UDC 547.834.3.07

47. Fumihiko Uchimaru : Studies on N-Substituted Nortropane Derivatives. II. Reduction of N-Substituted 3-Nortropanones.

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The preceding paper[1] reported the preparation of compounds considered to be 8-(1-alkoxycarbonylalkyl)-3-nortropanones by the Robinson-Schöpf condensation using the esters of α-amino acids. Among them, the keto compound obtained from glycine ester was reduced by complex metal hydride and the products were related to 3-tropanone (tropinone). As a result of these experiments it was confirmed that the above compound has the structure of N-substituted nortropane skeleton.

The condensation product obtained by the Robinson-Schöpf reaction from glycine ethyl ester hydrochloride was presumed to be ethyl 3-oxo-8-nortropaneacetate (I) because of the following reasons. First, it was reduced by lithium aluminium hydride in ether. After purification by alumina chromatography, two compounds without carbonyl absorption in the infrared spectra were obtained in 60% yield. The first crystalline product (A) formed a picrate of m.p. 118~120°, and the second product (B) was an oily substance forming a picrate of m.p. 98~101°. Analytical values of both picrates agreed with C_{15}-

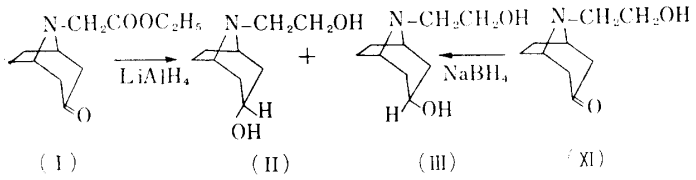

Chart 1

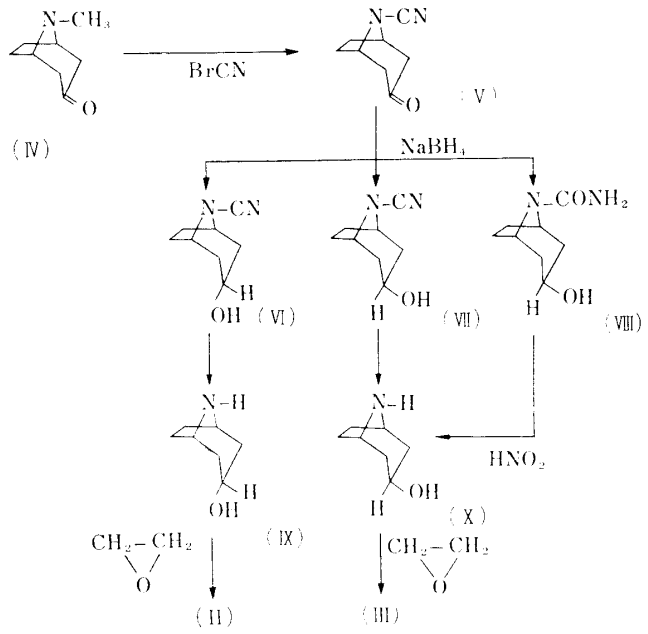

Chart 2

*1 Hirakawabashi, Sumida-ku, Tokyo (内丸文彦).

1) M. Shimizu, F. Uchimaru : This Bulletin, **9**, 300 (1961).

$H_{20}O_9N_4$. From the analytical data of their picrates, these two bases were considered to be diols. (A) was alloted to a diol possessing an axial hydroxyl group (II) and (B) to the one possessing an equatorial hydroxyl group (III) on the basis of the order of elution. To confirm this point, these bases (II) and (III) were prepared from 3-tropanone (IV). The synthesis of 3α-nortropanol (IX) and 3β-nortropanol (X) from (IV) was already reported by Fieser[2] as shown in Chart 2. Reaction of (IX) and (X) with ethylene oxide yielded 3α-hydroxy-8-nortropaneëthanol (II) and 3β-hydroxy-8-nortropaneëthanol (III). The picrates of (II) and (III) were respectively identical with those of above bases (A) and (B). By the reduction of 3-oxo-8-nortropanecarbonitrile (V), besides the two epimers (VI) and (VII), a third substance of m.p. 184~186°, $C_8H_{14}O_2N_2$, was obtained by alumina chromatography. In the infrared spectrum, it showed the amide absorption along with that of a hydroxyl group. This substance is identical with 3β-hydroxy-8-nortropanecarboxamide (VIII) described by Fieser[2] and it was further confirmed by its conversion to 3β-nortropanol with nitrous acid. Although 8-(2-hydroxyethyl)-3-nortropanone (XI) mentioned in the preceding paper[1] has already been reported in the literature,[3] (XI) was also converted to (II) and (III) by reduction with sodium borohydride in aqueous solution. These substances were identified by mixed fusion and infrared absorption spectra. All these experimental data clearly show that the condensation product from glycine ethyl ester hydrochloride has the structure of (I). Von Braun degradation to convert (I) to 3-oxo-8-nortropanecarbonitrile (V) was unsuccessful.

