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# 118. Makoto Suzuki: Studies on Streptomyces Antibiotic, Cycloheximide. VIII.[4] Hydroxycarbonylation of Optically Active 2,4-Dimethylcyclohexanone and Chemical Correlation of the Products. (1).[5]

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In the previous studies on cycloheximide and its isomers, the absolute configurations of cycloheximide and its two stereoisomeric antibiotics named Naramycin-B and isocycloheximide[1~4] were deduced, and optical rotatory dispersion (RD) curves played an important rôle for the elucidation of the configuration. The deductions were made by consulting RD curves of many polycyclic ketones and limited number of monocyclic ketones which were informed by Prof. C. Djerassi of the Stanford University, U.S.A.

Therefore the synthesis of more adequate reference compounds appeared desirable to re-confirm the previous deductions and at the same time such synthesis will make the total synthesis of cycloheximide possible which remains to be completed.

The present paper concerns the synthesis of some new model compounds having similar stereochemical environments as cycloheximide. In the succeeding papers[5,6] the chemical correlations and stereochemical features of the products will be discussed.

As the starting optically active ketone, *cis-d*-2,4-dimethylcyclohexanone (2R:4R)(I) was selected which is readily available by alkaline degradation of cycloheximide[7,8] and synthesis of optically active 2,4-dimethyl-6-(α-hydroxy(*p*-substituted)benzyl)cyclohexanones was attempted by the aldol condensation procedure using several kinds of basic catalysts as a condensation agent.

## Synthesis of Optically Active 2,4-Dimethyl-6-(α-hydroxy(*p*-substituted)benzyl)cyclohexanones

Hydroxycarbonylation (aldol condensation) of alicyclic ketones using basic condensation agents has been reported by many investigators,[9,10] but optically active cyclic ketone never seems to have been the subject of such a work.

Hydroxycarbonylation of *cis*-2,4-dimethylcyclohexanone with *p*-substituted benzaldehyde was attempted, using caustic alkali, tetramethylammonium hydroxide, or N-methylanilinomagnesium bromide and others as a basic catalyst.

1) Aldol condensation by Caustic Alkali — Huitric-Kumler[10] obtained two diastereoisomers by the condensation of cyclohexanone with *p*-halobenzaldehyde using 0.4% sodium hydroxide. Under the same experimental conditions, however, *cis-d*-2,4-dimethylcyclohexanone did not undergo condensation with *p*-bromobenzaldehyde. Even the more reactive *p*-acetamidobenzaldehyde behaved similarly and the starting material was recovered in both experiments. Modification of experimental conditions, e.g. modifications of

*1 Toda-machi, Kita-adachi-gun, Saitama-ken (鈴木真言).

1) Part IV. T. Okuda: This Bulletin, **7**, 659(1959).
2) Part V. *Idem*: *Ibid.*, **7**, 666(1959).
3) Part VI. *Idem*: *Ibid.*, **7**, 671(1959).
4) Part VII. T. Okuda, M. Suzuki, Y. Egawa: *Ibid.*, **8**, 335(1960).
5) Part VIII (Part 2). M. Suzuki: *Ibid.*, **8**, 713(1960).
6) Part IX. *Idem*: *Ibid.*, **8**, 717(1960).
7) E.C. Kornfeld, R.G. Jones, T.V. Parke: J. Am. Chem. Soc., **71**, 150(1949).
8) E.J. Eisenbraun, J. Osiecki, C. Djerassi: *Ibid.*, **80**, 1261(1958).
9) G. Vavon, J. Flurer: Bull. soc. chim. France, **45**, 754(1929); J. Kenner, W.H. Ritchie, F.S. Statham: J. Chem. Soc., **1937**, 1170; C. Mannich, W. Brose: Ber., **56**, 841(1923).
10) A.C. Huitric, W.D. Kumler: J. Am. Chem. Soc., **78**, 1147(1956).

reaction medium, kind of caustic alkali used, molar concentration of alkali, reaction time, and temperature, were all found without effect. On the other hand, cyclohexanone, instead of 2,4-dimethylcyclohexanone, underwent condensation with *p*-acetamidobenzaldehyde under Huitric's condition, but the product was not the desired ketol but its anhydro compound.

2) Aldol condensation by Tetramethylammonium Hydroxide—After numbers of fruitless experiments with caustic alkali under a variety of working conditions a search was made for other type of condensation agent and tetramethylammonium hydroxide was found to be suitable for the present purpose.

