UDC 615.779.931-011

120. **Makoto Suzuki**: Studies on Streptomyces Antibiotic, Cycloheximide. IX.[1] Absolute Configuration of Optically Active 2,4-Dimethyl-6-(α-hydroxy(*p*-substituted)benzyl)cyclohexanones.

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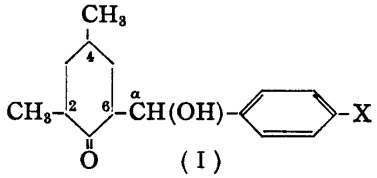
As was described in the preceding paper,[1] the aldol condensation of *cis-d*-2,4-dimethylcyclohexanone with *para*-substituted benzaldehydes, tetramethylammonium hydroxide or N-methylanilinomagnesium bromide as a basic condensation agent gave different types of stereoisomeric condensation products having positive and negative optical rotation, $[\alpha]_D$, values. The plane structure of these products is illustrated as (I).



(I)

The present paper concerns with elucidation of the absolute configuration of these products, comparing their stereochemical configurations with those of cycloheximides discussed previously.[2~5] 2,4-Dimethyl-6-(α-hydroxy-*p*-nitro- and -*p*-acetamidobenzyl)-cyclohexanone and their related compounds will be mainly discussed, because their chemical correlations were made clear as was described in the preceding part.[1] Physicochemical properties of synthetic ketols and their acetates are summarized in Tables I and II.

All of the synthesized 2,4-dimethyl-6-(α-hydroxy(*p*-substituted)benzyl)cyclohexanones including *para*-substituted ketol-As and -Ns[*2] showed in their infrared absorption spectra the absorption band for the OH valence-stretching vibration at 3200~3500 cm^{-1}, not only in solid state but also in dilute chloroform solution. This fact suggested that the intramolecular hydrogen-bonded hydroxyl group was present in the molecule and led to the conclusion that these compounds had equatorially situated α-hydroxy(*p*-substituted)-benzyl group at their C-6 position, as in the case of α-hydroxy-*p*-halobenzylcyclohexanones reported by Huitric and Kumler,[6] and cycloheximides discussed by the author and his collaborators.[2,5]

Based on the comparative $[M]_D$ values in methanol[*3] shown by the parent ketols and their acetates, synthetic ketols were distinctly classified into two groups tentatively denominated as (+)- and (−)-groups, implying either increase or decrease in $[M]_D$ value on acetylation. Among ketols to be discussed, compounds of N-series and A_1-series

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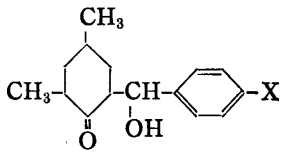
*2 Compounds designated with suffix "A" (A_1 and A_2) were prepared by aldol condensation method using tetramethylammonium hydroxide as a condensation agent and those with suffix "N" were synthesized by Nielsen-type of condensation procedure using N-methylanilinomagnesium bromide as a condensation agent.

*3 For comparison of $[M]_D$ values, $[\alpha]_D$ values in methanol were employed, because those in chloroform, as pointed out by Barton,[7] often showed anomality. $[M]_D$ value changes accompanied by benzoylation of nitro-ketol-A_1 and -N were interesting (cf. Experimental section).

1) Part VIII. M. Suzuki: This Bulletin, 8, 706, 713(1960).
2) Part IV. T. Okuda: *Ibid.*, 7, 659(1959).
3) Part V. *Idem*: *Ibid.*, 7, 666(1959).
4) Part VI. *Idem*: *Ibid.*, 7, 671(1959).
5) Part VII. T. Okuda, M. Suzuki, Y. Egawa: *Ibid.*, 8, 335(1960).
6) A.C. Huitric, W.D. Kumler: J. Am. Chem. Soc., 78, 1147(1956).

TABLE I. Physicochemical Properties of Synthesized Ketols[b]

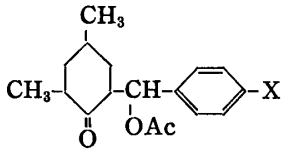


No.	Compound	X	m.p. (°C)	$[\alpha]_D$ MeOH	$[M]_D$	$[\alpha]_D$ $CHCl_3$	$[M]_D$	RD Cotton effect	RD Peak or trough (mμ)	IR ν_{OH} (cm^{-1}) Nujol	IR ν_{OH} (cm^{-1}) 0.5% $CHCl_3$	IR $\nu_{C=O}$ (cm^{-1}) Nujol	IR $\nu_{C=O}$ (cm^{-1}) 0.5% $CHCl_3$	UV (mμ) λ_{max}^{MeOH}	UV (mμ) ε
	Compounds of ketol-N series[a]														
1	Nitro-ketol-N	NO_2	151~152	−66.4°	−184	−58.6°	−162	−	——	3448	3440	1698	1709	270	11507
2	Acetamido-ketol-N	NHAc	171~172	−37.2°	−108	−48.0°	−139	−	312.5, trough −4676°	3354	3419	1704	1708	248	21155
3	Amino-ketol-N	NH_2	160~161	——	——	——	——	−	330, trough −2307°	3436	——	1697	——	244 289	13049 2309
4	Bromo-ketol-N	Br	139~140	−37.7°	−117	−49.7°	−155	−	315, trough −3456°	3413	3436	1700	1709	224 230(sh)	13995 12347
5	Hydroxy-ketol-N	OH	145.5 ~146.5	−51.2°	−127	−38.0°	− 94	−	312.5, trough −4174°	3279 3175	3509 3268~3257	1691	1704	228.5 278	11106 1927
	Compounds of ketol-A_1 series[a]														
6	Nitro-ketol-A_1	NO_2	147~148	+81.4°	+226	+115.2°	+319	+	——	3482	3463~3451	1689	1701	276	11493
7	Amino-ketol-A_1	NH_2	Oily	——	——	——	——	——	——	——	——	——	——	——	——
	Compounds of ketol-A_2 series[a]														
8	Nitro-ketol-A_2	NO_2	113~114	+65.4°	+181	+29.8°	+ 83	+	——	3497	3463	1697	1698	272.5	10470
9	Acetamido-ketol-A	NHAc	152~153	+52.1°	+151	+40.0°	+114	+	312.5, +674° (Shoulder)	3322	3419	1709	1709	246.5	18984
10	Amino-ketol-A_2	NH_2	134~135	——	——	——	——	+	325, peak +461°	3367	——	1724	——	240.5 288	12375 1741

a) cf. Footnote *3

b) Details are given in the Experimental section.

