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Stereochemical Studies. VI.[1] Steric Course of Intramolecular Alkylations using optically Active Amine Derivatives

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The following C–C bond formation from C–N bond were stereochemically investigated. The reaction of (*S*)-XII with $Na_2S_2O_4$, (*S*)-XIII with HgO and α-elimination of (*S*)-XIV, all gave (*R*)-XV in 50—70% yields with about 30% retention of configuration. Reaction of (*R*)-XVI with HgO afforded (*S*)-XVIII with the same degree of retention of configuration. Preliminary experiments on racemic compounds are also reported.

Dialkylamino nitrene (I) is known to be generated by reduction of N-nitroso-dialkylamine (II), oxidation of 1,1-dialkyl hydrazine (III), and α-elimination reaction of N-benzenesulfonyl-N′,N′-dialkylhydrazine (IV), and shows several interesting reactions, such as dimerization to a tetrazene derivative, fragmentation to olefins, and intramolecular alkylation with the elimination of the nitrogen molecule.[3]

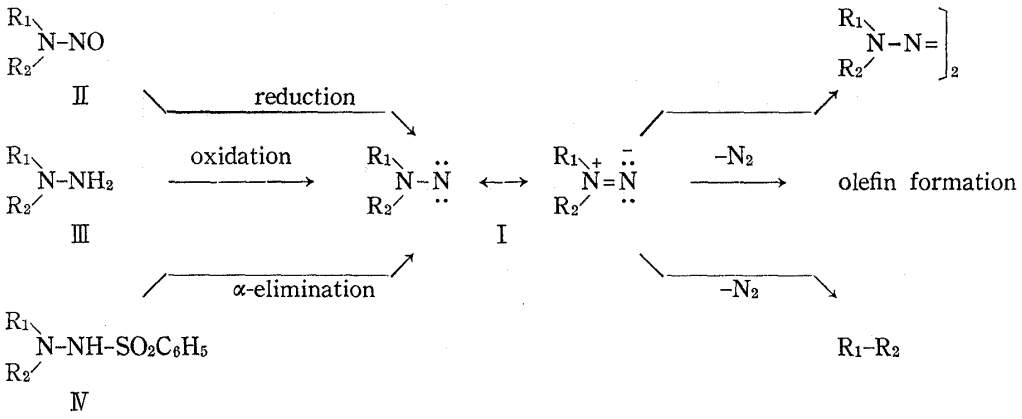

Chart 1

In order to prepare optically active hydrocarbon (VI) from optically active amine (V) by the direct displacement of amino group to alkyl group at an asymmetric center, we paid much attention to the intramolecular alkylation of I, since derivatives of amines such as II, III, IV are considered to be easily obtained from V.

This intramolecular reaction has been studied in detail by Overberger and his school.[3,4] They disclosed that piperidine derivatives (VII) afforded cyclopentane derivative (VIII) stereospecifically,[5,6] but con-

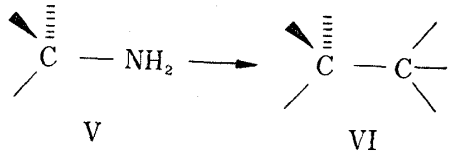

Chart 2

1) Part V: S. Terashima, M. Nara, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **18**, 1124 (1970).
2) Location: *Hongo, Tokyo.*
3) R.A. Abramovitch and B.A. Davis, *Chem. Rev.*, **64**, 149 (1964).
4) C.G. Overberger, M. Valentine, and J.P. Anselme, *J. Am. Chem. Soc.*, **91**, 687 (1969), and references therein.
5) C.G. Overberger, J.G. Lombardino, and R.G. Hiskey, *J. Am. Chem. Soc.*, **79**, 6430 (1957).
6) C.G. Overberger, J.G. Lombardino, and R.G. Hiskey, *J. Am. Chem. Soc.*, **80**, 3009 (1958).

siderable racemization[7] was observed in the conversion of open chain compounds such as IX to the optically active hydrocarbon (Xa).[8] In the latter case, formation of mesohydrocarbon (Xb) was also observed.

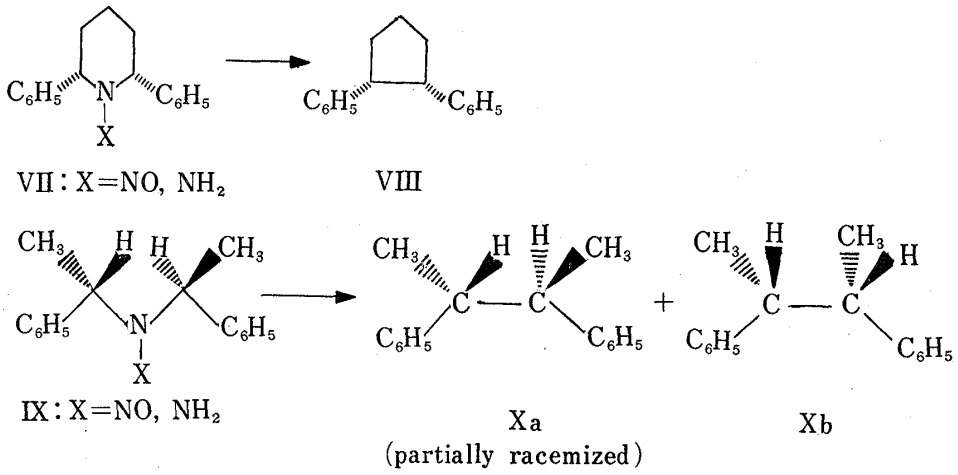

Chart 3

In this intramolecular alkylation, the steric course and percentage of configuration retention have never been studied using a reaction system which involves only one asymmetric carbon. We undertook this alkylation reaction using optically active (*S*)(−)-α-phenethylamine ((*S*)(−)-XIa)[9] carrying only one asymmetric carbon and having a very simple structure, since the stereospecificity of a reaction at the asymmetric center is most important in examining the availability of the reaction itself.