Thus, in 50% methanol containing 0.5% of tetramethylammonium hydroxide, *p*-acetamidobenzaldehyde condensed with 2,4-dimethylcyclohexanone to give the desired *β*-ketol, acetamido-ketol-A*[2] (IIa), though the yield was only 7%. This product was easily dehydrated by hydrochloric acid and gave the corresponding anhydro compound (IIIa). Under similar conditions, *p*-nitrobenzaldehyde condensed with 2,4-dimethylcyclohexanone and gave the aimed nitro-ketol-$A_1$ (IIb) as a main product (yield, 62%) and its stereoisomeric nitro-ketol-$A_2$ (IIc) (yield, 7.5%). Both nitro-ketols gave the same dehydrated product (IIIb) on boiling with a small amount of hydrochloric acid in ethanol. The fact that the above ketols were easily dehydrated to the corresponding anhydro compounds means that all of these ketols have their large substituent at C-6 position.

In a similar experiment carried out in 50% tetrahydrofuran solution instead of 50% methanol, acetamido-ketol-A (IIa) was obtained as a sole product with the similar yield as above, but in the experiment carried out in 50% pyridine solution, another kind of acetamido-ketol was obtained, which was found to be identical with acetamido-ketol-N (IVa) obtained by the modified Nielsen's method as will be described below. An attempt to condense 2,4-dimethylcyclohexanone with *p*-bromobenzaldehyde was not successful under all modifications of the experimental conditions so far tried.

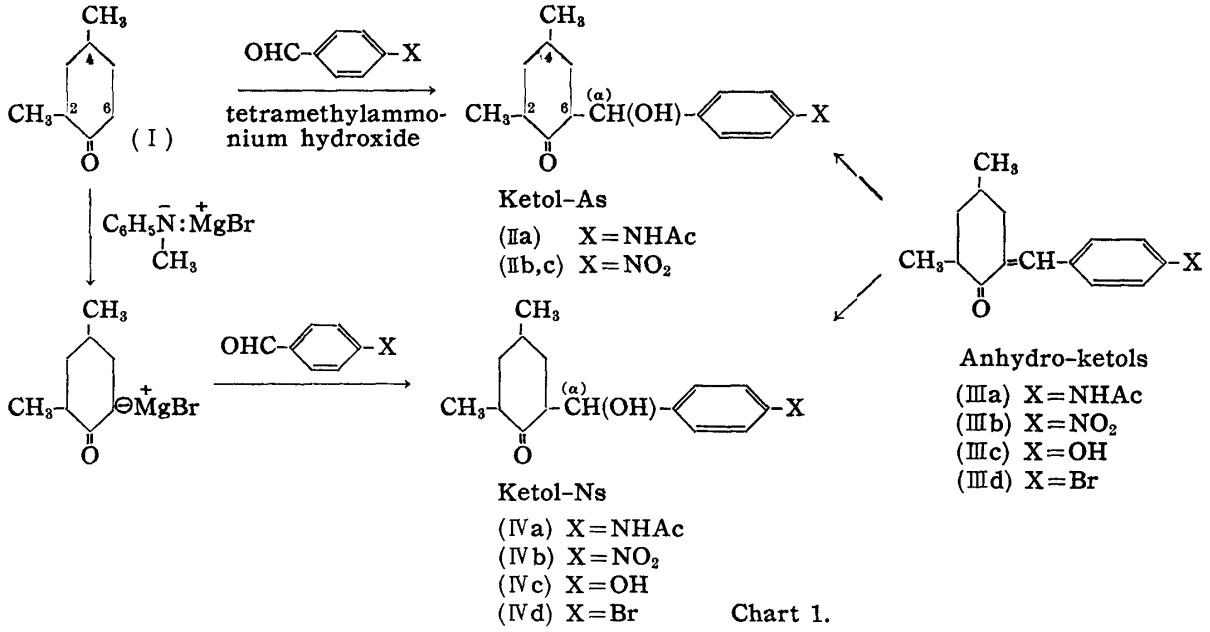


Chart 1.

