UDC 615.779.931-011

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

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The present paper concerns the chemical correlation of the optically active 2,4-dimethyl-6-(α-hydroxy(p-substituted)benzyl)cyclohexanones, whose syntheses were described in Part 1.[*2]

As described in the preceding part,[2] condensation products were definitely classified into A-series, having positive $[\alpha]_D$ values, and N-series, having negative ones. Of these products the stereochemical configurations of two acetamido- and three nitro-ketols could be interrelated by chemical isomerization or chemical derivation into O-acetyl-acetamido-ketols.

(1) Isomerization of (−)-2,4-Dimethyl-6-(α-hydroxy-p-acetamido- and p-nitro-benzyl)-cyclohexanone (Acetamido- and Nitro-ketol-N) (IVa, IVb).

As illustrated in Chart 3 treatment of nitro-ketol-N (IVb) with acid-treated alumina overnight at room temperature resulted in its smooth isomerization to nitro-ketol-A_1 (IIb) in 65% yield with a simultaneous formation of a small amount of the anhydro product (IIIb). The former was eluted with chloroform-benzene or ethyl acetate-benzene mixture, no nitro-ketol-A_2 being detected in the isomerization product. The inverted product was identified with the authentic nitro-ketol-A_1 by mixed melting point determination and also by the same type of $[\alpha]_D$ values, being higher in chloroform than in methanol. This observation explains well the formation of a small amount of nitro-ketol-A_1 in the preparation of nitro-ketol-N as a secondary product of isomerization of the latter through alumina and also gives chemical evidence as to the order of stability of ketol-A and -N, and identity of the absolute configuration at C-α position in nitro-ketol-N and -A_1.[*3]

By a similar procedure, acetamido-ketol-N (IVa) and its O-acetate (VIc) were dehydrated or deacetoxylated into the corresponding anhydro compound (IIIa) and gave no isomeric compounds.

Isomerization studies were also attempted in basic condition, which might throw some light on the clarification of reaction mechanisms of the aldol and Nielsen condensation reactions, and, as such, tetramethylammonium hydroxide solution was employed which was used in the preparation of ketol-As. After standing the solution at room temperature for five hours, the products were examined.

It was found that nitro-ketol-N (IVb) gave an isomer by this treatment, and was identified with nitro-ketol-A_1 (IIb) through direct comparison, whereas acetamido-ketol-N (IVa) did not isomerize but decomposed to give 2,4-dimethylcyclohexanone and p-acetamidobenzaldehyde in excellent yields. It was surprising that the difference of substituents in the *para*-position caused a quite different behavior on chemical treatment. These observations well explain the fact that, in aldol condensation, none of the acetamido-ketol whose configuration corresponds to nitro-ketol-A_1 was obtained, because acetamido-

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*2 Serial numbers were used for Charts, Tables and compounds in this and the preceding papers.

*3 This fact provided a further support for the author's view that the absolute configurations at C-α position of Naramycin-A and -B should be identical as was deduced from the Freudenberg's rule of shift adopted upon the $[\alpha]_D$ values of parent Naramycins and their acetates. Details on this point will be discussed in the succeeding paper.

1) Part VII. T. Okuda, M. Suzuki, Y. Egawa: This Bulletin, 8, 335(1960).

2) Part VIII (Part 1). M. Suzuki: *Ibid.*, 8, 706(1960).

ketol-A in hand was referred to nitro-ketol-A_2 as will be illustrated in succeeding section.

(2) Chemical Derivations of Nitro-ketols to Acetamido-ketols

Palladium on a carrier is occasionally employed as a catalyst in the partial reduction of cyclic ketones to keep the carbonyl function intact. Thus, by catalytic reduction using palladium on strontium carbonate, followed by acetylation, nitro-ketols should give corresponding N,O-diacetyl-amino-ketols (VI) without change in their stereochemical configuration, rendering their comparison with those derived from authentic acetamido-ketols possible.

Nitro-ketol-N (IVb), when reduced catalytically in ethanol using 2% palladium on strontium carbonate, gave amino-ketol-N (Vc) in a fair yield which gave N,O-diacetate