Sodium borohydride reduction of (I) in methanol was also attempted. Alumina chromatography of the product resulted in the isolation of two kinds of bases. The first eluted

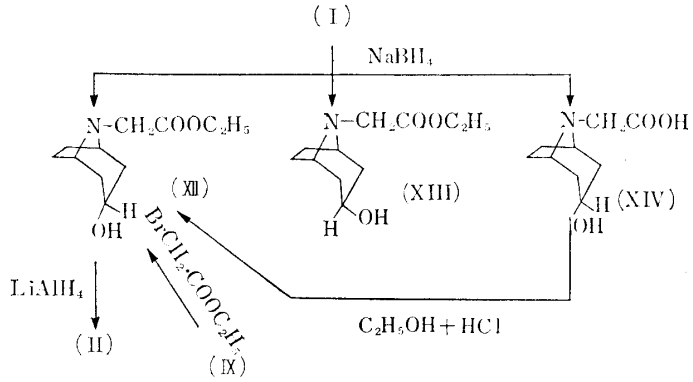

Chart 3.

oily base (C) afforded a picrate melting at 138~139°, $C_{17}H_{22}O_{10}N_4$, and a methiodide of m.p. 213~215° (decomp.), $C_{12}H_{22}O_3NI$. The picrate of the second eluted substance (D) did not crystallize but its methiodide formed crystals of m.p. 204~206° (decomp.), $C_{12}H_{22}O_3NI$. These two methiodides showed a distinct depression by mixed fusion and their infrared spectra were fairly different. As the base (C) was converted to (II) by lithium aluminium hydride, configuration of the hydroxyl group in 3-position is axial (tropine series). To substantiate this conclusion further, ethyl bromoacetate was reacted with 3α-nortropanol (XI) to give the same base (C). Consequently, the base (C) has the structure of ethyl 3α-hydroxy-8-nortropaneacetate (XII). Base (D) was characterized by its methiodide and from its infrared spectral data,*2 the configuration of its hydroxyl group in 3-position was assumed to be equatorial (pseudotropine series). In order to prove this configuration, the methiodide of (D) was refluxed in xylene for 15 hours and only the starting material was recovered. These two compounds (XII) and (XIII) had already been synthesized by

*2 The detailed conclusion will be shown in the next paper.

2) A. Nickon, L. F. Fieser: J. Am. Chem. Soc., 74, 5566 (1952).

3) L. C. Keagle, W. H. Hartung: *Ibid.*, **68**, 1608 (1946).

Fodor[4] in a different way, and the melting point of these methiodides showed good agreement with Fodor's data.

A third substance (E) was obtained in this reduction after chromatography. It was recrystallized from methanol to colorless needles of m.p. 274~276° (decomp.), $C_9H_{15}O_3N \cdot H_2O$. Its infrared spectrum showed absorptions for a hydroxyl group (3360 cm^{-1}), carboxylate ion (1603, 1395 cm^{-1}), and protonated nitrogen (2500~2900 cm^{-1}). As this substance was assumed to have an 8-carboxymethyl group, (E) was esterified with ethanol and hydrochloric acid and gave ethyl 3α-hydroxy-8-nortropaneacetate (XIII). Consequently, it is reasonable to assume that the third substance (E) is 3α-hydroxy-8-nortropaneacetic acid (XIV) possessing an axial hydroxyl group in 3-position.

Various N-substituted 3α- and 3β-nortropanols were obtained in the present work and their infrared spectral data will be reported in the forthcoming paper.

Experimental*3

Reduction of Condensation Product from Glycine Ester Hydrochloride with Lithium Aluminium Hydride——To a solution of 0.50 g. of $LiAlH_4$ in 15 cc. of dehyd. Et_2O, 0.73 g. of condensation product, reported in Part I, in 15 cc. of dehyd. Et_2O was added with stirring during 20 min. After refluxing in a water bath for 2 hr., the mixture was allowed to stand overnight. The mixture was added with H_2O and $CHCl_3$, extracted with $CHCl_3$, and the extract was dried over K_2CO_3. Evaporation of the solvent furnished 0.60 g. of an oily substance which was purified through a column of alumina (12 g.). The eluate with $CHCl_3$ gave 70 mg. of crystals (A), m.p. 93~97°, and the eluate with MeOH afforded 270 mg. of an oil (B) (total yield, 57.1%).*4

Picrate of (A): Yellow plates (from iso-PrOH), m.p. 118~120°. *Anal.* Calcd. for $C_{15}H_{20}O_9N_4$: C, 45.00; H, 5.04; N, 14.00. Found: C, 45.07; H, 4.72; N, 13.94.