As shown in Chart 4, condensation of (*S*)(−)-α-phenethylamine ((*S*)(−)-XIa), $[\alpha]_D^{33.5}$ −31.3° (ethanol) (100% optically pure)[10] with benzaldehyde, followed by reduction with $LiAlH_4$, gave (*S*)(−)-N-benzyl-α-phenethylamine ((*S*)(−)-XIb),[11] $[\alpha]_D^{28.5}$ −56.9° (ethanol), which was

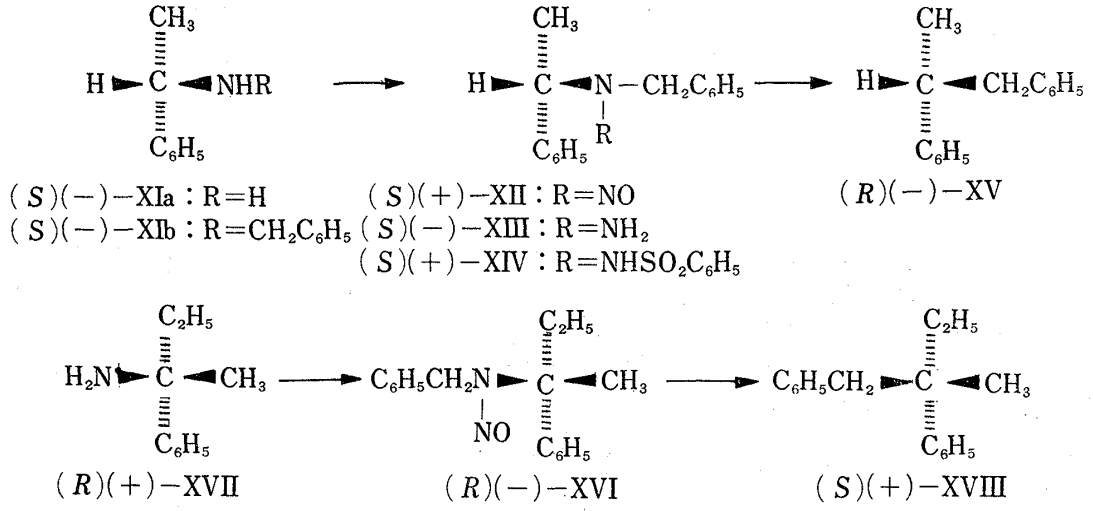

Chart 4

7) According to ref. 8, optically active Xa obtained in a 30—40% yield, shows 36% retention of its optical activity. However, since the starting material (IX) carries two asymmetric carbons which participate in the reaction, meso-hydrocarbon (Xb) was also formed in a 20—30% yield. Thus, this value for retention of optical activity is considered inadequate for the criterion of stereospecificity.

8) C.G. Overberger, N.P. Marullo, and R.G. Hiskey, *J. Am. Chem. Soc.*, **83**, 1374 (1961).

9) W. Leithe, *Monatsh. Chem.*, **51**, 381 (1929).

10) (*S*)(−)-IXa showing $[\alpha]_D^{20}$ −31.5° (*c*=3.2, EtOH), was assumed to be 100% optically pure (See ref. 9).

submitted to nitrosation, affording (*S*)(+)-N-benzyl-N-nitroso-α-phenethylamine ((*S*)(+)-XII), $[\alpha]_D^{30.5}$ +43.4° (ethanol). (*S*)(+)-XII was reduced with $LiAlH_4$ giving (*S*)(−)-N-benzyl-N-α-phenethyl-hydrazine ((*S*)(−)-XIII), $[\alpha]_D^{31.5}$ −27.3° (ethanol). Treatment of (*S*)(−)-XIII with benzenesulfonyl chloride-triethylamine in dimethyl formamide gave (*S*)(+)-N-benzenesulfonyl-N′-benzyl-N′-α-phenethyl-hydrazine ((*S*)(+)-XIV), $[\alpha]_D^{30}$ +18.9° (ethanol). Using the procedures described in the literature, reduction of (*S*)(+)-XII with sodium hydrosulfite,[8] oxidation of (*S*)(−)-XIII with mercuric oxide,[8] and α-elimination reaction[12] with a base were undertaken. (−)-2,3-diphenylpropane ((−)-XV) was isolated from the reaction mixture. The results are summarized in the following Table with results of preliminary experiments using racemic compounds.