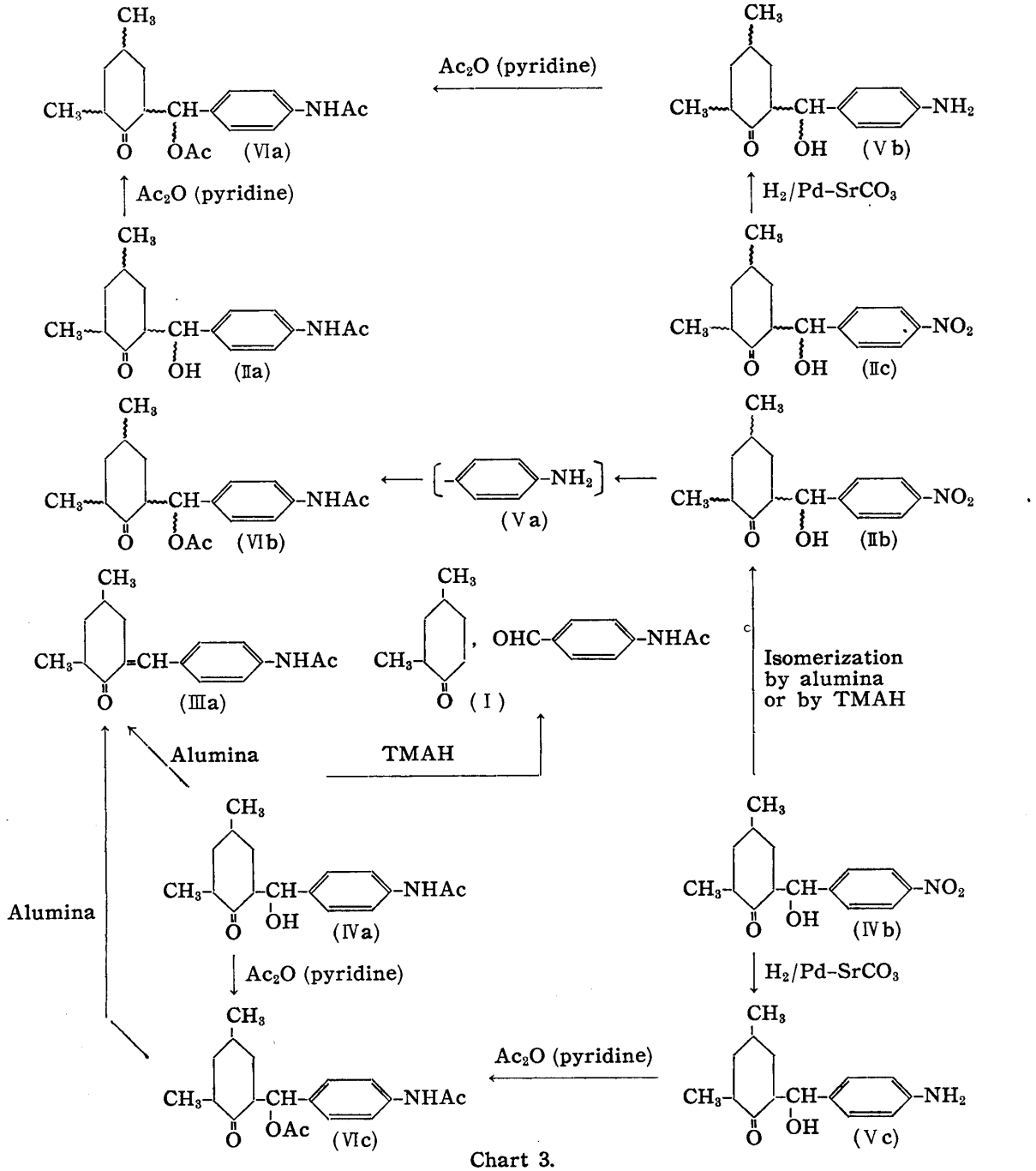

Chart 3.

(VIc) by acetylation. This diacetate (VIc) agreed with the acetate derived from acetamido-ketol-N (IVa). This finding showed that the products synthesized by Nielsen's method had the same type of stereochemical configuration.

In a similar experiment to derive acetamido-ketol-A from nitro-ketol-A, it was found that nitro-ketol-A_1 (IIb), the main product of the aldol condensation, gave amino-ketol-A_1 (Va) which was not induced to solidify but gave on acetylation N,O-diacetate (VIb) different from O-acetyl-acetamino-ketol-A (VIa), whereas nitro-ketol-A_2 (IIc) gave crystalline amino-ketol-A_2 (Vb) whose N,O-diacetate was identical with O-acetyl-acetamido-ketol-A (VIa). From these observations it became certain that the stereochemical configuration of acetamido-ketol-A was the same as that of nitro-ketol-A_2 and that aldol condensation did not always give the product of the same configuration. Chemical correlation of the ketols is summarized in Chart 3.

The detailed configurational considerations of these ketols deduced from their physicochemical properties including their optical rotatory dispersion curves will be discussed in the succeeding paper.

Experimental

Isomerization of (−)-2,4-Dimethyl-6-(α-hydroxy-*p*-nitrobenzyl)cyclohexanone (Nitro-ketol-N) (IVb) to (+)-Isomer (Nitro-ketol-A_1) (IIb)

1) **Treatment with Acid-treated Alumina**—A solution of 100 mg. of nitro-ketol-N dissolved in 2 cc. of benzene was poured in a column filled with 7 g. of acid (HCl)-treated alumina and allowed to stand at 25° over night, after which the column was eluted with $CHCl_3$ into 2 fractions of 20 cc. each. From the first fraction, 62 mg. of colorless scaly crystals (m.p. 136~139°) and 11 mg. of pale yellowish fine needles (m.p. 89~93°) were obtained. From the second fraction, 9 mg. of scaly product (m.p. 136~138°) was obtained, this product being identical with that obtained from the first fraction.

