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Stereochemical Studies. XI.[1] Changes in the Stereochemical Course of 1,2-Asymmetric Induction in the Reduction of N-Substituted 2-Aminopropiophenone Derivatives with Sodium Borohydride[2]

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Changes in the stereochemical course of 1,2-asymmetric induction in the reduction of N-substituted 2-aminopropiophenones with sodium borohydride were examined. It was concluded that substitution for the two hydrogens of the amino group by two bulky groups is important for the synthesis of *threo*-isomer, while at least one of the two hydrogens of the amino group must be left attached for the synthesis of *erythro*-isomer. This stereochemical outcome was considered to be attributable to the steric phenomena.

In the preceding paper[1] of this series, the present authors reported results of investigations on the 1,2-asymmetric induction in the sodium borohydride reduction of propiophenone derivatives having -NH_2HCl, -OH or OCH_3 groups at α- and/or β-positions to the carbonyl group. It was found that the stereochemical course of th reduction was highly dependent on the position of these functional groups, *i.e. erythro*-rich products were obtained in the reduction of ketones having a functional group at α-position to the carbonyl group, while *threo*-rich products were obtained in the reduction of ketones having a functional group at β-position to the carbonyl group. It was also recognized that 2-aminopropiophenone hydrochloride (I) exhibited the highest stereoselectivity in the sodium borohydride reduction among the eight propiophenone derivatives examined.

In connection with these findings, it seems quite interesting from the synthetic point of view to investigate how is the way to alter the stereochemical course of this 1,2-asymmetric induction. Examples[4] are known in which the stereochemistry of the reduction differs among the ketones having substituents on the amino group in I. However, due to the lack of descriptions of the minor diastereomers produced, these data are inadequate for observation of change in stereoselectivities. Therefore, a ketone (I) was chosen as parent substrate and the stereochemical course in the sodium borohydride reduction of its N-substituted derivatives (II—IX) were examined.

It is inevitable for the present purpose to establish a method for determination of diastereomeric ratios in the products. An initial attempt to use the method of nuclear magnetic resonance (NMR) directly on reduction products was abandoned (except in the case of that from VI) due to incomplete separation of diastereomeric signals. However, deacylation and debenzylation of reduction products could be performed without affecting the diastereomeric ratios; at least within experimental error. As shown in Chart 1, alkaline hydrolysis of N-benzoyl-DL-norephedrine (*erythro*-X) followed by continuous extraction of the reaction mixture with ether afforded DL-norephedrine (*erythro*-XI) in excellent yield. Lithium aluminum hydride reduction of *erythro*-X to the corresponding N-benzyl derivative followed by debenzylation with palladium on charcoal and hydrogen in ethanol at atmospheric pressure afforded

1) Part X: K. Koga and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 526 (1972).
2) For a preliminary communication on this work, see S. Yamada and K. Koga, *Tetrahedron Letters*, **1967**, 1711.
3) Location: *Hongo, Bunkyo-ku, Tokyo.*
4) *a*) H. Pfanz and H. Müller, *Arch. Pharm.*, **288**, 11 (1955); *b*) H. Takamatsu, *Yakugaku Zasshi*, **76**, 1227 (1956); *c*) H.K. Müller, *Ann.*, **598**, 70 (1956); *d*) H.K. Müller and H. Werchan, *ibid.*, **689**, 127 (1965); *e*) H.K. Müller and E. Müller, *ibid.*, **689**, 134 (1965).