Table I. Results of Intramolecular Alkylations under Varing Conditions

Run. No.	Starting material	Reagents	Compds.	Reaction products: Crude yield (%)	Optical rotations of crude samples	Reten. of config(%) (crude sample)	Optical rotations of pure sample[a]	Reten. of config[a] (%) (pure sample)*1
1	(±)-XII	$Na_2S_2O_4$ –NaOH	(±)-XV	51				
2	(*S*)(+)-XII	$Na_2S_2O_4$ –NaOH	(*R*)(−)-XV	61	$[\alpha]_D^{31.5}$ −23.6° ($CHCl_3$)	29[b]	$[\alpha]_D^{25}$ −24.4° ($CHCl_3$)	31[b]
3	(±)-XIII	HgO	(±)-XV	48				
4	(*S*)(−)-XIII	HgO	(*R*)(−)-XV	51	$[\alpha]_D^{34}$ −19.4° ($CHCl_3$)	24[b]		
5	(±)-XIV	NaOH	(±)-XV	62				
6	(*S*)(+)-XIV	NaOH	(*R*)(−)-XV	51	$[\alpha]_D^{30.5}$ −22.8° ($CHCl_3$)	28[b]		
7	(*S*)(+)-XIV	CH_3ONa	(*R*)(−)-XV	71	$[\alpha]_D^{34}$ −22.9° ($CHCl_3$)	29[b]		
8	(*S*)(+)-XIV	*t*-BuOK	(*R*)(−)-XV	73	$[\alpha]_D^{32.5}$ −19.6° ($CHCl_3$)	25[b]		
9	(±)-XVI	$Na_2S_2O_4$ ·NaOH	(±)-XVIII	46				
10	(*R*)(−)-XVI	$Na_2S_2O_4$ ·NaOH	(*S*)(+)-XVIII	36	α_D^{26} +1.885° (l=0.1, neat)	28[e]	α_D^{20} +2.130° (l=0.1, neat)	32[c]

a) obtained by purification of the crude saample by column chromatography
b) See ref. 15 and 16. *c*) See ref. 21.

This (−)-XV was identified by comparison of its infrared and nuclear magnetic resonance (NMR) spectra with those of authentic (±)-XV prepared by the reduction of (±)-α-methyldeoxybenzoin.[13]

Based on absolute configuration and optical purity of (*S*)(+)-XV, which were recently established by Watson, *et al.*,[14] it is evident that these three types of intramolecular alkylations produced (*R*)(−)-XV with about 30% retention of configuration.[15,16]

11) K. Prark, *J. prakt. Chem.*, **86**, 285 (1912).
12) L.A. Carpino, *J. Am. Chem. Soc.*, **79**, 4427 (1957).
13) V. Meyer and L. Oelkers, *Ber.*, **21**, 1925 (1888).
14) H.B. Watson and G.W. Toungson, *J. Chem. Soc.*, **1968**, 258.
15) (*S*)(+)-XV showing $[\alpha]_D^{20}$ +80.7° ($CHCl_3$), was assumed to be 100% optically pure (See ref. 14).
16) As shown in the Table, measurements of optical rotation of (−)-XV were performed using samples containing small amounts of impurities in runs 4, 6, 7, 8. These impurities were considered to be the same as those in run 2 based on gas chromatographic analyses. Also in run 2, complete purification of the reaction product gave no serious change in its retention of configuration. In runs 4, 6, 7, 8, also, the impurities in (−)-XV did not seem to seriously affect the calculation percentage of configuration retention.

When the reaction conditions were changed as in the case of (*S*)(+)-XIV, considerable improvement in yields of (−)-XV was also observed.

From these results, it is obvious that the three reactions studied were not very effective for the preparation of highly optically active VI from V, but chemical correlation between optically active V and VI can be accomplished with these intramolecular alkylations.

As one of the reasons for racemization of reaction product, it is thought that dialkylamino nitrene (I) (R_1=α-phenethyl; R_2=benzyl) generated from (*S*)(+)-XII, (*S*)(−)-XIII, and (*S*)(+)-XIV, contains an α-phenethyl group, and the hydrogen of the benzylic position can be removed as hydrogen ion in the course of the reaction.[17] Accordingly, (*R*)(−)-N-nitroso-N-benzyl-1-methyl-1-phenylpropylamine ((*R*)(−)-XVI), $\alpha_D^{18.5}$ −7.565° (*l*=0.1, neat), having no amine ((*R*)(−)-XVI), α_D^{19} −7.565° (*l*=0.1, neat), having no benzylic hydrogen, was prepared from (*R*)(+)-1-methyl-1-phenylpropylamine[18] ((*R*)(+)-XVII), α_D^{19} +1.503° (*l*=0.1, neat) (100% optically pure),[19] according to the procedure described for (*S*)(+)-XII. This (*R*)(−)-XVI underwent reduction using sodium hydrosulfite, and gave partically racemized (+)-1,2-diphenyl-2-methylbutane[20] ((+)-XVIII), α_D^{20} +2.130° (*l*=0.1, neat). Based on the report from Cram, *et al.*,[21] the (+)-XVIII obtained above, had (*S*)-configuration and was 32% optically pure;[21] that is, (+)-XVIII was prepared with 32% retention of configuration. (+)-XVIII was also confirmed by comparison of its spectral data with data from authentic (±)-XVIII prepared independently.

The results indicate that the hydrogen at the benzylic position took no part in the racemization of (*R*)(−)-XV which was observed in the intramolecular alkylations of (*S*)(+)-XII, (*S*)(−)-XIII and (*S*)(+)-XIV.