The crystals melting at 136~139° were recrystallized from 70% MeOH as colorless crystals of m.p. 144~146°, which were ascertained to agree with nitro-ketol-A_1 (yield, 65%).

The crystals melting at 89~93° were recrystallized from 80% MeOH to pale yellowish needles of m.p. 94~95° and this product was found to be the same as the anhydro compound (IIIb) mentioned in Part 1.

In another experiment, elution from the alumina column was made by benzene-AcOEt (1:1) mixture, when nitro-ketol-A_1 was obtained in 56% yield and the anhydro compound was not detected in the eluate.

2) **Treatment with Tetramethylammonium Hydroxide (TMAH)**—A solution of 100 mg. of nitro-ketol-N dissolved in 7.5 cc. of 50% MeOH was added with 0.2 cc. of 10% TMAH solution and allowed to stand at room temperature for 5 hr. The solution was then neutralized with 1% HCl and diluted with 5 cc. of water under ice-cooling. 71 mg. of the precipitate was collected, dried in a desiccator, and recrystallized from 70% MeOH to 62 mg. of colorless scaly crystals, m.p. 145~146°, which were identical with nitro-ketol-A_1 (IIb) mentioned in Part 1.

Isomerization Studies on (−)-2,4-Dimethyl-6-(α-hydroxy-*p*-acetamidobenzyl)cyclohexanone (IVa) and its Acetate (VIc)

1) **Treatment with Acid-treated Alumina**—A solution of 100 mg. of acetamido-ketol-N (IVa) dissolved in 4 cc. of tetrahydrofuran was poured into 7.0 g. of acid-treated alumina at room temperature over night and eluted with the same solvent. From the eluate, 78 mg. of pale yellowish crystals (m.p 125~135°) was obtained, which on recrystallization from 90% MeOH gave 67 mg. of yellowish prisms, m.p. 163~164°. This product was identified with anhydro compound (IIIa) by mixed m.p. determination (yield, 71%).

A solution of 100 mg. of O-acetyl-acetamido-ketol-N (VIc) dissolved in 5 cc. of benzene was treated as above. From the eluted benzene-AcOEt solution, 80 mg. of the above-mentioned anhydro compound (IIIa) was obtained (yield, 85%).

2) **Treatment with Tetramethylammonium Hydroxide**—A solution of 100 mg. of acetamido-ketol-N (IVa) dissolved in 10 cc. of 50% MeOH was added with 0.25 cc. of 10% TMAH solution and allowed to stand at room temperature for 5 hr., distinct menthol-like fragrance due to 2,4-dimethylcyclohexanone being noticed. The reaction mixture was neutralized with 1% HCl, concentrated *in vacuo* to one-half the original volume, diluted with 5 cc. of water, and extracted with AcOEt. The extract was dried and concentrated *in vacuo*. The residue, which soon solidified, was washed with Et_2O and recrystallized from 80% MeOH to 32.5 mg. of colorless prisms, m.p. 152~153°. The product was identified with authentic *p*-acetamidobenzaldehyde, m.p. 154~154.5°, by mixed m.p. determination

(mixed m.p. 152~153°). Mixed m.p. with authentic acetamido-ketol-A (m.p. 152~153°), 125~129°.

Reduction of Nitro-ketol-N; Preparation of Amino-ketol-N (Vc)—200 mg. of nitro-ketol-N (IVb) was catalytically reduced at atmospheric pressure in 20 cc. of EtOH using 100 mg. of 2% Pd-$SrCO_3$ catalyst. Reduction was completed after 3.4 moles of H_2 had been absorbed (3 min.). The solution was filtered and EtOH was removed *in vacuo* in N_2 atmosphere. The product, which soon crystallized, was recrystallized from benzene to 157 mg. of pure amino-ketol-N as grayish white needles, m.p. 160~161°, $[\alpha]_D^{26}$ −46.0° (c=0.1, MeOH) (yield, 88%). *Anal.* Calcd. for $C_{15}H_{21}O_2N$: C, 72.94; H, 8.57; N, 5.67. Found : C, 73.13; H, 8.37; N, 5.66.

Amino-ketol-N thus obtained gave N,O-diacetate (VIc), m.p. 134~135°, $[\alpha]_D^{24}$ +8.0° (c=1.0, MeOH), which was identical with the acetate derived from acetamido-ketol-N mentioned below.