TABLE II. Physicochemical Properties of Ketol-Acetates[b]



No.	X	m.p. (°C)	$[\alpha]_D$ MeOH	$[M]_D$	$[\alpha]_D$ $CHCl_3$	$[M]_D$	RD Cotton effect	RD Peak or trough (mμ)	IR $\nu_{C=O}$ (cm^{-1}) Nujol		UV (mμ) λ_{max}^{MeOH}	UV (mμ) ε
	Acetates of ketol-N series[a]											
1′	NO_2	114～115	−29.0°	− 92.5	− 48.0°	−153	−	——	——		265	11835
2′	NHAc	135～136	+11.2°	+ 32	+ 9.8°	+ 28	−	320, trough −2837°	Ester Ketone Amide	1728 1706 1667	248.5	21539
3′	NH_2	(N,O-DiAc) 135～136	+ 8.0°	+ 26.5	+ 5.8°	+ 19	−	〃	〃		248.5	21539
4′	Br	80～80.5	− 3.8°	− 12.5	− 1.0°	− 3.3	——	——	Ester Ketone	1733 1712	——	——
5′	OH	71～72	+ 4.0°	+ 13	+ 2.1°	+ 7	——	——	Phenol ester Ester Ketone	1754 1739 1709	——	——
	Acetates of ketol-A_1 series[a]											
6′	NO_2	155.5～156.5	+75.4°	+241	+100.8°	+322	+	——	——		271	12218
7′	NH_2	(N,O-DiAc) 198～199	+86.8°	+287	+ 97.8°	+324	+	312.5, peak +496°	Ester Ketone Amide	1724 1715 1681	247～247.5	18774
	Acetates of ketol-A_2 series[a]											
8′	NO_2	118～119	+20.5°	+ 68	+ 16.8°	+ 53.5	+	——	——		——	——
9′	NHAc	178～179	+46.6°	+154	+ 46.2°	+153	+	312.5, peak +680°	Ester Ketone Amide	1731 1710 1661	247	18602
10′	NH_2	(N,O-DiAc) 178～179	+43.9°	+145	+ 43.2°	+143	+	〃	〃		247	18602

a) cf. Footnote *3
b) Details are given in the Experimental section.

belonged to the (+)-group and those of A_2-series to the (−)-group, as illustrated in Table I. Adoption of the Freudenberg's rule of shift to these observations suggested that all of the compounds belonging to (+)-group had the hydroxyl in the same absolute configuration, whereas those of (−)-group had the opposite configuration. The soundness of such a deduction was confirmed chemically as described before.[1]

As seen in Table I, following tendencies were observed in the $[\alpha]_D$ values of ketols measured in methanol and in chloroform. $[\alpha]_D$ values of ketol-Ns showed only a slight change in the two solvents and those of ketol-A_1's were higher in chloroform than in methanol and those of ketol-A_2's were reverse.

For elucidation of the absolute configurations of synthetic ketols and related compounds recourse was had to their RD curves, which also served to establish the absolute configuration of cycloheximides.[2,3,5] This method is based on the following principles: (1) A single alkyl substituent situated axially in C-2 or C-6 position of a cyclohexanone contributes to partial rotation as if it is an axial halogen substituent obeying Djerassi's "axial haloketone dispersion rule"[8] as to the sign of the Cotton effect, and the effect of an equatorial substituent can be predicted after arranging this substituent axially by full or partial inversion of cyclohexanone ring*4; (2) the effect of C-4 methyl group upon partial rotation is out of consideration because of the "distance factor" according to Djerassi, *et al.*[9]; and (3) the effect of C-2 methyl group obeys the above principle (1) but, when another predominant asymmetric center is present at the same time, for example, at C-6 position, the effect of C-2 methyl group is too weak to surpass that of C-6 substituent as discussed in detail in the previous paper.*5,2)

As illustrated in Figs. 1~5, the negative Cotton-effect curves shown by ketol-Ns were in contrast with the positive ones shown by ketol-As.*6 This contrast was the same as that shown by cycloheximide of negative Cotton-effect curve and its two isomers (Naramycin-B and isocycloheximide) of positive Cotton-effect curve. Therefore, as in the case of cycloheximides, the difference in the sign of Cotton effect between ketol-Ns and -As was ascribable to the difference in absolute configuration of the asymmetric center at C-6 position of the two ketols, in other words, they may be either of 4,6-*cis* or 4,6-*trans* configuration.

Prior to the discussion on absolute configurations of *para*-substituted ketols, the configuration and RD curve of the following deoxy compound will be examined as a suitable reference compound. On the catalytic hydrogenation using palladium on strontium carbonate as a catalyst, 2,4-dimethyl-6-(*p*-acetamidobenzylidene)cyclohexanone (II) gave 2,4-dimethyl-6-(*p*-acetamidobenzyl)cyclohexanone (deoxy-acetamido-ketol) (III), which showed

*4 The author thinks it better to assume a latent effect of an equatorial alkyl substituent at C-2 or C-6 positions on the sign of the Cotton effect, especially so in such monocyclic ketones as cycloheximides and present model compounds which hardly seem to bring on ring-inversion to unstable forms.

*5 After completion of the present paper, it was found that "octant rule" had been published by Prof. C. Djerassi (Record of Chemical Progress, **20**, 101(1959); cf. "Optical Rotatory Dispersion Applications to Oraganic Chemistry," 178(1960), McGraw-Hill Book Co., New York). The "axial haloketone dispersion rule" cited above is only a more specific case of the general octant rule. The present findings on the rotatory dispersion curves are well interpreted by this octant rule, without any different conclusion.

*6 Full charts of the RD curves of nitro-ketols, absorbing in the region of about 275 mμ, were not obtained because of deep absorbance of the light in lower wave length, but these curves showed similar tendency as their related compounds as seen in the graphs.

7) D. H. R. Barton : J. Chem. Soc., **1946**, 1116; **1948**, 783.