Although the precise mechanism for the formation of hydrocarbon from dialkylamino nitrene (I) has not been clear,[4] it is now evident that mechanisms involving heterolytic and/or homolytic cleavage in the solvent cage[17] play an important role in the formation of considerably racemized products, when open chain compounds such as (*S*)(+)-XII, (*S*)(−)-XIII and (*S*)(+)-XIV, undergo intramolecular alkylations.

Experimental[22]

(±)-N-Benzyl-α-phenethylamine ((±)-XIb)——A mixture of (±)-XIa (35.0 g, 0.29 mole) and benzaldehyde (32.0 g, 0.30 mole) in anhyd. benzene (80 ml) was refluxed for 3 hr using Copes' apparatus. After evaporation of the solvent *in vacuo*, the residual Schiffs' base was dissolved in anhyd. ether (100 ml). This ether solution was added to an ether solution (150 ml) of $LiAlH_4$ (5.98 g, 0.156 mole) under stirring and ice-cooling. After refluxing for 2 hr, the metal complex was decomposed by adding H_2O. The ether layer was separated and dried over anhyd. K_2CO_3. An oil obtained by evaporation of the ether solution, underwent fractional destillation, giving (±)-XIb (44.9 g, 74%) as a colorless oil, bp 155—157° (5.6 mmHg) (lit.,[23] bp 176° (19 mmHg)). (±)-XIb was confirmed as its hydrochloride, mp 180—181.5° (recrystallized from H_2O), colorless prisms (lit.,[11] mp 184°).

(*S*)(−)-N-Benzyl-α-phenethylamine ((*S*)(−)-XIb)——The same treatment of (*S*)(−)-XIa ($\alpha_D^{27.5}$ −3.747° (*l*=0.1, neat), $[\alpha]_D^{33.5}$ −31.3° (*c*=2.82, EtOH))[9,10,24] (49.0 g, 0.40 moel) as for (±)-XIa gave (*S*)(−)-XIb

17) C.G. Overberger and N.P. Marullo, *J. Am. Chem. Soc.*, **83**, 1378 (1961).
18) H. Mizuno, S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 1749 (1967).
19) (*R*)(+)-XVII showing $\alpha_D^{9.5}$ +1.516° (*l*=0.1, neat), was assumed to be 100% optically pure (See ref. 18).
20) D.J. Cram and J. Allinger, *J. Am. Chem. Soc.*, **79**, 2864 (1957).
21) (*S*)(+)-XVIII showing α_D^{25} +66.5° (*l*=1, neat), was assumed to be 100% optically pure (See ref. 20).
22) All melting points are uncorrected. Infrared (IR) spectra were measured with Spectrameter, Model IR-S and DS-402, Japan Spectroscopic Co., Ltd. NMR spectra measurements were performed with a Spectrometer Model 3H-60 (60 Mc), Japan Electron Optics Lab using TMS as an internal standard. Optical activities were determined with a Yanagimoto Photo Direct Reading Polarimeter, Model OR-20. Gas chromatographic analyses were performed using Yanagimoto GCG-550-T and Shimazu GC-3AH instruments.
23) H. Bergmann, *Ann.*, **463**, 294 (1928).
24) W. Theilacker and H.G. Winkler, *Ber.*, **87**, 690 (1954).

(66.0 g, 77%) as a colorless oil, bp 133—135° (4 mmHg), $\alpha_D^{28.5}$ −3.911° (l=0.1, neat), $[\alpha]_D^{28.5}$ −56.9° (c=4.504, EtOH) (lit.,[11] bp 171° (15 mmHg), $[\alpha]_D^{20}$ −56.1° (c=3.1, EtOH)).

(±)-N-Benzyl-N-nitroso-α-phenethylamine ((±)-XII)——$NaNO_2$ (23.5 g, 0.34 mole) was added portionwise to a mixture of H_2O (80 ml) and conc. HCl (40 ml) containing (±)-XIb (55.0 g, 0.26 mole) under stirring at 60—65°. This was stirred at the same temperature for 1 hr. The yellow oil which separated was extracted with ether. The combined ether extracts were washed with satd. NaCl and dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave an oil, which underwent fractional distillation under reduced pressure, affording (±)-XII (55.0 g, 87%) as a yellow oil, bp 157—160° (3 mmHg). *Anal.* Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.08; H, 6.84; N, 11.80. IR ν_{max}^{Cap} cm^{-1}: 1605, 1587, 1447, 760, 728, 695. NMR (in CCl_4): 8.83, 8.23 τ (3H, 2 doublets, J=7.2 cps, –CH–C<u>H</u>$_3$), 5.95, 5.50 τ (2H, 2 quartets, J=15 cps, C_6H_5–C<u>H</u>$_2$–), 4.63 τ (1H, quartet, J=7.2 cps, –C<u>H</u>–CH_3), 2.60—3.20 τ (10H, mutilplet, 2 benzene rings' protons).

(*S*)(+)-N-Benzyl-N-nitroso-α-phenethylamine ((*S*)(+)-XII)——(*S*)(−)-XIb (64.0 g, 0.30 mole) was treated the same as (±)-XIb, giving (*S*)(+)-XII (65.0 g, 89%) as a colorless oil, bp 157—159° (4 mmHg), $\alpha_D^{30.5}$ +4.094° (l=0.1, neat), $[\alpha]_D^{30.5}$ +43.4° (c=4.81, EtOH). Infrared and NMR spectra of (*S*)(+)-XII were identical with those of (±)-XII in the same states. *Anal.* Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.60; H, 6.54; N, 11.69.

