : 6S)-configuration (4:6-*trans*). Meanwhile, Naramycin-B would be formulated as (III) and has (4S : 6R)-configuration (4:6-*cis*).

8) The absolute configuration of 2-methyl group preliminarily belongs to (2R)-series but actually is uncertain, for, if both 2- and 4-methyl groups are obliged to possess diaxial conformation, 1,3-diaxial repulsion might cause the epimerization of 2-methyl group, and in the case of all equatorial conformation, 2-methyl group has the chance to epimerize due to 2-alkyl ketone effect.⁹⁾

For the purpose of making the above assumption more certain, a desoxycycloheximide (2,4-dimethyl-6- β -(2,6-dioxo-4-piperidinyl)ethyl)cyclohexanone (VI) was synthesized from anhydrocycloheximide. (VI) is thought to have (4S : 6S)-configuration from the stereochemical consideration of the reduction procedure. (VI) exhibited a positive Cotton effect curve as was expected.

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9) R. Cornubert, *et al.* reported on 2,6-dimethylcyclohexanone (Bull. soc. chim. France, 1950, 631, 636; 1954, 367).