8) C. Djerassi, W. Klyne : J. Am. Chem. Soc., **79**, 1506(1957); C. Djerassi, J. Osiecki, B. Riniker: *Ibid.*, **80**, 1216(1958); C. Djerassi, I. Fornaguera, O. Mancera : *Ibid.*, **81**, 2383(1959); C. Djerassi, N. Finchi, R, Mauli : *Ibid.*, **81**, 4997(1959).

9) C. Djerassi, G. W. Krakower : *Ibid.*, **81**, 237(1959); C. Djerassi, L. E. Geller : *Ibid.*, **81**, 2789(1959).

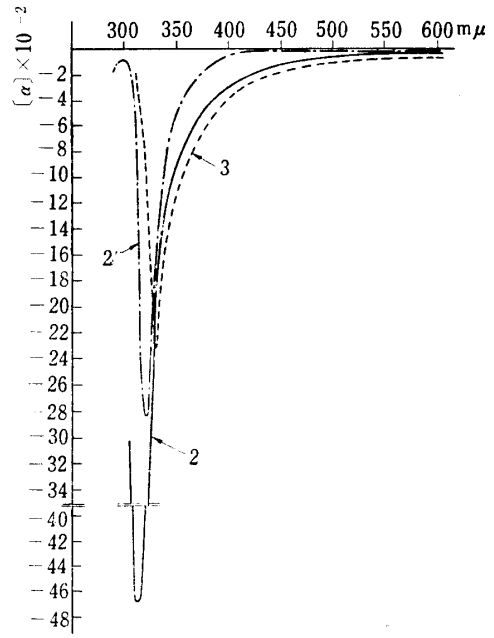


Fig. 1. RD Curves of Ketol-Ns

2 Acetamido-ketol-N
2′ O-Acetyl-acetamido-ketol-N
3 Amino-ketol-N

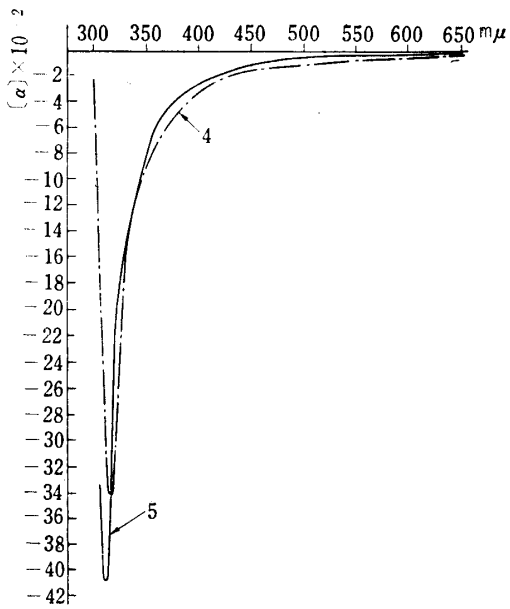


Fig. 2. RD Curves of Ketol-Ns

4 Bromo-ketol-N
5 Hydroxy-ketol-N

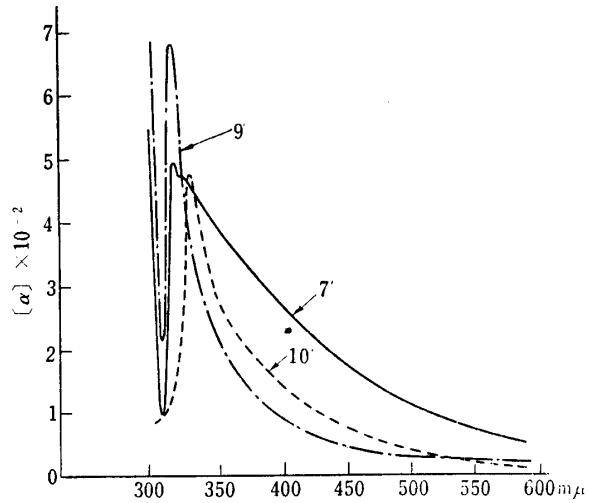


Fig. 3. RD Curves of Ketol-As

7′ N,O-Diacetyl-amino-ketol-A_1
9′ O-Acetyl-acetamido-ketol-A_2
10 Amino-ketol-A_2

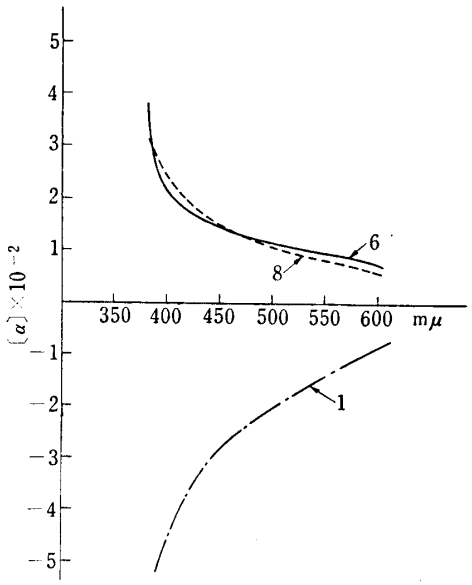


Fig. 4. RD Curves of Ketols

1 Nitro-ketol-N
6 Nitro-ketol-A_1
8 Nitro-ketol-A_2

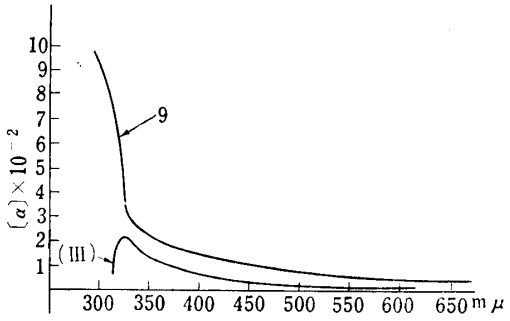
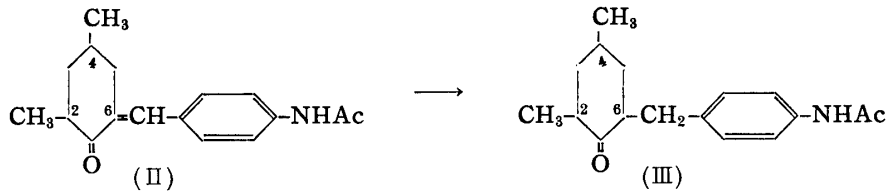