(±)-N-Benzyl-N-α-phenethyl-hydrazine ((±)-XIII)——An anhyd. ether (15 ml) solution of (±)-XII (4.0 g, 0.017 mole) was added to an anhyd. ether (10 ml) solution containing $LiAlH_4$ (0.8 g, 0.021 mole) under stirring at room temperature. The whole was refluxed under stirring for 3.5 hr. After cooling, H_2O (4 ml) was added to the reaction mixture to decompose the metal complex. The inorganic salt which precipitated was filtered off. The ether layer was dried over anhyd. K_2CO_3, followed by filtration and evaporation *in vacuo*, giving crude (±)-XIII (3.7 g, 100%) as a pale yellow oil. The (±)-XIII obtained, was confirmed by conversion to its hydrochloride, mp 178.5—180° (decomp.) (recrystallized from EtOH–ether). *Anal.* Calcd. for $C_{15}H_{18}N_2 \cdot HCl$: C, 68.56; H, 7.28; N, 10.65. Found: C, 68.61; H, 7.43; N, 10.77. IR ν_{max}^{KBr} cm^{-1}: 2670, 1600, 1525, 767, 697.

(*S*)(−)-N-Benzyl-N-α-phenethyl-hydrazine ((*S*)(−)-XIII)——The same treatment of (*S*)(+)-XII as for (±)-XII gave (*S*)(−)-XIII (31.0 g, 91%) as a pale yelolw oil. This oil solidified as colorless prisms when cooled in an ice bath. $[\alpha]_D^{29.5}$ −23.7° (c=2.245, EtOH). (*S*)(−)-XIII was also confirmed as its hydrochloride, mp 175—176° (decomp.) (recrystallized from EtOH–iso-Pr_2O). *Anal.* Calcd. for $C_{15}H_{18}N_2 \cdot HCl$: C, 68.61; H, 7.28; N, 10.65. Found: C, 68.73; H, 7.27; N, 11.04. IR ν_{max}^{KBr} cm^{-1}: 2690, 1603, 1545, 760, 705. $[\alpha]_D^{31.5}$ −27.3° (c=1.084, EtOH).

(±)-N-Benzenesulfonyl-N′-benzyl-N′-α-phenethyl-hydrazine ((±)-XIV)——Benzenesulfonyl chloride (7.0 g, 0.040 mole) was added to a mixture of (±)-XIII (8.6 g, 0.040 mole) and triethylamine (4.0 g, 0.040 mole) in dimethyl formamide (16 ml) under stirring at 10—15°. Stirring was continued for 1.5 hr at the same temperature. H_2O (30 ml) was added to the reaction mixture, and extracted with benzene. Combined benzene extracts were successively washed with 10% AcOH, and satd. NaCl, and dried over anhyd. Na_2SO_4. Filtration and evaporation gave a residue, which was recrystallized from iso-Pr_2O giving (±)-XIV (5.2 g, 36%) as colorless needles, mp 116—118° (decomp.). Further recrystallization from iso-Pr_2O–MeOH afforded a pure sample, which showed a mp of 122—122.5° (decomp.). *Anal.* Calcd. for $C_{21}H_{22}O_2N_2S$: C, 68.82; H, 6.04; N, 7.65. Found: C, 69.07; H, 6.01; N, 7.71. IR ν_{max}^{KBr} cm^{-1}: 3180, 1603, 1586, 1450, 1327, 1164. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3010, 1605, 1495, 1450, 1327, 1160. NMR (in $CDCl_3$): 8.85 τ (3H, doublet, J=7.2 cps, –CH–C<u>H</u>$_3$), 8.46 τ (2H, quartet, J=13.8 cps, C_6H_5–C<u>H</u>$_2$–), 6.22 τ (1H, quartet, J=7.2 cps, –C<u>H</u>–CH_3), 4.55 τ (1H, singlet, N<u>H</u>), 1.96—2.93 τ (15H, multiplet, 3 benzene rings' protons).

(*S*)(+)-N-Benzenesulfonyl-N′-benzyl-N′-α-phenethyl-hydrazine ((*S*)(+)-XIV)——The same treatment of (*S*)(−)-XIII (5.0 g, 0.022 mole) as for (±)-XIII gave an orange oil (8.0 g) after evaporation of the benzene extracts. This oil was purified with column chromatography using silica gel (200 g, solvent hexane–benzene (1:5)), giving (*S*)(+)-XIV (3.2 g, 40%), mp 93—95°. Recrystallization of this sample from iso-Pr_2O afforded pure (*S*)(+)-XIV as colorless crystals showing mp 95.0—95.5° and $[\alpha]_D^{30}$ +18.9° (c=1.100, EtOH). *Anal.* Calcd. for $C_{21}H_{22}O_2N_2S$: C, 68.82; H, 6.04; N, 7.65. Found: C, 68.66; H, 5.99; N, 7.75. IR ν_{max}^{KBr} cm^{-1}: 3180, 1606, 1585, 1450, 1337, 1166. The infrared spectrum of (*S*)(+)-XIV in chloroform solution was identical with that of (+)-XIV in the same state. The NMR spectrum of (*S*)(±)-XIV was also superimposable on that of (±)-XIV in the same state.