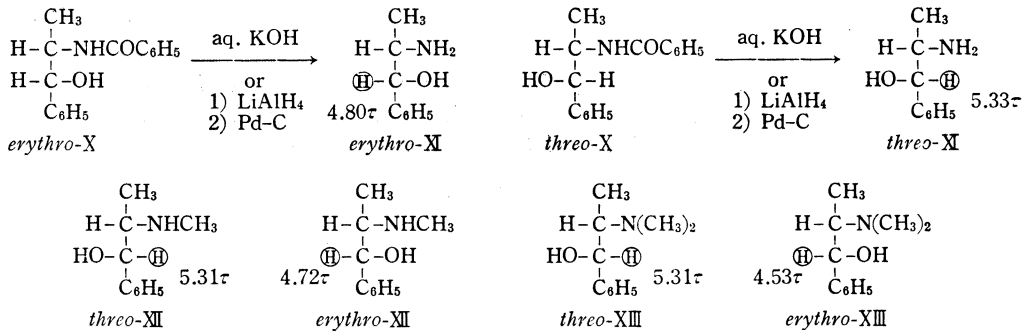


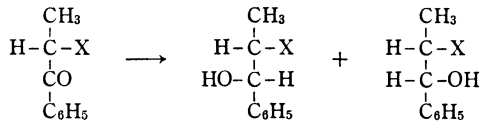
Chart 1

erythro-X in good yield. NMR spectra of the crude products exhibited no signals due to *threo*-XI. Similarly, N-benzoyl-DL-norpseudoephedrine (*threo*-X) afforded *threo*-XI by both routes, whose NMR spectra also exhibited no signals due to *erythro*-XI. Moreover, the ratios of diastereomers did not change under this catalytic hydrogenation condition as shown in a subsequent paper.[5] Therefore, analyses of diastereomeric ratios in reduction products by NMR were performed after deacylation and/or debenzylation under the above conditions except for VI. As reported in a previous paper on *threo*-XI and *erythro*-XI,[1] separation of signals in NMR spectra of diastereomeric pairs of *threo*-XII and *erythro*-XII, as well as *threo*-XIII and *erythro*-XIII, went quite well at benzylic protons, as shown in Chart 1.

Reduction of ketones (II—IX) with sodium borohydride was performed in ethanol under reflux. Marked differences in stereoselectivities were observed, as shown in Table I. Clearly, it is impossible to predict the stereochemical course of these data simply by a five-membered cyclic model.[6]

It is apparent that the stereochemical course of the reduction changes gradually from an *erythro*-rich product to a *threo*-rich product as the number of substituents attached to the

TABLE I. Diastereomeric Ratios in Reduction Products



starting material *threo*-isomer *erythro*-isomer

Compound	X	*threo*:*erythro*
I	NH_2HCl	1 : 11.5[a]
II	$NHCH_2C_6H_5HCl$	1 : 7—8
III	$NHCOCH_3$	3 : 10
IV	$NHCOCF_3$	3 : 10
V	$NHCOC_6H_5$	3 : 10
VI	$N(CH_3)_2HCl$	1—1.5 : 1
VII	$N(CH_3)CH_2C_6H_5HCl$	3 : 1
VIII	$N(CH_3)CH_2C_6H_5$	7—8 : 1
IX	$N(CH_2C_6H_5)COC_6H_5$	7—8 : 1

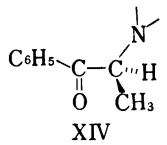
a) reference 1

5) K. Koga, Y. Yamamoto, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), to be submitted.
6) *a*) D.J. Cram and K.R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959); *b*) D.J. Cram and D.R. Wilson, *ibid.*, **85**, 1245 (1963); *c*) S. Yamada and K. Koga, "Selective Organic Transformations," Vol. 1, ed. by B.S. Thyagarajan, Wiley-Interscience, New York, 1970, p. 1.

amino group in I increases. The increase in steric bulkiness of the substituent also seems to show the same tendency. Although the basic character of the nitrogen functional groups in these ketones differs widely, this does not seem to contribute to changes in the stereochemical course. Therefore, we concluded that the steric bulkiness of the nitrogen groups in ketones (II—IX) is the main reason for changes in the stereochemical course.

Although it is not certain what influence the existence of hydrochloric acid has in the reaction of I, II, VI, and VII, the following general rule may be stated, from the synthetic point of view, for the sodium borohydride reduction of 2-aminoketone derivatives. "Substitution for the two hydrogens of the amino group by two effectively bulky groups is important for the synthesis of *threo*-isomer, while at least one of the two hydrogens of the amino group must be left attached for the synthesis of *erythro*-isomer."

Assuming that the transition state of the reduction is reactant-like, the stereochemical outcome of the present data may be posited as the approach of hydride ion in conformation XIV, in which the carbonyl oxygen and the bulky nitrogen group orient themselves in *trans* position due to steric reasons. This empirical model is conformationally similar to the dipolar model[6b,7] proposed for the electronic phenomena in the reactions of α-halo ketones. However, it is also important to consider the relative stabilities of the diastereomers produced.[8] Although efforts to obtain an equilibrium mixture of diastereomers with aluminum isopropoxide, palladium on charcoal, and Raney nickel were unsuccessful, details of this point will be reported in the future.