Picrate of (B): Yellow needles (from iso-PrOH), m.p. 98~101°. *Anal.* Found: C, 45.11; H, 4.90; N, 13.75.

3α-Hydroxy-8-nortropaneëthanol (II)——Freshly prepared ethylene oxide (ca. 1 g.) was bubbled through a solution of 100 mg. of 3α-nortropanol in 2 cc. of MeOH while warming on a water bath and the mixture was allowed to stand overnight. Evaporation of the solvent furnished 150 mg. of colorless needles, m.p. 95~99°. Chromatography on 3 g. of alumina and elution with $CHCl_3$ gave 100 mg. (74.7%) of colorless needles, m.p. 104~106°. *Anal.* Calcd. for $C_9H_{17}O_2N$: C, 63.13; H, 10.00; N, 8.18. Found: C, 62.65; H, 9.46; N, 8.15.

Picrate: Yellow plates (from iso-PrOH), m.p. 119~121°. *Anal.* Calcd. for $C_{15}H_{20}O_9N_4$: C, 45.00; H, 5.04; N, 14.00. Found: C, 45.45; H, 5.02; N, 13.78. The melting point of this picrate showed no depression in mixed fusion with the picrate of the above product (A).

3β-Hydroxy-8-nortropaneëthanol (III)——In entirely the same way as above, 260 mg. of oily substance was obtained from 200 mg. of 3β-nortropanol (X). The crude base was converted to its picrate in MeOH to give 530 mg. (84.4%) of crystals, m.p. 98~102°. Repeated crystallization from iso-PrOH gave yellow feathery crystals, m.p. 99~101°. *Anal.* Found: C, 44.52; H, 4.87; N, 13.63. The identity of this picrate with the picrate of above (B) was confirmed by mixed fusion.

3β-Hydroxy-8-nortropanecarboxamide (VIII)——According to the description of Fieser,[2] 3-oxo-8-nortropanecarbonitrile (V) was subjected to reduction with $NaBH_4$ in water. After separation of 3α- and 3β-hydroxy-8-nortropanecarbonitrile (total yield, 59.8%, ratio about 2:3), the third fraction was eluted with the solvent mixture of $CHCl_3$-MeOH (3:1). Combined fraction (31.2%) after repeated recrystallization from MeOH furnished colorless prisms, m.p. 184~186°. *Anal.* Calcd. for $C_8H_{14}O_2N_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.17; H, 8.30; N, 16.58. IR ν_{max}^{KBr} cm^{-1}: 1645 (amide), 3375, 3310 (NH_2).

3β-Nortropanol (X) from 3β-Hydroxy-8-nortropanecarboxamide (VIII)——To a solution of 450 mg. of (VIII) dissolved in 10 cc. of 5% HCl a solution of 230 mg. of $NaNO_2$ in water was added dropwise with ice-cooling and the mixture was allowed to stand overnight. After extraction with Et_2O, the aqueous layer was made alkaline and extracted with $CHCl_3$, which was dried over Na_2SO_4. Evaporation of $CHCl_3$ yielded 250 mg. (61.2%) of crystals which was purified by sublimation in reduced pressure followed by immediate conversion to its picrate as yellow needles (from H_2O), m.p. 183~185°.

*3 All m.p.s are uncorrected.

*4 Besides the two products, an oily substance which did not form a picrate was detected in this chromatography.

4) G. Fodor: Magyar Kémiai Folyóirat, **59**, 242 (1953) (C. A., **48**, 10029 (1954)); G. Fodor, K. Koczka, J. Lestyán: J. Chem. Soc., **1956**, 1411.

The picrate was found to be identical with the picrate of (X) by mixed fusion.

Reduction of 8-(2-Hydroxyethyl)-3-nortropanone (XI) with Sodium Borohydride——To 2.70 g. of (XI) in 50 cc. of water, 300 mg. of $NaBH_4$ was gradually added and the solution was allowed to stand at room temperature overnight. It was thoroughly extracted with $CHCl_3$, which was dried over Na_2SO_4. Evaporation of the extract left 2.10 g. (77.5%) of an oily substance which was purified by chromatography on 60 g. of alumina. Combined fractions (1.57 g.) eluted with $CHCl_3$–MeOH (9:1) was further chromatographed on alumina (30 g.) and gave 0.33 g. of crystals (m.p. 101~104°) eluted with pure $CHCl_3$ and 0.82 g. of an oily substance eluted with $CHCl_3$–MeOH (1%). The crystalline substance was chromatographed on alumina (6 g.) again and gave colorless crystals melting at 104~106°. The product proved to be identical by mixed fusion and infrared spectrum with (II) synthesized from 3α-nortropanol. *Anal.* Calcd. for $C_9H_{17}O_2N$: C, 63.13; H, 10.00; N, 8.18. Found : C, 63.44; H, 9.62; N, 8.25.