3) Condensation by N-methylanilinomagnesium Bromide—As reported in the literature and also as experienced in the present work, aldol condensation of a ketone with alde-

*[2] Compounds with the suffix -A and -N are respectively those prepared by aldol condensation procedure using tetramethylammonium hydroxide and by Nielsen's procedure using N-methylanilinomagnesium bromide as a condensation agent.

hyde using ordinary basic catalyst did not always give the objective ketols, especially so in the case of less reactive or hindered ketones. By adjusting molar concentrations of the reactants and the reaction temperature appropriately, Nielsen, *et al.*[11] found that the condensation of aldehyde with less reactive ketone was possible by using N-methylanilinomagnesium bromide as a condensation agent which was hitherto known to be a condensation agent of ketones with ketones.[12~16]

According to Nielsen's private communication, this N-methylanilinomagnesium bromide-catalyzed reaction is not fundamentally different from the typical base-catalyzed aldol condensation as illustrated by the following formulae, in which the N-methylanilide ion ($C_6H_5N^-Me$) serves as the base for the base-catalyzed proton removal in step 1. According to him, the principal difference (with ordinary aldol condensation) lies in the position of the equilibrium in step 1, which with N-methylanilide ion is shifted far to the right to form N-methylaniline, but with ordinary hydroxide ion lies far to the left. The concentration of active intermediate (c) in the solution is thus very high, (which reacts easily) with aldehyde and results in the high yield of desired aldehyde-ketone condensation products.*3

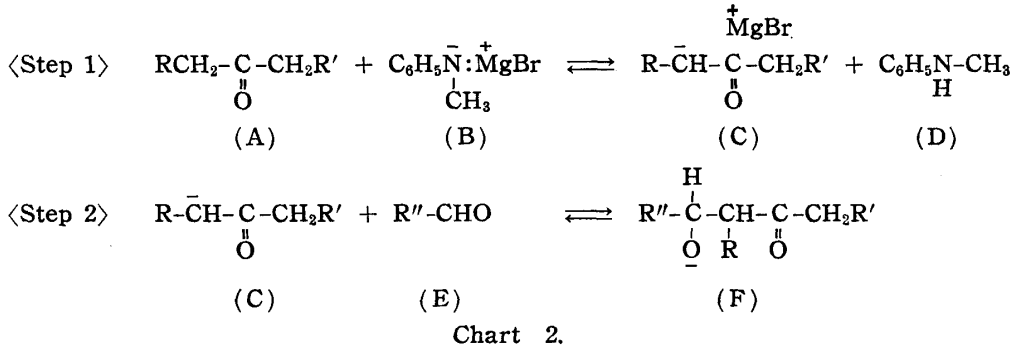


Chart 2.

Experiments were carried out by the procedures similar to that described and recommended by Nielsen, *et al.*[11] in the condensation of ketones with aliphatic aldehyde, in which the molar concentrations of N-methylanilinomagnesium bromide, ketone to be condensed, and aldehyde to condense were 30.5 m*M*, 35 m*M*, and 24 m*M*, respectively, and the reactions were run in the solvent of benzene series. When satisfactory results were not obtained, especially when the aldehyde such as *p*-nitrobenzaldehyde consumed the active intermediate (c in Chart 2) or when the aldehyde used was hardly soluble in the above solvent, modifications were made on 1) molar concentrations of N-methylanilinomagnesium bromide, ketone, and aldehyde to 30.5 m*M*, 35 m*M*, and 12 m*M*, respectively, and 2) selection of a solvent such as benzene-tetrahydrofuran mixture in the reaction.

*cis-d*-2,4-Dimethylcyclohexanone (I) underwent condensation with *p*-hydroxy-, *p*-acetamido-, and *p*-bromobenzaldehyde by Nielsen's original method and gave the anticipated hydroxy-ketol-N*2 (IVc), acetamido-ketol-N (IVa), and bromo-ketol-N (IVd). By modifying

*3 It is interesting, as was made clear in the present experiments using an optically active ketone, that the N-methylanilinomagnesium bromide-catalyzed condensation product was not the same as those obtained by tetramethylammonium hydroxide-catalyzed aldol condensation procedure. The problems would be discussed again in the succeeding paper.[6]

11) A. T. Nielsen, C. Gibbons, C. A. Zimmerman : J. Am. Chem. Soc., **73**, 4696(1951).
12) J. Colonge : Bull. soc. chim. France : (5) **1**, 1101(1934).
13) V. V. Chelintsev, A. V. Pataraya : J. Gen. Chem. U. S. S. R., **11**, 461(1941)[C. A., **35**, 6571(1941)].
14) V. I. Aksenova : Uchenye Zapiski Saratov, Gosudarst Univ. N. G. Chernyshevskogo, Sbornik, Nauch. Rabot Studentov No. 2, 92(1939) [C. A., **35**, 6238(1941)].
15) J. E. Dubois : Compt. rend., **224**, 1506(1947).
16) W. D. Garden, F. D. Gunstone : J. Chem. Soc., **1952**, 2650.