Fig. 5. RD Curves of Acetamido-ketol-A and Deoxy-acetamido-ketol

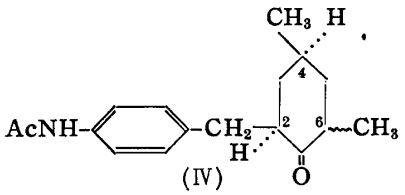
9 Acetamido-ketol-A
(III) Deoxy-acetamido-ketol

a positive Cotton-effect curve as illustrated in Fig. 5. Judging from conclusions regarding the stereochemical configurations of deoxycycloheximides,[3] it seemed that the present deoxy-acetamido-ketol had the most stable configuration, e.g. 4(eq.), 6(eq.)-configuration.



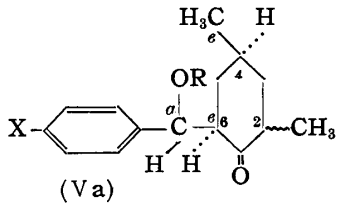
(II) (III)

The fact that this deoxy compound showed the same sign (positive) of Cotton effect as the deoxycycloheximide previously reported indicated that this deoxy-acetamido-ketol had an expected conformation illustrable as (IV) conforming to the above principle (1) and, furthermore, the phenyl function as a second chromophore exerted too small an effect upon the partial rotation to cause a marked change of the sign of the Cotton effect.

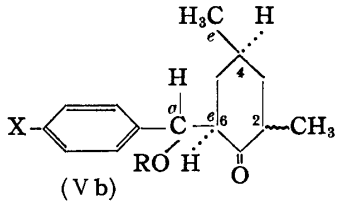


(IV)

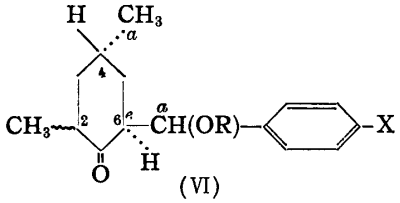
Nitro-ketol-A_1 and $-A_2$, and O-acetylacetamido-ketol-A and $-A_1$, in spite of their different configurations at α-position, showed the same sign (positive) of the Cotten-effect curves as that of deoxy-acetamido-ketol mentioned above. Thus, it would be understood according to the principle (1) that these ketol-As may be considered as the compound in which a hydroxyl group was introduced from different direction onto the α-carbon of deoxy-acetamido-ketol without the sign of the Cotton effect being changed. From this consideration it was concluded that the ketol-As had the 4,6-*cis* or 4S:6R-configuration as depicted by (Va) or (Vb). Further extension of this consideration led to the conclusion that ketol-Ns had, in contrast to ketol-As, 4,6-*trans* or 4S:6S-configuration as formulated in (VI), because ketol-Ns of the negative Cotton effect must have antipodal system to ketol-As of the positive Cotton effect at their C-6 asymmetric center, as referred before.



(Va)
R=H or Ac



(Vb)
R=H ro Ac



(VI)
R=H or Ac

If these considerations and conclusions therefrom were correct, it would be expected that ketol-Ns were less stable than ketol-As, because the former had 4(ax.),6(eq.)-conformation, whereas the latter had more stable 4(eq.),6(eq.)-conformation. The experiments on chemical correlations of these ketols, as reported in the preceding paper, gave definite support to this view, for the nitro-ketol-N was successfully isomerized into the corresponding ketol-A in the presence of acid-treated alumina as well as of tetramethylammonium hydroxide, and acetamido-ketol-N was dehydrated or decomposed by similar means, while nitro-ketol-A_1 and $-A_2$, and acetamido-ketol-A remained intact by the same treatment.

On the elucidation of the absolute configuration of cycloheximides it was assumed previously[10] that when the C-α configuration in cycloheximides was the same, the partial rotation due to this center would be the same, even if the absolute configurations of adjacent C-6 were different. However, considering from the present informations, especially from the attitude on RD curves shown by nitro-ketol-A_1 vs. the epimeric -A_2, and O-acetyl-acetamido-ketol-A_1 vs. the epimeric -A, this assumption should be revised to read "asymmetric carbon at C-α position, whatever its configuration might be, played so little a contribution to partial rotation that it did not cause any change of the Cotton-effect sign and seemed to play a rôle in increasing the Cotton effect of adjacent C-6 center." However, different conclusions were not drawn at all on the absolute configuration of cycloheximides presented previously.

Mentions should be made about the phenyl group in the molecule. The influence of the phenyl function as a second chromophore seemed to be weak in these present ketols as inferred from observations on the deoxy-ketol cited above and also from the recent report on the RD curves of α,β-disubstituted phenethyl alcohols made by Mateos and Cram.[11] To find out the background rotation of these ketols, attempts were made to derive them into 1-deoxy or 1-hydroxy compound in which the phenyl group is a possible function of the Cotton effect as the sole chromophore. After numerous trials, it was found that the reduction of O-acetyl-acetamido-ketol-N with sodium borohydride gave the corresponding 1-dihydro compound. This compound definitely showed a positive Cotton-effect curve, but the $[\alpha]$ value at the peak in its RD curve was too small to explain the strong Cotton effect shown by these ketols.

It was not possible to draw any conclusion on the configuration of 2-methyl group in these ketols only from their RD curves and the initial conformation (2e:4e:6e) may not be the most stable one in ketol-As due to the 2-alkylketone effect and in the initial conformation (2a,4a,6e) of ketol-Ns, 1,3-diaxial repulsion exists as an instability factor, but judging from their chemical behavior of ketol-As, 2-methyl groups were considered to be equatorially situated.

If the absolute configuration at the C-α position of ketol-Ns and -A_1s of (+)-group was assumed to be the same as that in cycloheximides, because of their increasing positive $[M]_D$ values on O-acetylation, stereochemical environments of cycloheximides and the present synthesized ketols would be summarized as in Table III. Thus, cycloheximide (Naramycin-A) would have environment similar to that of ketol-Ns, and Naramycin-B and isocycloheximide, to that of ketol-A_1s. The fact that isocycloheximide was derived from cycloheximide[12] gave good support to this view.