Picrate : Yellow plates (from iso-PrOH), m.p. 119~121°. *Anal.* Calcd. for $C_{15}H_{20}O_9N_4$: C, 45.00; H, 5.04; N, 14.00. Found : C, 44.63; H, 5.41; N, 13.83. The picrate was also identical with the picrate of (II).

The later eluted oily substance after further chromatography on 14 g. of alumina and elution with $CHCl_3$–MeOH (19:1) left 0.64 g. of an oil.

Picrate : Yellow prisms (from iso-PrOH), m.p. 99~101° identical with the picrate of (III). *Anal.* Found : C, 44.40; H, 5.19; N, 14.22.

Reduction of Ethyl 3-Oxo-8-nortropaneacetate (I) with Sodium Borohydride——To 2.85 g. of (I) in 30 cc. of MeOH 0.38 g. of $NaBH_4$ was added slowly with stirring and the resulting solution was allowed to stand at room temperature overnight. Further 30 cc. of $CHCl_3$ and 10 cc. of H_2O were added to the mixture and the aqueous layer was thoroughly extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to furnish 2.90 g. of a yellow oil. Chromatography on 90 g. of alumina yielded following fractions. The fraction eluted with petr. ether–Et_2O (1:5) gave 0.65 g. of an oil (C), IR $\nu_{max}^{liq.}$ cm^{-1} : 1046 (C-O), 1747 (ester C=O). The fraction eluted with Et_2O–MeOH (7:1) afforded 0.22 g. of an oil (D), IR $\nu_{max}^{liq.}$ cm^{-1} : 1065 (C-O), 1745 (ester C=O) (yield of C+D, 30.2%). The fraction eluted with Et_2O–MeOH (1:1) yielded 0.16 g. (5.8%) of a crystalline substance (E).

Picrate of (C) : Yellow plates (from H_2O), m.p. 138~139°. *Anal.* Calcd. for $C_{17}H_{22}O_{10}N_4$: C, 46.15; H, 5.01; N, 12.67. Found : C, 46.23; H, 5.21; N, 12.53.

Methiodide of (C) : Colorless needles (from MeOH), m.p. 213~215° (decomp.). *Anal.* Calcd. for $C_{12}H_{22}O_3NI$: C, 40.54; H, 6.24; N, 3.94. Found : C, 40.81; H, 6.16; N, 3.70.

Methiodide of (D) : Colorless plates (from MeOH), m.p. 204~206° (decomp.). *Anal.* Found : C, 40.66; H, 6.44; N, 4.08. Mixed m.p. of the methiodides of (C) and (D) was 195~199° (decomp.) and the infrared spectra of the two methiodides clearly showed difference. Picrate of (D) did not crystallize.

(E) : Colorless prisms (from MeOH), m.p. 274~276° (decomp.). IR ν_{max}^{KBr} cm^{-1} : 3350 (O-H), 1603, 1395 (COO^-), 2500~2900 (N^+-H). *Anal.* Calcd. for $C_9H_{15}O_3N \cdot H_2O$: C, 53.19; H, 8.43; N, 6.89. Found : C, 53.02; H, 8.45; N, 7.22.

Reduction of (C) with Lithium Aluminium Hydride——To a suspension of 0.19 g. of $LiAlH_4$ in 10 cc. of dehyd. Et_2O, 0.49 g. of (C) in 20 cc. of dehyd. Et_2O was added with stirring during 20 min., and refluxed for 2 hr. on a water bath. Water and K_2CO_3 were added to the mixture which was extracted with Et_2O–$CHCl_3$, and the extract dried over K_2CO_3. Evaporation of the solvent *in vacuo* gave 0.35 g. (90.2%) of crystalline substance, m.p. 75~85°. After chromatographic purification on alumina (10 g.), it gave 150 mg. of crystals melting at 103~106° which proved to be identical with (II) by mixed fusion.

Picrate : Yellow prisms (from iso-PrOH), m.p. 118~120°. *Anal.* Found : C, 45.17; H, 4.99; N, 14.37. Also identical with that of (II).