Nielsen's method, starting ketone and *p*-acetamidobenzaldehyde gave the above-mentioned acetamido-ketol-N (IVa) in a better yield and the nitro-ketol-N (IVb) with *p*-nitrobenzaldehyde, which was not obtained by the original Nielsen's method. In the latter case, treatment of the residual crude product, which was removed from crystalline nitro-ketol-N with acid-treated alumina, gave a small amount of another isomer, which was identified with the above-mentioned nitro-ketol-$A_1$ (IIb). Origin of (IIb) would be considered in Part 2 of this series.

It must be emphasized here that Nielsen's method enabled the condensation of 2,4-dimethylcyclohexanone with some aldehydes which resisted aldol condensation. It is noteworthy that the ketol-Ns were not identical but were stereoisomeric with ketol-As obtained by aldol condensation, because these ketol-Ns were readily dehydrated and produced the corresponding anhydro compounds which were identical with those derived from ketol-As. These reaction sequences are illustrated in Chart 1.

As shown in Table I, it is interesting that the products of A-series exhibit positive $[\alpha]_D$ values in methanol, whereas those of N-series, negative $[\alpha]_D$ values. This phenomenon would be closely related to the stereochemical configuration of the products.

Table I. Physical Constants of Optically Active 2,4-Dimethyl-6-(α-hydroxy(*p*-substituted)benzyl)cyclohexanones

| Ketols | X | m.p.[c] (°C) | $[\alpha]_D$ (in MeOH) | Condensation agent[d] | Yield[e] (%) | Formula | Analytical data (%) [Calcd. (Found)] C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| | Compound of A-series[a] | | | | | | | | |
| (IIa) | NHAc | 152~153 | +52.1° (20°; c, 2.0) | TMAH | 7 | $C_{17}H_{23}O_3N$ | 70.65 (70.38) | 8.02 (8.03) | 4.85 (4.91) |
| (IIb) | $NO_2$ | 147~148 | +81.4° (24°; c, 1.0) | 〃 | 62 | $C_{15}H_{19}O_4N$ | 65.04 (64.81) | 6.86 (6.92) | 5.06 (4.98) |
| (IIc) | 〃 | 113~114 | +65.4° (24°; c, 1.0) | 〃 | 7.5 | $C_{15}H_{19}O_4N$ | 65.04 (65.23) | 6.86 (7.06) | 5.06 (5.19) |
| | Compound of N-series[b] | | | | | | | | |
| (IVa) | NHAc | 171~172 | −37.2° (14°; c, 2.0) | MAMB | 28 36[f] 59[g] | $C_{17}H_{23}O_3N$ | 70.65 (70.69) | 8.02 (8.03) | 4.85 (4.94) |
| (IVb) | $NO_2$ | 151~152 | −66.4° (24°; c, 1.0) | 〃 | 37 | $C_{15}H_{19}O_4N$ | 65.04 (64.96) | 6.86 (7.11) | 5.06 (5.28) |
| (IVc) | OH | 145.5~146.5 | −51.2° (17°; c, 1.9) | 〃 | 32* | $C_{15}H_{20}O_3$ | 72.64 (72.45) | 8.13 (8.17) | |
| (IVd) | Br | 139~140 | −37.7° (18°; c, 2.5) | 〃 | 32* | $C_{15}H_{19}O_2Br$ | 57.93 (58.01) | 6.16 (5.95) | Br:25.70 (26.09) |

(IIa) Acetamido-ketol-A. (IIb) Nitro-ketol-$A_1$. (IIc) Nitro-ketol-$A_2$.
(IVa) Acetamido-ketol-N. (IVb) Nitro-ketol-N. (IVc) Hydroxy-ketol-N. (IVd) Bromo-ketol-N.
*a*) Compounds of A-series were obtained by aldol-condensation procedures.
*b*) Compounds of N-series were obtained by Nielsen's condensation procedures.
*c*) All melting points were determined in $H_2SO_4$ bath and are not corrected.
*d*) TMAH=tetramethylammonium hydroxide. MAMB=N-methylanilinomagnesium bromide.
*e*) Yields asterisked are those discounting recovered starting aldehyde.
*f*) Yield when modified Nielsen's method was adopted.
*g*) Yield when further modifications were made on Nielsen's method.