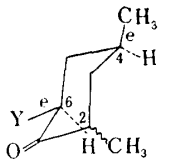
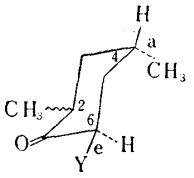
The absolute configuration of 2-methyl group in cycloheximide and ketol-Ns was not evident as described above, but it is probable that these 2-methyl groups assumed the stable conformation and thus they were of the same configuration.

Now, some discussions will be made on the reaction mechanisms of the aldol and Nielsen condensations. From the informations presented by many investigators on the formation of *threo-erythro* isomers of aldol condensation, it would be difficult to explain the present findings that the aldol and Nielsen condensations gave different kinds of product, though the two procedures were said by Nielsen to belong fundamentally to the same type of condensation using basic reagents. Therefore, the present facts would give important suggestions on the reaction mechanisms of the said reactions.

Based on the mechanism of the Nielsen condensation as explained by him, the reaction conditions adopted, the elucidated configuration of the sole product obtained therefrom,

10) T. Okuda : This Bulletin, **7**, 662(1959)
11) J. L. Mateos, D. J. Cram : J. Am. Chem. Soc., **81**, 2756(1959).
12) J. H. Ford : U. S. Pat. 2,903,457 (1959); A. J. Lemin : U. S. Pat. 2,903,458 (1959).

Table III. Relative Stereochemical Configurations of Cycloheximides and Synthesized β-Ketols

Configuration on cyclohexanone ring	Configuration at C-α position*	Cycloheximides Y=-CH(OH)-CH$_2$-	Synthetic ketols Y=-CH(OH)-
	(+)	Naramycin-B (2S:4S:6R:αS)	Ketol-A$_1$s (4S:6R:αR:2 prob. R)
		Isocycloheximide (2R:4S:6R:αS)	
	(−)		Ketol-A$_2$s (4S:6R:αS:2 prob. R)
	(+)	Cycloheximide (=Naramycin-A) (4S:6S:αS)	Ketol-Ns (4S:6S:αR)
	(−)		

* (+) and (−) mean that $[M]_D$ values increase or decrease on O-acetylation.

and also on their stability, it may be considered that Nielsen procedure is kinetic-controlled condensation. Thus, the approach of aldehyde moiety to C-6 carbanion of 2e,4e-dimethylcyclohexanones was initiated from axial direction of the latter*[7] and the product stabilized itself by ring inversion to form 4a,6e-conformation.

On the aldolization using tetramethylammonium hydroxide as a condensation agent, it would be difficult to give definite answer, because the aldol condensation products were the same in their C-6 configuration but different in their C-α configuration to which secondary hydroxyl group was attached. However, it may be considered from the isomerization studies of nitro- and acetamido-ketol-Ns in the presence of tetramethylammonium hydroxide that in the case of preparation of nitro-ketol-A$_1$, a main product of the reaction, approach of aldehyde moiety was made in a similar manner as in the case of the Nielsen condensation, and the product, under thermodynamic conditions, stabilized itself by epimerization at C-6 center. The fact that an acetamido-ketol, whose configuration should correspond to nitro-ketol-A$_1$, could not be obtained, was well explained by the instability of the acetamido-ketol-N in tetramethylammonium hydroxide solution.

It was not clear how nitro-ketol-A$_2$ and acetamido-ketol-A were formed, but it may be understood by assuming that, whatever the reaction mechanisms might be, the aldehyde took a different course of approach from that in the Nielsen condensation, because the configuration of these C-α hydroxyl groups was different from those of ketol-Ns and nitro-ketol-A$_1$.

Experimental

(All m.p.s are not corrected.)

Acetylation of β-Ketols; General Procedure—β-Ketol was dissolved in 10~15 vols. of dehyd. pyridine and added with 10 vols. of Ac_2O under ice-cooling. The mixture was allowed to stand at room temperature overnight. The solvent was distilled off and the residual product was treated with H_2O to solidify. The crude acetate thus obtained was recrystallized repeatedly from benzene in case of acetamido-ketols or from 50~90% MeOH in case of nitro-, bromo-, and hydroxy-ketols (yield, 78~86%).

Benzoylation of β-Ketols; General Procedure—β-Ketol dissolved in 7.5~10 vols. of dehyd. pyri-

*[7] This consideration is not contradictory to the fact described by Beton (J. Chem Soc., **1957**, 753) and others on the steroidal ketone in basic condition.

dine was added with 1.2 molar equivalent BzCl under ice-cooling. The mixture was allowed to stand at room temperature for 3 hr. and then in a refrigerator overnight. Excess solvent was removed *in vacuo*. The residue was treated with H_2O, dried in a desiccator and recrystallized from hydr. MeOH (yield, 75~85%). Physicochemical data of individual benzoate are shown below.

(+)-2,4-Dimethyl-6-(*p*-acetamidobenzyl)cyclohexanone (Deoxy-acetamido-ketol) (III)—A solution of 140 mg. of 2,4-dimethyl-6-(*p*-acetamidobenzylidene)cyclohexanone (II) dissolved in 15 cc. of EtOH containing 85 mg. of 2% Pd-$SrCO_3$ saturated with H_2 and reduced at atmospheric pressure. The reaction ceased after 1.5 moles of H_2 had been absorbed (20 min.). The filtered solution was concentrated *in vacuo* to a colorless syrup, which, on treatment with Et_2O soon solidified. Crude product thus obtained was recrystallized repeatedly from Et_2O to 62 mg. of fine colorless prisms, m.p. 118.5~120°. *Anal.* Calcd. for $C_{17}H_{23}O_2N$: C, 74.79; H, 8.49; N, 5.13. Found: C, 74.42; H, 8.76; N, 5.34. RD in MeOH (c=0.10, Xe*[8]): $[\alpha]_{589}^{25.2}$ +23°, $[\alpha]_{350}$ +141°, $[\alpha]_{322.5}$ +215°(peak), $[\alpha]_{317.5}$ +204°, $[\alpha]_{310}$ +75°. UV: λ_{max}^{MeOH} 246.5 mμ (ε 18,514) and 285 mμ (1,608). IR (in Nujol) cm^{-1}: ν_{NH} 3215, $\nu_{C=O(ketone)}$ 1715, $\nu_{C=O(amide)}$ 1664, δ_{NH} 1550.