(±)-N-Benzyl-1-methyl-1-phenylpropylamine——Anyhd. benzene (50 ml) containing (±)-XVII[18] (5.5 g, 0.038 mole), benzaldehyde (6.0 g, 0.056 mole) and a catalytic amount of *p*-toluenesulfonic acid, was refluxed for 2.5 hr using Copes' apparatus. The solvent and an excess amount of benzaldehyde were then evaporated *in vacuo*. Anhyd. ether (25 ml) was added to the residual oil, and the whole was added to an ether (25 ml) solution of $LiAlH_4$ (1.2 g, 0.031 mole). The reaction mixture was refluxed for 4.5 hr. The metal complex was decomposed by the addition of H_2O (5 ml) under ice-cooling. Inorganic salt was filtered off, and washed with ether. The combined filtrate and washings were washed with satd. NaCl, and dried over anhyd. K_2CO_3. Filtration and evaporation *in vacuo* gave the objective amine (7.3 g, 82%) as a colorless oil, bp 153—155° (3 mmHg). IR ν_{max}^{KBr} cm^{-1}: 3350, 1600, 1500, 1450, 755. This amine was confirmed as its hydrochloride,

which was recrystallized from iso-Pr_2O–MeOH as colorless plates and showed a mp of 241—242° (decomp.). *Anal.* Calcd. for $C_{17}H_{21}N \cdot HCl$: C, 74.03; H, 7.68; N, 5.07. Found: C, 73.82; H, 8.04; N, 5.33. IR ν_{max}^{KBr} cm^{-1}: 2700 (broad), 1590, 1450.

(*R*)(−)-N-Benzyl-1-methyl-1-phenylpropylamine——(*R*)(+)-XVII[18] (α_D^{19} +1.503° (l=0.1, neat)) (lit.,[18] $\alpha_D^{9.5}$ +1.516° (l=0.1, neat)) (5.0 g, 0.034 mole) was treated the same as (±)-XVII, affording the objective amine (6.5 g, 81%) as a colorless oil, bp 152—153° (5 mmHg), α_D^{17} −3.129° (l=0.1, neat), $[\alpha]_D^{17}$ −32.7° (c=0.491, EtOH). The infrared spectrum of this sample was superimposable on that of the racemic compound in the same state. This optically active amine was confirmed by conversion to its hydrochloride, which was recrystallized from iso-Pr_2O–MeOH as colorless plates, and showed a mp of 231—233°. *Anal.* Calcd. for $C_{17}H_{21}N \cdot HCl$: C, 74.03; H, 7.68; N, 5.07. Found: C, 74.01; H, 7.87; N, 5.14. IR ν_{max}^{KBr} cm^{-1}: 2700 (broad), 1590, 1450.

(±)-N-Benzyl-1-methyl-N-nitroso-1-phenylpropylamine ((±)-XVI)——$NaNO_2$ (4.7 g, 0.068 mole) was added portionwise to a mixture of (±)-N-benzyl-1-methyl-1-phenylpropylamine (8.2 g, 0.034 mole), benzene (40 ml), H_2O (30 ml), and conc. HCl (8.5 ml) under stirring at 65—70°. Stirring was continued for 40 min at the same temperature. After cooling, the benzene layer was separated, and the lower aqueous layer was extracted with benzene. Combined organic layers were washed with satd. NaCl, and dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave a residual oil, which underwent fractional distillation, giving (±)-XVI (8.3 g, 90%) as a yellow oil, bp 180—182° (3 mmHg). *Anal.* Calcd. for $C_{17}H_{20}ON_2$: C, 76.08; H, 7.81; N, 10.44. Found: C, 76.07; H, 7.32; N, 10.47. IR ν_{max}^{Cap} cm^{-1}: 1603, 1590, 1500, 1440, 1130, 760. NMR (in CCl_4): 9.15 τ (3H, triplet, J=7.2 cps, $-CH_2-C\underline{H}_3$), 8.23 τ (3H, singlet, $-\underset{|}{\overset{|}{C}}-C\underline{H}_3$), 7.56 τ (2H, multiplet, $-C\underline{H}_2-CH_3$), 5.52 τ (2H, quartet, J=15.0 cps, $C_6H_5-C\underline{H}_2-$), 2.50—3.20 τ (10H, multiplet, 2 benzene rings' protons).

(*R*)(−)-N-Benzyl-1-methyl-N-nitroso-1-phenylpropylamine ((*R*)(−)-XVI)——The same treatment of (*R*)(−)-N-benzyl-1-methyl-1-phenylpropylamine (6.0 g, 0.025 mole) as for the racemic compound, giving (*R*)(−)-XVI (5.8 g, 86%) as a yellow oil, bp 182—183° (3 mmHg), $\alpha_D^{18.5}$ −7.565 (l=0.1, neat). *Anal.* Calcd. for $C_{17}H_{20}ON_2$: C, 76.08; H, 7.51; N, 10.44. Found: C, 75.90; H, 7.44; N, 10.49. Infrared and NMR spectra of this sample were identical with those of (±)-XVI in the same states.