XIV

Experimental[9]

Materials——$NaBH_4$ was purchased from Kawaken Fine Chemicals Co. Ltd. and its purity was assumed to be 95%. Commercial AcOH, special grade, was used as solvent to measure NMR spectra. Starting materials were prepared according to the reported methods.

2-Benzylaminopropiophenone Hydrochloride (II)——mp 188—190° (reported[10] mp 189—190°). IR ν_{max}^{KBr} cm^{-1}: 1695 (C=O). *Anal.* Calcd. for $C_{16}H_{17}ONHCl$: N, 5.08. Found: N, 5.30.

2-Acetamidopropiophenone (III)——mp 87—89° (reported[11] mp 90—91°). IR ν_{max}^{KBr} cm^{-1}: 1693 (C=O). *Anal.* Calcd. for $C_{11}H_{13}O_2N$: N, 7.33. Found: N, 7.50.

2-Trifluoroacetamidopropiophenone (IV)——This sample was prepared from 2-aminopropiophenone hydrochloride (I)[1] in a manner similar to that for the preparation of III. mp 76—77.5°. IR ν_{max}^{KBr} cm^{-1}: 3342 (NH), 1725 (amide), 1680 (C=O). *Anal.* Calcd. for $C_{11}H_{10}O_2NF_3$: N, 5.71. Found: N, 5.89.

2-Benzamidopropiophenone (V)——mp 104—106° (reported[12] mp 104—105°). IR ν_{max}^{KBr} cm^{-1}: 1689 (C=O). *Anal.* Calcd. for $C_{16}H_{15}O_2N$: N, 5.53. Found: 5.38.

2-(N,N-Dimethylamino)propiophenone Hydrochloride (VI)——mp 204—204.5° (decomp.) (reported[4b] mp 202—204° (decomp.)). IR ν_{max}^{KBr} cm^{-1}: 1698 (C=O). *Anal.* Calcd. for $C_{11}H_{15}ONHCl$: N, 6.56. Found: N, 6.77.

2-(N-Benzyl-N-methylamino)propiophenone (VIII)——bp 142—144° (0.025 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 1688 (C=O).

Hydrochloride (VII): mp 177—178° (decomp.) (reported[13] mp 174—175° (decomp.)). IR ν_{max}^{KBr} cm^{-1}: 1696 (C=O). *Anal.* Calcd. for $C_{17}H_{19}ONHCl$: N, 4.86. Found: N, 4.62.

2-(N-Benzylbenzamido)propiophenone (IX)——mp 93.5—95.5° (reported[4c] mp 97—98°). IR ν_{max}^{KBr} cm^{-1}:

7) J.W. Cornforth, R.H. Cornforth, and K.K. Mathews, *J. Chem. Soc.*, **1959**, 112.
8) G.J. Karabatsos and T.H. Althuis, *Tetrahedron Letters*, **1967**, 4911.
9) All melting and boiling points are uncorrected. IR spectra were measured with a Koken DS-402G spectrometer and NMR spectra were measured with a JNM 3H-60 spectrometer operating at 60 MHz using TMS as an internal standard. Microanalyses and spectral measurements were performed by the members of the Central Analysis Room of this Faculty.
10) S.D. Wilson and L-h. Sun, *J. Chinese Chem. Soc.*, **2**, 243 (1934); *C. A.*, **29**, 758 (1953).
11) M. Bachstez, *Ber.*, **47**, 3163 (1914).
12) G.H. Cleland and C. Niemann, *J. Am. Chem. Soc.*, **71**, 841 (1949).
13) H.D. Müller and B. Renk, *Ann.*, **600**, 239 (1956).

1684 (C=O). *Anal.* Calcd. for $C_{23}H_{21}O_2N$: N, 4.08. Found: N, 4.23.

***l*-Ephedrine (*erythro*-XII)**——The corresponding hydrochloride obtained commercially was made free in the usual manner. NMR (in AcOH) τ: 8.91 (3H, doublet, $J=6$ Hz, CH_3-CH-), 7.15 (3H, singlet, -NCH_3), ~6.5 (1H, multiplet, CH_3-CH(NH-)-CH-), 4.72 (1H, doublet, $J=3$ Hz, C_6H_5-CH(OH)-CH-), 2.68 (5H, singlet, C_6H_5-).