## Experimental[*4]

***cis-d*-2,4-Dimethylcyclohexanone (I)**—(I) was derived from Naramycin-A (cycloheximide) according to the procedure described by Kornfeld, *et al.*[7] and purified through its semicarbazone, b.p. 175~176°, $[\alpha]_D^{16}$ +10.8°(c=5, MeOH). Overall yield from crystalline Naramycin-A was 68~70%.

[*4] All m.p.s are not corrected. Analytical data of synthesized ketols are summarized in Table I. Other physicochemical properties of ketols and their acetates will be described in the following paper.[6]

**Preparation of Ketol-As using Tetramethylammonium Hydroxide (TMAH) as a Condensation Agent** 1) **(+)-2,4-Dimethyl-6-(α-hydroxy-*p*-nitrobenzyl)cyclohexanones : Nitro-ketol-$A_1$ and -$A_2$ (IIb and IIc)**—To the hydr. MeOH solution ($H_2O$, 100 cc., MeOH, 50 cc.) containing 7.87 g. (62.5 m*M*) of *cis-d*-2,4-dimethylcyclohexanone and 5 cc. of 10% TMAH solution, a solution of 1.89 g. (12.5 m*M*) of *p*-nitrobenzaldehyde in 50 cc. of MeOH was added dropwise with stirring during 30 min. while keeping the temperature at ca. 35° and kept under continuous agitation. After 2 and 4 hr., 2.5 cc. of 10% TMAH was added and 3 hr. later, reaction mixtures turned opaque and crystals began to precipitate out. After 8 hr., the reaction mixture was kept in a refrigerator over night and then acidified slightly with 10% HCl. The crystalline precipitate was collected, washed with $H_2O$, dried, and recrystallized from 80% MeOH with activated carbon to 2.01 g. of colorless scaly crystals (nitro-ketol-$A_1$) (IIb), m.p. 147~148°.

The mother liquor was diluted with 3 vol. of $H_2O$, saturated with NaCl, and extracted repeatedly with AcOEt. The extract was washed with $H_2O$, dried over $Na_2SO_4$, and evaporated *in vacuo*. Residual oil was dissolved in hexane, fixed on acid treated alumina, and eluted. The starting ketone mixed with *p*-nitrobenzaldehyde was eluted by hexane (150 cc.), 12 mg. of anhydro compound (IIIa) by benzene, 165 mg. of crude nitro-ketol-$A_1$, which gave 115 mg. of pure sample on recrystallization, by 20% AcOEt-benzene mixture, and finally 315 mg. of pale yellow substance of m.p. 106~108° was eluted by 50% EtOH-benzene and by AcOEt. The last compound, more soluble in 50% $Et_2O$-hexane mixture than nitro-ketol-$A_1$, was recrystallized from 60% MeOH to 261 mg. of colorless plates (nitro-ketol-$A_2$) (IIc) of m.p. 113~114°, mixed m.p. 101~104° with nitro-ketol-$A_1$. Total yield of nitro-ketol-$A_1$ and -$A_2$ was 62% and 7.5%, respectively.

When the condensation was carried out at above 40°, the amount of anhydro compound eluted in the second fraction increased.