Reduction of O-Acetyl-acetamido-ketol-N—A solution of 500 mg. of O-acetyl-acetamido-ketol-N dissolved in 12 cc. of MeOH was added with a solution of 60 mg. of $NaBH_4$ in 3 cc. of MeOH and stirred for 2 hr. at room temperature. The reaction mixture, after being acidified slightly with 10% AcOH was evaporated *in vacuo* to dryness. White crystals thus obtained were recrystallized from 80% MeOH to 325 mg. of colorless prisms, mp. 262~264°. Analytical data of this product corresponded to $(C_{19}H_{26}O_4N)_2B(OH)$. *Anal.* Calcd.: C, 65.95; H, 7.72; N, 4.05; B, 1.59. Found: C, 65.53; H, 7.40; N, 4.21; B, 1.25. RD in MeOH (c=0.1, Zr): $[\alpha]_{589}^{23.6}$ −3.0°, $[\alpha]_{400}$ −1.0°, $[\alpha]_{350}$ +17.0°; $[\alpha]_{320}$ +30.0°, $[\alpha]_{310}$ +53.0°, $[\alpha]_{305}$ +93.0°(peak), $[\alpha]_{300}$ +75.0°.

Physicochemical Properties of Optically Active *para*-Substituted 2,4-Dimethyl-6-(α-hydroxy)-cyclohexanones and their Acylates*[9]

Nitro-ketol-N: m.p. 151~152°. $[\alpha]_D^{24}$ −66.4°(c=1.0, MeOH), $[\alpha]_D^{24}$ −58.6°(c=1.0, $CHCl_3$). RD in MeOH (c=0.1, Hg): $[\alpha]_{589}^{25}$ −93°, $[\alpha]_{436}$ −313°, $[\alpha]_{400}$ −459°, $[\alpha]_{390}$ −509°. IR (in Nujol) cm^{-1}: ν_{OH} 3448, $\nu_{C=O(ketone)}$ 1698, ν_{NO_2} 1515, 1348; (in $CHCl_3$)(c=0.5, 1-mm. cell) cm^{-1}: ν_{OH} 3440, $\nu_{C=O(ketone)}$ 1709.

Acetamido-ketol-N: m.p. 171~172°. $[\alpha]_D^{14}$ −37.2°(c=2.0, MeOH), $[\alpha]_D^{14}$ −48.0°(c=0.5, $CHCl_3$), RD in MeOH (c=0.1, Zr, Xe): $[\alpha]_{589}^{25}$ −40°, $[\alpha]_{400}$ −279°, $[\alpha]_{325}$ −2,882°, $[\alpha]_{312.5}$ −4,676°(trough), $[\alpha]_{307.5}$ −3420°. IR (in Nujol) cm^{-1}: ν_{OH} 3354, ν_{NH} 3311, $\nu_{C=O(ketone)}$ 1704, $\nu_{C=O(amide)}$1675, δ_{NH} 1600, ν_{C-N} 1309; (in $CHCl_3$)(c=0.5, 1-mm. cell) cm^{-1}: ν_{OH} 3419, ν_{NH} 3279, $\nu_{C=O(ketone)}$ 1708, $\nu_{C=O(amide)}$1695.

Amino-ketol-N: m.p. 160~161°. RD in MeOH (c=0.1, Zr): $[\alpha]_{589}^{26.1}$ −46°, $[\alpha]_{400}$ −362°, $[\alpha]_{350}$ −1,079°, $[\alpha]_{330}$ −2,307°(trough), $[\alpha]_{325}$ −1,804°, $[\alpha]_{310}$ −203°. IR (in Nujol) cm^{-1}: ν_{OH} 3436, ν_{NH_2} 3356, $\nu_{C=O}$ 1697, δ_{NH_2} 1633.

Bromo-ketol-N: m.p. 139~140°. $[\alpha]_D^{18}$ −37.7°(c=2.5, MeOH), $[\alpha]_D^{18}$ −49.7°(c=1.5, $CHCl_3$). RD in MeOH (c=0.1, Zr): $[\alpha]_{700}^{22.7}$ −32°, $[\alpha]_{589}$ −56°, $[\alpha]_{400}$ −308°, $[\alpha]_{350}$ −891°, $[\alpha]_{320}$ −3,015°, $[\alpha]_{315}$ −3,456°(trough), $[\alpha]_{310}$ −2,394°, $[\alpha]_{300}$ −249°. IR (in Nujol) cm^{-1}: ν_{OH} 3413, $\nu_{C=O}$ 1700; (in $CHCl_3$)(c=0.5, 1-mm. cell): ν_{OH} 3436, $\nu_{C=O}$ 1709.

Hydroxy-ketol-N: m.p. 145.5~146.5°. $[\alpha]_D^{17}$ −51.2°(c=1.0, MeOH), $[\alpha]_D^{17}$ −38.0°(c=0.5, $CHCl_3$). RD in MeOH (c=0.1, Hg): $[\alpha]_{589}^{25.3}$ −25°, $[\alpha]_{436}$ −128°, $[\alpha]_{366}$ −452°, $[\alpha]_{335}$ −1,429°, $[\alpha]_{312.5}$ −4,174°(trough), $[\alpha]_{310}$ −3,688°. IR (in Nujol) cm^{-1}: ν_{OH} 3279 (shoulder), 3175, $\nu_{C=O}$ 1713, 1691; (in $CHCl_3$)(c=0.5, 1-mm. cell) cm^{-1}: ν_{OH} 3509 (shoulder), 3268~3257, $\nu_{C=O}$ 1704, 1681 (shoulder).