Reduction of Nitro-ketol-A_1 (IIb); Preparation of O-Acetyl-acetamido-ketol-A_1 (VIb)—200 mg. of nitro-ketol-A_1 was reduced in EtOH using 100 mg. of 2% Pd-$SrCO_3$ catalyst. The reduction mixture was treated as described above. Amino-ketol-A_1 thus obtained did not solidify and the oily product was immediately acetylated with 2 cc. of Ac_2O in 2 cc. of pyridine. The reaction mixture was treated as usual. The crude product was recrystallized from benzene to 145 mg. of O-acetyl-acetamido-A_1 as colorless prisms, m.p. 198~199°, $[\alpha]_D^{27}$ +86.8° (c=1, MeOH), $[\alpha]_D^{27}$ +97.8° (c=1, $CHCl_3$) (yield, 60.5%). *Anal.* Calcd. for $C_{19}H_{25}O_4N$: C, 68.94; H, 7.61; N, 4.23. Found : C, 68.97; H, 7.79; N, 4.16.

Reduction of Nitro-ketol-A_2 (IIc); Preparation of Amino-ketol-A_2 (Vb)—Under a similar procedure as described above, nitro-ketol-A_2 (IIc) gave amino-ketol-A_2 (Vb) colorless scaly crystals, m.p. 134~135°, $[\alpha]_D^{26}$ +16.0° (c=0.1, MeOH). *Anal.* Calcd. for $C_{15}H_{21}O_2N$: C, 72.94; H, 8.57; N, 5.67. Found: C, 72.65; H, 8.41; N, 5.79.

Amino-ketol-A_2 thus obtained gave N,O-diacetate on acetylation with Ac_2O and was the same as O-acetyl-acetamido-ketol-A (VIa) mentioned below (yield, 82%), m.p. 178~179°, $[\alpha]_D^{25}$ +43.9° (c=0.5, MeOH). *Anal.* Calcd. for $C_{19}H_{25}O_4N$: N, 4.23. Found : N, 4.41.

O-Acetyl-acetamido-ketol-A (VIa)—A solution of 56 mg. of acetamido-ketol-A (IIa) dissolved in 1 cc. of dehyd. pyridine was added with 1 cc. of Ac_2O with ice-cooling and kept at room temperature over night, after which the solvent was distilled off *in vacuo* to give crude crystalline acetate. The crude product was washed with Et_2O and recrystallized from 2 cc. of benzene to 54 mg. of colorless fine prisms (yield, 84%), m.p. 178~179°, $[\alpha]_D^{18}$ +46.6° (c=1.0, MeOH). *Anal.* Calcd. for $C_{19}H_{25}O_4N$: C, 68.94; H, 7.61; N, 4.23. Found : C, 68.69; H, 7.72; N, 4.33.

The same product was also derived from amino-ketol-A_2 (Vb) as described before.

O-Acetyl-acetamido-ketol-N (VIc)—By treating 100 mg. of acetamido-ketol-N with 1.5 cc. of dehyd. pyridine and 1.5 cc. of Ac_2O similarly as above, 92 mg. of O-acetyl-acetamido-ketol-N was obtained (yield, 80%) as colorless prisms, m.p. 135~136°, $[\alpha]_D^{17}$ +11.2° (c=1.0, MeOH) (two recrystallizations from dehyd. benzene).

The same product was also obtained by acetylation of amino-ketol-N (Vc) prepared by catalytic reduction of nitro-ketol-N described above. *Anal.* Calcd. for $C_{19}H_{25}O_4N$: C, 68.94; H, 7.61; N, 4.23. Found : C, 69.14; H, 7.55; N, 4.41.

The author expresses his deepest gratitude to Emeritus Professor S. Sugasawa and Professor S. Yamada of the University of Tokyo for their kind and helpful guidances. He is also grateful to Dr. K. Abe, the Director of this Laboratory, for his encouragement and to Dr. T. Okuda and Mr. Y. Egawa of this laboratory for their kind advices throughout this work. His thanks are due to Dr. Y. Satō and Mr. K. Kotera for infrared analysis, and to Mrs. F. Hisamichi, and Messrs. T. Yoda and T. Kōno for elemental analysis.

Summary

The chemical correlations were examined of optically active 2,4-dimethyl-6-(α-hydroxy(*p*-substituted)benzyl)cyclohexanones whose preparations were reported in the preceding paper. From the present experiments, together with the previous informations, following facts were noticed.

1) All of the optically active 2,4-dimethyl-6-(α-hydroxy(*p*-substituted)benzyl)cyclohexanones prepared by Nielsen's condensation procedure had the same configuration, whereas those by aldol condensation had not always the same one.

2) Some of Nielsen's condensation products were converted chemcially into more stable isomers of positive $[\alpha]_D$ value and some of the converted products tallied with the product obtained by aldol condensation procedure.

(Received December 9, 1959)