Ethyl 3α-Hydroxy-8-nortropaneacetate (XII)——To a solution of 30 mg. of 3α-nortropanol (IX) in 10 cc. of benzene, 0.1 cc. of $BrCH_2COOEt$ was added dropwise, the mixture was refluxed in a water bath for 1 hr., and allowed to stand overnight. The crystals that formed were collected, washed with benzene, and the combined filtrate and washing was evaporated to dryness. The residue was converted to its picrate as yellow plates (from H_2O), m.p. 136~138°. The identity with the picrate of (C), the $NaBH_4$ reduction product of (I), was confirmed by mixed fusion.

Esterification of (E)——The above reduction product (E) (170 mg.) was dissolved in 15 cc. of dehyd. EtOH and dry HCl-gas was bubbled through the solution first with ice-cooling for 20 min., then at bath temperature of 50~60° for 3 hr. Evaporation of the solvent yielded 230 mg. of a crystalline mass which was taken up in a small amount of water, made alkaline with KOH with cooling, and extracted with $CHCl_3$, which was dried over Na_2SO_4. Evaporation of the solvent *in vacuo* provided 100 mg. of a yellow oil which was dissolved in ether and directly converted to its picrate of yellow plates (from H_2O), m.p. 136~138°. A mixed m.p. with the picrate of (XII) was not depressed. *Anal.* Calcd. for $C_{17}H_{22}O_{10}N_4$: C, 46.15; H, 5.01; N, 12.67. Found : C, 45.63; H, 5.18; N, 12.62.

The author expresses his deep gratitude to Dr. Junzo Shinoda, President of this Company, and to Dr. Takeo Ishiguro, Director of this Laboratory, for their kind encouragement, and to Dr. Masao Shimizu, Acting Director, for kind and unfailing guidance. The author is also indebted to Messrs. B. Kurihara and K. Abe for elemental analyses.

Summary

Condensation product obtained by the Robinson-Schöpf method using glycine ester hydrochloride was reduced by lithium aluminium hydride and sodium borohydride. Some of the reduction products were synthesized from 3-tropanone (IV) and, on the basis of these experimental data, the structure of the above compound was established as (I).

(Received July 6, 1960)

UDC 547.834.3:543.422.4

48. Fumihiko Uchimaru : Studies on N-Substituted Nortropane Derivatives. III. The Infrared Spectra of N-Substituted 3α- and 3β-Nortropanols.

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In a preceding work of this series[1] N-substituted 3-nortropanones were reduced with complex metal hydride and corresponding 3α- and 3β-ols were obtained. The present report is concerned with the infrared spectra of these alcohols, especially on the difference between 3α- and 3β-ols in the region of C-O stretching vibration. This difference was utilized to presume the configuration of epimers obtained by reduction of some N-substituted 3-nortropanones.

1. Infrared Spectra of N-Substituted 3-Nortropanones

The infrared spectra of N-substituted 3-nortropanones, described in Part I,[2] are briefly summarized. The main absorptions of nine 3-nortropanones are shown in Table I.

Table I. Infrared Spectra of N-Substituted 3-Nortropanones (liquid film) (cm^{-1})

No.	Substituent at N N-R	Ketone $\nu_{C=O}$	Active methylene CO-CH_2-	Methine $\nu_{HC\equiv}$	Methine $\delta_{HC\equiv}$	C-N	Ester $\nu_{C=O}$	Others
1	N-H	1708	1398	2880	1335	1006		N-H 3260
2	N-CH_3	1709	1409	2875	1347	1006		
3	N-CH_2CH_2OH	1709	1407	2860	1348	1006		C-O 1049
4	N-CH_2COOCH_3	1713	1409	2880	1349	1008	1749	
5	N-$CH_2COOC_2H_5$	1714	1400	2880	1348	1007	1747	
6	N-$CH_2COOCH_2C_6H_5$	1714	1393	2880	1350	1007	1745	
7	N-$CH\langle^{CH_3}_{COOC_2H_5}$	1715	1412	2880	1347	1005	1742	
8	N-$CH\langle^{CH_2CH_2SCH_3}_{COOC_2H_5}$	1725	(1420)[b]	(2875)	1348	1005	1739	
9	N-CN[a]	1713	1403 1415	2890	1351	999		C≡N 2205

a) This sample was measured in KBr tablet.
b) Figures in parentheses indicate weak absorption or shoulder.

*1 Hirakawabashi, Sumida-ku, Tokyo (内丸文彦).
1) Part II. F. Uchimaru : This Bulletin, **9**, 304 (1961).
2) Part I. *Ibid.*, **9**, 300 (1961).