Nitro-ketol-A_1: m.p. 147~148°. $[\alpha]_D^{24}$ +81.4°(c=1.0, MeOH), $[\alpha]_D^{24}$ +115.2°(c=1.0, $CHCl_3$). RD in MeOH (c=0.1, Hg): $[\alpha]_{589}^{24.7}$ +75°, $[\alpha]_{436}$ +105°, $[\alpha]_{400}$ +223°, $[\alpha]_{390}$ +270°. IR (in Nujol) cm^{-1}: ν_{OH} 3482, $\nu_{C=O}$ 1689, ν_{NO_2} 1514, 1344; (in $CHCl_3$)(c=0.5, 1-mm. cell) cm^{-1}: ν_{OH} 3463~3451, $\nu_{C=O}$ 1701.

Nitro-ketol-A_2: m.p. 113~114°. $[\alpha]_D^{24}$ +65.4°(c=1.0, MeOH), $[\alpha]_D^{24}$ +29.8°(c=1.0, $CHCl_3$). RD in MeOH (c=0.1, Hg): $[\alpha]_{589}^{24.7}$ +64.5°, $[\alpha]_{436}$ +169°, $[\alpha]_{400}$ +234.3°, $[\alpha]_{390}$ +271°. IR (in Nujol) cm^{-1}: ν_{OH} 3497, $\nu_{C=O}$ 1697, ν_{NO_2} 1516, 1349; (in $CHCl_3$)(c=0.5, 1-mm. cell) cm^{-1}: ν_{OH} 3463, $\nu_{C=O}$ 1698.

Acetamido-ketol-A_1: m.p. 152~153°. $[\alpha]_D^{18}$ +52.1°(c=2.0, MeOH), $[\alpha]_D^{18}$ +40.0°(c=1.0, $CHCl_3$). RD in MeOH (c=0.1, Hg): $[\alpha]_{589}^{21.3}$ +16°, $[\alpha]_{436}$ +37°, $[\alpha]_{366}$ +108°, $[\alpha]_{313}$ +675°. IR (in Nujol) cm^{-1}: ν_{OH} 3322, ν_{NH} 3247, $\nu_{C=O(ketone)}$ 1709, $\nu_{C=O(amide)}$1667, δ_{NH} 1606, ν_{C-N} 1312; (in $CHCl_3$)(c=0.5, 1-mm. cell) cm^{-1}: ν_{OH} 3419, ν_{NH} 3300, $\nu_{C=O(ketone)}$ 1709, $\nu_{C=O(amide)}$1692.

Amino-ketol-A_2: m.p. 134~135°. RD in MeOH (c=0.1, Zr): $[\alpha]_{589}^{26}$ +16°, $[\alpha]_{400}$ +142°, $[\alpha]_{325}$ +461°(peak), $[\alpha]_{310}$ +119°, $[\alpha]_{300}$ +103°. IR (in Nujol) cm^{-1}: ν_{OH} 3367, ν_{NH_2} 3279 (shoulder), 3185, $\nu_{C=O}$ 1724, δ_{NH_2} 1613.

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*[8] Xe=Xenon lamp used as the source of light. Zr=Zirconium lamp used as the source of light.

*[9] Absorption maxima in ultraviolet spectra are illustrated in Tables I and II, except those of benzoates. Analytical data are limited to illustrate only the compounds prepared, others having been shown in the preceding paper.[1]

O-acetyl-nitro-ketol-N : m.p. 114~115°. *Anal.* Calcd. for $C_{17}H_{21}O_5N$: C, 64.00; H, 6.64; N, 4.39. Found : C, 63.96; H, 7.02; N, 4.53. $[\alpha]_D^{26}$ −29.0°(c=1.0, MeOH), $[\alpha]_D^{26}$ −48.0°(c=1.0, $CHCl_3$). RD in MeOH (c=0.01, Hg) : $[\alpha]_{400}^{25}$ −420°, $[\alpha]_{375}$ −1,130°, $[\alpha]_{366}$ −940°, $[\alpha]_{360}$ −630°, $[\alpha]_{357.5}$ −270°, $[\alpha]_{355}$ −1,650°.

O-Acetyl-acetamido-ketol-N : m.p. 135~136°. $[\alpha]_D^{17}$ +11.2°(c=1.0, MeOH), $[\alpha]_D^{17}$ +9.8°(c=1.0, $CHCl_3$). RD in MeOH (c=0.1, Xe) : $[\alpha]_{589}^{26.8}$ −1.5°, $[\alpha]_{400}$ −21°, $[\alpha]_{325}$ −2,235°, $[\alpha]_{320}$ −2,837°(trough), $[\alpha]_{315}$ −2,488°, $[\alpha]_{310}$ −512°, $[\alpha]_{300}$ −80°(peak), $[\alpha]_{290}$ −168°. IR (in Nujol) cm^{-1} : ν_{NH} 3257, $\nu_{C=O(ester)}$ 1728, $\nu_{C=O(ketone)}$ 1706, $\nu_{C=O(amide)}$ 1667, δ_{NH} 1541, ν_{C-N} 1319, $\nu_{C-O(ester)}$ 1231.

O-Acetyl-bromo-ketol-N : m.p. 80~80.5°. *Anal.* Calcd. for $C_{17}H_{21}O_3Br$: C, 57.84; H, 6.00. Found: C, 57.83; H, 6.02. $[\alpha]_D^{18}$ −3.8° (c=1.0, MeOH), $[\alpha]_D^{18}$ −1.0 (c=1.0, $CHCl_3$). IR (in Nujol) cm^{-1}: $\nu_{C=O(ester)}$ 1737, $\nu_{C=O(ketone)}$ 1712, $\nu_{C-O(ester)}$ 1220.

O,O-Diacetyl-hydroxy-ketol-N : m.p. 71~72°. *Anal.* Calcd. for $C_{19}H_{24}O_5$: C, 68.73; H, 7.29. Found: C, 68.45; H, 7.07. $[\alpha]_D^{17}$ +4.0°(c=1.0, MeOH), $[\alpha]_D^{17}$ +2.1°(c=1.0, $CHCl_3$). IR (in Nujol) cm^{-1} : $\nu_{C=O(phenol\ ester)}$ 1754, $\nu_{C=O(ester)}$ 1739, $\nu_{C=O(ketone)}$ 1709, $\nu_{C-O(ester)}$ 1220, 1192.