2) **(+)-2,4-Dimethyl-6-(α-hydroxy-*p*-acetamidobenzyl)cyclohexanone: Acetamido-ketol-A (IIa)**—Similar to the procedures adopted in the preparation of nitro-ketol-A, 15.74 g. (125 m*M*) of 2,4-dimethylcyclohexanone was condensed with 2.72 g. (18 m*M*) of *p*-acetamidobenzaldehyde (m.p. 154~156°) adding initial 10 cc., 5 cc. after 4 hr., and 5 cc. after 8 hr. of 10% TMAH solution as a condensation agent. The reaction mixture was kept at 35° for 16 hr. with continuous stirring, during which the solution turned yellow but crystals did not appear. Acidified reaction mixture, after being diluted with $H_2O$ and saturated with NaCl, was extracted repeatedly with AcOEt. The extract was concentrated *in vacuo* to an oily residue, which was dissolved in hexane, fixed on acid-treated alumina, and then fractionated as follows : The starting ketone and 2.16 g. of *p*-acetaminobenzaldehyde were recovered by elution with hexane and 50% AcOEt-benzene mixture, respectively, and the latter was identified as its thiosemicarbazone of m.p. 214°(decomp.). The desired acetamido-ketol-A (382 mg.) was eluted by 80% AcOEt-benzene mixture and by AcOEt, and recrystallized from benzene-AcOEt mixture and then from 80% MeOH to 315 mg. of colorless prisms, m.p. 152~153°, the yield being 7% of the theory on discounting starting aldehyde. Condensation carried out at 45° gave similar results.

**Preparation of Ketol-Ns using N-Methylanilinomagnesium Bromide (MAMB) as a Condensation Agent** 1) **Preparation of Active Intermediate (Substance (c) in Chart 2)**—Two methods have been reported for the preparation of MAMB solution, the one being reported by Aksenova[14] and Nielsen,[11] and the other by Garden and Gunstone.[16] The former procedure was employed in the present experiment. To 8 cc. of an $Et_2O$ solution of EtMgBr (prepared from 4.0 g. (36.4 m*M*) of EtBr and 0.8 g. (33 m*M*) of Mg ribbon), a solution of 3.26 g. (30.5 m*M*) of freshly distilled dry methylaniline in 10 cc. of dehyd. benzene was added in $N_2$ atmosphere with ice-cooling (5°) and stirring. Reaction mixtures turned with foaming of ethane into viscous liquid with pale brownish tinge. To the above freshly prepared solution, a solution of 4.41 g. (35.0 m*M*) of *cis-d*-2,4-dimethylcyclohexanone in 5 cc. of dehyd. benzene was added during 10 to 15 min., while keeping the temperature at ca. 15°. After adding the ketone, the solution was allowed to stand for 30 min. and used for further procedures.

2) **(−)-2,4-Dimethyl-6-(α-hydroxy-*p*-acetamidobenzyl)cyclohexanone: Acetamido-ketol-N (IVa)**—To the above freshly prepared solution of active intermediate, a solution of 3.9 g. (24.0 m*M*) of *p*-acetamidobenzaldehyde in 25 cc. of dehyd. tetrahydrofuran was added dropwise with chilling (−15° to −10°) during 20 min., during which white precipitate deposited on the bottom of glass vessel. After addition of the aldehyde, the solution was allowed to stand at −5°±2° for 2.5 hr. with continuous stirring. About 2 hr. later, the initial white precipitate turned pale yellowish. The reaction mixture was chilled to −10° and acidified slightly with 10% HCl (precipitates disappeared). The organic layer was separated from the aqueous layer, the latter being repeatedly extracted with AcOEt. The organic layer and AcOEt extracts were combined and washed thoroughly with 15% HCl to remove basic contaminants produced and then with $H_2O$, dried over anhyd. $Na_2SO_4$, and concentrated *in vacuo* to 1/10 the original volume, when the colorless crystals precipitated out.

The crystals were filtered off, the mother liquor was added with excess $Et_2O$, and allowed to stand over night, from which further crop of crystals came out. These crystals were collected and

recrystallized from benzene-AcOEt mixture to pure acetamido-ketol-N (IVa) as colorless prisms, m.p. 171~172°; yield, 1.93 g. (28%).

Evaporation of the above $Et_2O$ mother liquor and fractional chromatography on acid-treated alumina of the residue gave 820 mg. of the starting aldehyde and a small amount of aldehyde-aldehyde condensation products. Thus, the yield of acetamido-ketol-N was 36% on discounting the starting aldehyde. Any other product was not detected in the reaction mixtures.

In an experiment with reducing the amount of the starting aldehyde to one-half of the above procedure (1.95 g. (12.0 m*M*) of aldehyde in 12.5 cc. of dehyd. tetrahydrofuran), *cet. par.*, yield of the anticipated acetamido-ketol-N increased to 46%, discounting the starting aldehyde. If one increases the amount of tetrahydrofuran used (1.95 g. of *p*-acetamidobenzaldehyde dissolved in 37.5 cc. of tetrahydrofuran, *cet. par.*), no deposit was observed during the reaction and yield of the products increased to 59% and 66%, respectively, without and with discounting the starting aldehyde.