(±)-1,2-Diphenylpropane ((±)-XV)——A mixture of (±)-α-methyldesoxybenzoin[13] (5.0 g, 0.024 mole), 80% hydrazine hydrate (3. 0ml), and NaOH (2.5 g) in diethylene glycol (40 ml) was refluxed for 1 hr at *ca.* 160°. The temperature of the reaction mixture was gradually raised in order to distilled H_2O and an excess amount of hydrazine; it was kept at 195—210° for 3 hr. After cooling, the mixture was poured into H_2O (160 ml) and extracted with ether. The ether layer was washed with 10% HCl and satd. NaCl, and dried over anhyd. Na_2SO_4. Filtration and evaporation gave an oil, which was purified with column chromatography using slica gel (15 g, solvent hexane–benzene (4:1)). This crude (±)-XV underwent fractional distillation affording pure (±)-XV (3.0 g, 64%) as a colorless oil, bp 110—111° (2.5 mmHg). *Anal.* Calcd. for $C_{15}H_{16}$: C, 91.78; H, 8.22. Found: C, 91.48; H, 8.22. IR ν_{max}^{Cap} cm^{-1}: 1604, 1500, 1455, 755. NMR (in CCl_4): 8.78 τ (3H, doublet, J=7.2 cps, $-C\underline{H}_3$), 6.85—7.36 τ (3H, multiplet, $C_6H_5-C\underline{H}-C\underline{H}_2-C_6H_5$), 2.63—3.26 τ (10H, multiplet, 2 benzene rings' protons). Gas chromatographic analysis[25] of this oil showed single peaks, whose retention times were 5.7 min (A; 212°) and 7.4 min (B; 190°), respectively. The (±)-XV prepared above was used as the authentic sample for intramolecular alkylation.

(±)-1,2-Diphenyl-2-methylbutane ((±)-XVIII)——The acid chloride (7.5 g), bp 92—93° (2 mmHg), prepared from (±)-2-methyl-2-phenylbutyric acid[18] (7.0 g, 0.042 mole) in a 96% yield by the treatment with $SOCl_2$ in ether, was dissolved in ether (130 ml), and added to an ether (130 ml) solution of diphenyl cadmium prepared from phenylmagnesium bromide (0.055 mole) and $CdCl_2$ (5.5 g, 0.030 mole). The whole was refluxed for 6 hr, and then evaporated. Toluene (60 ml) was added to the residue, and refluxing and stirring were continued for 3 hr. The metal complex was decomposed by adding 5% H_2SO_4 under ice-cooling, and the organic layer was separated. The aqueous layer was further extracted with benzene. The combined organic layers were washed with satd. $NaHCO_3$ and satd. NaCl. After being dried over anhyd. Na_2SO_4, the organic layer was evaporated *in vacuo*, giving an oily residue (8.1 g), which was purified using column chromatography with silica gel (300 g, solvent hexane–benzene (1:1), followed by fractional distillation giving (±)-(2-methyl-2-phenyl)butyrophenone (6.1 g, 64%) as a pale yellow oil, bp 156—159° (5 mmHg). *Anal.* Calcd. for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.58; H, 7.56. IR ν_{max}^{Cap} cm^{-1}: 1683, 1600, 1580, 964, 760. This (±)-(2-methyl-2-phenyl)butyrophenone (3.0 g, 0.013 mole) was reduced using the Huang-Minlon procedure, as was the case for (±)-XV, giving (±)-XVIII (0.6 g, 21%) as a colorless oil, bp 135—136° (4 mmHg). *Anal.* Calcd. for $C_{17}H_{20}$: C, 91.01; H, 8.99. Found: C, 91.04; H, 9.10. IR ν_{max}^{Cap} cm^{-1}: 1603, 1500, 1450, 1380, 760, 745. NMR (in CCl_4): 9.33 τ (3H, triplet, J=7.2 cps, $-CH_2-C\underline{H}_3$), 8.80 τ (3H, singlet, $>C-C\underline{H}_3$), 8.30 τ (2H, multiplet, $-C\underline{H}_2-CH_3$), 7.15 τ (2H, quartet, J=13.2 cps, $C_6H_5-C\underline{H}_2-$), 2.75—3.50 τ (10H, multiplet, 2 benzene rings' protons). Gas chromatographic analysis[25] of (±)-XVIII showed

25) Gas chromatographic analyses were performed using the following conditions: (A) Carbowax 20M on Diasolid L, 2.1 m; (B) 20% SE-30 on Diasolid L, 1.5 m.

only one peak whose retention time was 6.7 min (A; 220°). This sample was used as the authentic sample in the comparisons of products from (±)-XVI and (*R*)(−)-XVI.