O-Acetyl-nitro-ketol-A_1 : m.p. 155.5~156.5°. *Anal.* Calcd. for $C_{17}H_{21}O_5N$: C, 64.00; H, 6.64; N, 4.39. Found : C, 64.13; H, 6.88; N, 4.47. $[\alpha]_D^{24}$ +75.4°(c=1.0, MeOH), $[\alpha]_D^{24}$ +100.8°(c=1.0, $CHCl_3$). RD in MeOH (c=0.1, Hg) : $[\alpha]_{589}^{25.2}$ +61°, $[\alpha]_{436}$ +95°, $[\alpha]_{400}$ +170°, $[\alpha]_{395}$ +174°; RD in MeOH (c=0.01, Hg): $[\alpha]_{400}^{25.2}$ +70°, $[\alpha]_{375}$ −100°, $[\alpha]_{366}$ −10°, $[\alpha]_{357.5}$ +510°.

N,O-Diacetyl-acetamido-ketol-A_1 : m.p. 198~199°. $[\alpha]_D^{27}$ +86.8°(c=1.0, MeOH), $[\alpha]_D^{27}$ +97.8°(c=1.0, $CHCl_3$). RD in MeOH (c=0.1, Xe) : $[\alpha]_{589}^{28.2}$ +60°, $[\alpha]_{400}$ +262°, $[\alpha]_{320}$ +482°, $[\alpha]_{312.5}$ +496°(peak), $[\alpha]_{310}$ +45°(trough), $[\alpha]_{307.5}$ +635°. IR (in Nujol) cm^{-1} : ν_{NH} 3311, $\nu_{C=O(ester)}$ 1724, $\nu_{C=O(ketone)}$ 1715, $\nu_{C=O(amide)}$ 1681, δ_{NH} 1527, ν_{C-N} 1307, $\nu_{C-O(ester)}$ 1259.

O-Acetyl-nitro-ketol-A_2 : m.p. 118~119.° *Anal.* Calcd. for $C_{17}H_{21}O_5N$: C, 64.00; H, 6.64; N, 4.39. Found : C, 63.91; H, 6.72; N, 4.50. $[\alpha]_D^{26.7}$ +20.5°(c=0.687, MeOH), $[\alpha]_D^{26.7}$ +16.8°(c=0.687, $CHCl_3$). RD in MeOH (c=0.1, Zr) : $[\alpha]_{589}^{26.7}$ +9°, $[\alpha]_{400}$ +107°, $[\alpha]_{375}$ +129°.

O-Acetyl-acetamido-ketol-A : m.p. 178~179°. $[\alpha]_D^{18}$ +46.6°(c=1.0, MeOH), $[\alpha]_D^{18}$ +46.2°(c=1.0, $CHCl_3$). RD in MeOH (c=0.1, Hg, Xe) : $[\alpha]_{589}^{24.3}$ +26°, $[\alpha]_{436}$ +52°, $[\alpha]_{366}$ +140°, $[\alpha]_{312.5}$ +680°(peak), $[\alpha]_{307.5}$ +215°(trough), $[\alpha]_{300}$ +680°. IR (in Nujol) cm^{-1} : ν_{NH} 3275, $\nu_{C=O(ester)}$ 1724, $\nu_{C=O(ketone)}$ 1715, $\nu_{C=O(amide)}$ 1681.

O-Benzoyl-acetamido-ketol-N : m.p. 91~92°. *Anal.* Calcd. for $C_{24}H_{27}O_4N\cdot\frac{1}{2}H_2O$: C, 71.64; H, 6.91; N, 3.48. Found : C, 71.45; H, 6.61; N, 3.31. $[\alpha]_D^{26}$ −28.6°(c=1.0, MeOH), $[\alpha]_D^{26}$ −53.6°(c=1.0, $CHCl_3$).

O-Benzoyl-nitro-ketol-N : m.p. 127~127.5°. *Anal.* Calcd. for $C_{22}H_{23}O_5N$: C, 69.35; H, 6.09; N, 3.68. Found : C, 69.25; H, 6.08; N, 3.78. $[\alpha]_D^{24}$ −79.7°(c=0.75, MeOH), $[\alpha]_D^{24}$ −82.9°(c=0.75, $CHCl_3$).

O-Benzoyl-nitro-ketol-A_1 : m.p. 147.5~148°. *Anal.* Calcd. for $C_{22}H_{23}O_5N$: C, 69.35; H, 6.09; N, 3.68. Found : C, 68.92; H, 5.99; N, 3.73. $[\alpha]_D^{24}$ −45.3°(c=0.75, MeOH), $[\alpha]_D^{24}$ −45.9°(c=0.75, $CHCl_3$).

O-Benzoyl-acetamido-ketol-A : m.p. 177~178°. *Anal.* Calcd. for $C_{24}H_{27}O_4N$: C, 73.34; H, 6.85; N, 3.56. Found : C, 73.28; H, 7.04; N, 3.40. $[\alpha]_D^{26}$ +84.8°(c=0.5, MeOH), $[\alpha]_D^{26}$ +48.8°(c=0.5, $CHCl_3$).

The author expresses his sincerest gratitude to Emeritus Professor S. Sugasawa and Professor S. Yamada of the University of Tokyo for their kind guidances and encouragements, and also to Professor C. Djerassi of the Stanford University, U. S. A., for his kind favor for informations on rotatory dispersion curves through private communications. The author is also indebted to the kind encouragement of Dr. K. Abe, the Director of this Laboratory, and to collaborations shown by Dr. T. Okuda and Mr. Y. Egawa of this Laboratory throughout the present work. His thanks are due to Professor Y. Hirata and his circle at the University of Nagoya and to Dr. Y. Mashiko and Mr. A. Kato of the Government Chemical and Industrial Research Institute in Tokyo for their generous favor in taking rotatory dispersion curves. The author is grateful to Dr. Y. Sato and Mr. K. Kotera for infrared analyses and to Mrs. F. Hisamichi and Messrs. T. Yoda and T. Kono for elementary analyses.

Summary

Absolute configurations of optically active 2,4-dimethyl-6-(α-hydroxy(*p*-substituted)-benzyl)cyclohexanones were elucidated and compared with those of cycloheximides, the findings being summarized in Table III. Reaction mechanisms of aldol condensation were discussed.

(Received December 15, 1959)