3) (−)-**2,4-Dimethyl-6-(α-hydroxy-*p*-bromobenzyl)cyclohexanone: Bromo-ketol-N (IVd)**—To the above freshly prepared solution of active intermediate, a solution of 4.65 g. (24 m*M*) of *p*-bromobenzaldehyde (m.p. 56~57°) dissolved in 10 cc. of dehyd. benzene and 5 cc. of dehyd. tetrahydrofuran was added dropwise with chilling (−15° to −14°), and kept at −5° to −3° for 2 hr., after which the reaction mixture was treated as described above. AcOEt extract was concentrated *in vacuo*, residual syrup was treated with hexane, and the white crystals were collected and recrystallized repeatedly from $Et_2O$-hexane mixture to colorless fine needles, m.p. 139~140°.

Fractionation of the mother liquor by chromatography on acid-treated alumina afforded further amount of the above crystals from 50% MeOH-benzene fraction, besides which ca. 1 g. of the starting aldehyde and a small smount of the starting ketone were recovered from the hexane-benzene (1:1) fraction. A total of 1.82 g. of bromo-ketol-N was obtained, the yield being 24.2% and 32.4%, without and with discounting the starting aldehyde respectively.

4) (−)-**2,4-Dimethyl-6-(α-hydroxy-*p*-hydroxybenzyl)cyclohexanone; Hydroxy-ketol-N (IVc)**—To the above freshly prepared solution of active intermediate, the solution of 2.92 g. (24.0 m*M*) of *p*-hydroxybenzaldehyde (m.p. 115°) dissolved in 10 cc. of dehyd. tetrahydrofuran was added dropwise as described above, during which white precipitate came out. After having been kept at −5°±1° for 2.5 hr., the reaction mixture was treated as above. In this case, 1.94 g. of the starting aldehyde was recovered (recovery, 66%). The starting aldehyde and hydroxy-ketol-N were separated by repeated fractional recrystallization from $Et_2O$, the former being more soluble than the latter, and 0.65 mg. of the desired hydroxy-ketol-N was obtained as colorless prisms, m.p. 145~146°; yield, 32% on discounting the starting aldehyde.

5) (−)-**2,4-Dimethyl-6-(α-hydroxy-*p*-nitrobenzyl)cyclohexanone: Nitro-ketol-N (IVb)**—The nitro-ketol-N was not obtained under the experimental conditions described by Nielsen, *et al.*, and the experimental conditions were modified as follows:

For the preparation of a solution of active intermediate, a slight excess of N-methylaniline (3.37 g. = 31.5 m*M*) was used to remove remaining Grignard reagent thoroughly, but other conditions were unchanged. To this solution, a solution of 1.80 g. (12 m*M*) of *p*-nitrobenzaldehyde (m.p. 105~106°) in 15 cc. of dehyd. tetrahydrofuran was added dropwise during 20 min., while keeping the temperature at −15° to −10°. After adding the aldehyde, the solution was allowed to stand at −8° to −5° for 1.5 hr., but precipitate did not appear. The reaction mixture was acidified slightly 7.5% HCl at −10° and the organic layer was separated. The aqueous layer was extracted with AcOEt and the extract combined with the above organic layer was washed with 10% HCl and with $H_2O$, dried, and concentrated *in vacuo* to a syrup, which, on treatment with hexane, partially solidified. The mixture was treated with hexane-$Et_2O$ (1:1) mixture, in which the syrup dissolved. The crystals were collected and recrystallized repeatedly from 60% MeOH to 1.22 g. of pure nitro-ketol-N (yield, 37%) as fine colorless prisms, m.p. 151~152°.

The hexane-$Et_2O$ mother liquor was concentrated *in vacuo* to an oily syrup, which was fractionated chromatographically on acid-treated alumina. From the benzene fraction, 12 mg. of colorless scaly crystals, m.p. 145~146.5°, were obtained, which were identical with the previously mentioned nitro-ketol-$A_1$ (IIb), no mixed m.p. depression being observed. 58 mg. of nitro-ketol-$A_1$ was further obtained from AcOEt-benzene fraction.