Hydrochloride: mp 214—214.5° (reported[14] mp 216—217°). *Anal.* Calcd. for $C_{10}H_{15}ONHCl$: N, 6.95. Found: N, 6.87.

N-Methyl-*l*-ephedrine (*erythro*-XIII)——mp 84—85° (reported[14] mp 87—87.5°). NMR (in AcOH) τ: 8.89 (3H, doublet, $J=6$ Hz, CH_3-CH), 7.02 (6H, singlet, -$N(CH_3)_2$), 4.53 (1H, doublet, $J=1.8$ Hz, C_6H_5-CH-(OH)-CH-), 2.65 (5H, singlet, C_6H_5-).

DL-Norephedrine (*erythro*-XI)——a) A suspension of *erythro*-X[15] (510 mg, 2 mmoles) and $LiAlH_4$ (300 mg, 8 mmoles) in THF (50 ml) was refluxed for 5 hr. 10% aq. NaOH (0.45 ml) and H_2O (1.05 ml) was added to the reaction mixture. Precipitates were filtered off and washed with a small amount of THF. The combined filtrate and the washings were evaporated *in vacuo* to give an oil (480 mg), which was subjected to hydrogenolysis with 5% Pd-C (250 mg) in EtOH (30 ml) at the atmospheric pressure of H_2. The catalyst was filtered off and washed with a small amount of EtOH.

The combined filtrate and washings were evaporated to dryness *in vacuo* to give crude *erythro*-XI (280 mg, 93% yield). The NMR spectrum of this sample in AcOH was identical with that of an authentic specimen.[1] No signals at τ 5.33 due to *threo*-XI were observed.

b) A mixture of *erythro*-X[15] (510 mg) in 30% aq. KOH (12 ml) and EtOH (6 ml) was refluxed for 8 hr. The reaction mixture was extracted with ether continuously. The ether solution was dried over anhyd. Na_2SO_4. Evaporation of the ether solution to dryness *in vacuo* afforded crude *erythro*-XI (290 mg, 97% yield), whose NMR spectrum was superimposable with that of the authentic specimen.[1] No signals at τ 5.33 due to *threo*-XI were observed.

DL-Norpseudoephedrine (*threo*-XI)——a) A sample of *threo*-X (prepared according to the reported method,[14] mp 127.5—129° (reported mp 128°)) (510 mg) was reduced with $LiAlH_4$, then subjected to hydrogenolysis (as with *erythro*-X) to give crude *threo*-XI (270 mg, 90% yield). The NMR spectrum of this sample in AcOH was superimposable with that of an authentic specimen.[1] No signals at τ 4.80 due to *erythro*-XI were observed.

b) A sample of *threo*-X (510 mg) was hydrolyzed and its product was extracted (as with *erythro*-X) to give crude *threo*-XI (290 mg, 97% yield). The NMR spectrum of this sample in AcOH was superimposable with that of an authentic specimen.[1] No signals at τ 4.80 due to *erythro*-XI were observed.

General Procedure for the Reduction of Ketones (II—IX) with Sodium Borohydride——Reduction of ketones (1 mmoles) was carried out with $NaBH_4$ (3 mmoles for III, IV, V, VIII, and IX; 4 mmoles for II, VI, and VII) in EtOH (20 ml) under reflux for 5 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was taken up in H_2O and the whole was extracted continuously with ether. The ether extract was dried over anhyd. Na_2SO_4, and evaporated to dryness to give the reduction products.

Analyses of Reduction Products——Reduction products were analyzed directly by NMR[1] with VI; after deacylation with KOH in aq. EtOH with III, IV, and V; after debenzylation with II, VII, and VIII; and after hydrolysis followed by debenzylation with IX, as described above. Results are shown in Table I in a summarized form.

Examinations on the synthetic mixture of diastereomers revealed that 4.4% contamination of one diastereomer in the other diastereomer could be detected by the present NMR method.

14) W.N. Nagai and S. Kanao, *Ann.*, **470**, 157 (1929).
15) K. Koga, H. Matsuo, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 243 (1966).