**Dehydration of Ketols**

1) **2,4-Dimethyl-6-(*p*-acetamidobenzylidene)cyclohexanone (IIIa)**—85 mg. of acetamido-ketol-A (IIa) was dissolved in 6 cc. of EtOH containing 2 drops of conc. HCl and boiled for 3 min. The reaction mixture was concentrated *in vacuo* to 1/2 the original volume, added with $H_2O$, and extracted repeatedly with AcOEt. The extract was washed with $H_2O$, dried, and concentrated *in vacuo*. Residual yellow crystals were recrystallized from 80% MeOH (active carbon) to 41 mg. of (IIIa) as pale yellow prisms, m.p. 163~164°, $[\alpha]_D^{24}$ +269.8° (c=1, MeOH). *Anal.* Calcd. for $C_{17}H_{21}O_2N$: C, 75.34; H, 8.49; N, 5.17. Found: C, 75.59; H, 8.30; N, 5.29. IR in Nujol $cm^{-1}$: $\nu_{NH}$ 3175, $\nu_{C=O(conj.)}$ 1675, $\nu_{C=O(amide)}$ 1657, $\nu_{C=C(conj.)}$ 1590. UV: $\lambda_{max}^{MeOH}$ mμ: 233.5 (ε 9512), 311.5 (23,010).

The same product was obtained by treating acetamido-ketol-N (IVa) as above.

2) **2,4-Dimethyl-6-(*p*-nitrobenzylidene)cyclohexanone (IIIb)**—50 mg. of nitro-ketol-$A_1$ and -$A_2$ (IIb and IIc) were respectively boiled for 3 min. in EtOH containing 2 drops of conc. HCl. Reaction mixture was concentrated *in vacuo*. The residual solid was washed with $H_2O$, dried, and recrystallized from 80% MeOH to pale yellowish fine needles of m.p. 96~97°, $[\alpha]_D^{24}$ +187.8°(c=1, MeOH). The anhydro compounds thus obtained from both nitro-ketel-As were the same, the yield being 29 mg. and 20.5 mg., respectively. *Anal.* Calcd. for $C_{15}H_{17}O_3N$ : C, 69.56; H, 6.62; N, 5.41. Found : C, 69.55; H, 6.72; N, 5.69. IR in Nujol $cm^{-1}$ : $\nu_{C=O(conj.)}$ 1681, $\nu_{C=C(conj.)}$ 1608, $\nu_{NO_2}$ 1513, 1340. UV : $\lambda_{max}^{MeOH}$ 303 mμ ($\varepsilon$ 18376).

The same anhydro compound was also obtained from nitro-ketol-N (IVb) by a similar procedure. No mixed m.p. depression were observed among these products.

3) **2,4-Dimethyl-6-(*p*-hydroxybenzylidene)cyclohexanone (IIIc)**—By treating 50 mg. of hydroxy-ketol-N (IVc) with conc. HCl as above, 21 mg. of the anhydro compound (IIIc) was obtained as pale yellowish plates, m.p. 158.5~160°(from benzene-hexane). *Anal.* Calcd. for $C_{15}H_{18}O_2$ : C, 78.33; H, 7.87. Found: C, 78.03; H, 7.82. UV $\lambda_{max}^{MeOH}$ mμ : 230 ($\varepsilon$ 8188), 317 (18,750).

4) **2,4-Dimethyl-6-(*p*-bromobenzylidene)cyclohexanone (IIId)**—By treating 200 mg. of bromo-ketol-N (IVd) dissolved in 10 cc. of EtOH with 0.1 cc. of conc. HCl for 15 min. in a water bath, 85 mg. of pale yellowish plates of anhydro compound was prepared, m.p. 153~154°(from $Et_2O$). *Anal.* Calcd. for $C_{15}H_{17}OBr$ : C, 61.48; H, 5.85; Br, 27.28. Found : C, 61.21; H, 5.62; Br, 26.96. UV : $\lambda_{max}^{MeOH}$ 285 mμ ($\varepsilon$ 19,850).

## Summary

The condensation of *cis-d*-2,4-dimethylcyclohexanone with *para*-substituted benzaldehyde was carried out using tetramethylammonium hydroxide (aldol condensation) or N-methylanilinomagnesium bromide (Nielsen's condensation) as a basic condensation agent. Aldol and Nielsen's condensation gave the stereoisomeric hydroxycarbonylation products, ketol-As and ketol-Ns, respectively, the former showing positive $[\alpha]_D$ values and the latter, negative values.

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