Reduction of (±)- and (*S*)(+)-N-benzyl-N-nitroso-α-phenethylamine ((±)- and (*S*)(+)-XII) with $Na_2S_2O_4$——a) Reduction of (±)-XII: $Na_2S_2O_4$ (3.5 g, 0.020 mole) was added to a mixture of (±)-XII (2.4 g, 0.010 mole) and 20% NaOH (30 ml) in EtOH (30 ml) under stirring and in a nitrogen atmosphere at 60—64°. Stirring was continued for 4.5 hr at the same temperature, and the oil which separated from the reaction mixture was extracted with ether. The ether extract was successively washed with satd. NaCl, 10% HCl, and satd. NaCl, and dried over anhyd. Na_2SO_4. Filtration and evaporation afforded a pale yellow oil (1.4 g), which was purified by column chromatography using silica gel (40 g, solvent hexane), giving (±)-XV as an oil. This oil underwent fractional distillation to give (±)-XV (1.0 g, 51%) as a colorless oil, bp 108—109° (3 mmHg). Infrared and NMR spectra of this sample were identical with those of the authentic (±)-XV in their respective states. However, gas chromatographic analysis [25](B; 190°) clearly demonstrated that this sample contained a small amount of impurity (retention time, 9.0 min) other than (±)-XV (retention time, 7.4 min).

b) **Reduction of (*S*) (+)-XII**: The same treatment of (*S*) (+)-XII (7.2 g, 0.030 mole) with $Na_2S_2O_4$ as for (±)-XII afforded (*R*) (−)-XV (3.6 g, 61%) as a colorless oil, bp 108—109° (3 mmHg), which showed $[\alpha]_D^{31.5}$ −23.6° (*c*=2.567, $CHCl_3$). The optical purity of (*R*)(−)-XV obtained above, appeared to be 29%. The infrared spectrum of this sample was identical with that of authentic (±)-XV in the same state. Gas chromatographic analysis[25] (B; 190°) of this sample showed the presence of a small amount of impurity (retention time, 9.0 min). Further purification with column chromatography using Al_2O_3 (720 g, solvent hexane) gave pure (*R*)(−)-XV (0.37 g, 6.2%), which showed only one peak on gas chromatographic analysis[25] (A; 212°). It's retention time (5.7 min) was identical with that of the authentic (±)-XV. This oil showed $[\alpha]_D^{25}$ −24.4° (*c*=1.210, $CHCl_3$). Thus, the optical purity of this sample appeared to be 31%.[15] It's infrared spectrum in capillary was superimposable on that of the authentic (±)-XV.

Oxidation of (±)- and (*S*)(−)-N-benzyl-N-α-phenethyl-hydrazine ((±)- and (*S*)(−)-XIII) with HgO——a) Oxidation of (±)-XIII: An ethanol solution (40 ml) of (±)-XIII (4.5 g, 0.020 mole) was added to a suspension of HgO (8.7 g, 0.040 mole) in EtOH (40 ml) under stirring at 60—65° for 30 min. Stirring was continued for an additional hour at the same temperature. Inorganic compounds were filtered off, and the EtOH was evaporated *in vacuo*. Extraction of a neutral fraction from the residue, followed by evaporation *in vacuo*, gave a yellow oil (4.1 g), which was purified with column chromatography using silica gel (82 g, solvent hexane). This underwent fractional distillation, giving (±)-XV (1.9 g, 48%) as a colorless oil, bp 105—106° (3 mmHg). (±)-XV was identified with the authentic sample *via* their infrared and NMR spectra. Gas chromatographic analysis[25] (B; 190°) clearly showed the presence of a small amount of impurity (retention time 9.0 min) besides the (±)-XV.

b) Oxidation of (*S*)(−)-XIII: (*S*)(−)-XIII (2.2 g, 0.010 mole) was treated the same as (±)-XIII, giving (*R*)(−)-XV (1.0 g, 51%) as a colorless oil, bp 105—106.5° (3 mmHg), $[\alpha]_D^{24}$ −19.4° (*c*=2.235, $CHCl_3$). The optical purity of this sample appeared to be 24%.[15] This oil showed the presence of a small amount of impurity (retention time 9.0 min) on gas chromatographic analysis[25] (B; 190°). The infrared spectrum of this sample was identical with that of the authentic (±)-XV in capillary.

α-Elimination Reaction of (±)- and (*S*)(+)-N-benzenesulfonyl-N′-benzyl-N′-α-phenethyl-hydrazine ((±)- and (*S*)(+)-XIV)——a) Reaction of (±)-XIV: An ethanol solution (9 ml) of (±)-XIV (1.5 g, 0.0040 mole) was added to an aqueous 20% NaOH solution (14 ml) under stirring at 60—63°. Evolution of N_2 was observed, immediately. The whole was stirred at the same temperature for 15 min. After evaporation *in vacuo*, the reaction mixture was poured into ice–water. The neutral fraction was extracted with ether as was the case for reactions of (±)-XII and (±)-XIII. This fraction was purified with column chromatography using silica gel (14 g, solvent hexane). Fractional distillation *in vacuo* produced (±)-XV (0.5 g, 62%) as a colorless oil, bp 107—108° (3 mmHg). Infrared and NMR spectra of this oil were identical with those of the authentic (±)-XV in the same states. Gas chromatographic analysis[25] (B; 190°) of this sample demonstrated the presence of a small amount of impurity (retention time 9.0 min).

b) Reaction of (*S*)(+)-XIV: The same treatment of (*S*)(+)-XIV as for (±)-XIV gave (*R*)(−)-XV (0.4 g, 51%) as a colorless oil, bp 105—106° (3 mmHg), $[\alpha]_D^{30.5}$ −22.8° (*c*=1.220, $CHCl_3$). The optical purity of (*R*)(−)-XV appeared to be 28%.[15] Gas chromatographic analysis[25] (B; 190°) showed the presence of a small amount of impurity (retention time 9.0 min) in this oil. The infrared spectrum of (*R*)(−)-XV was identical with the authentic (±)-XV in the same state.

When this reaction was carried out with CH_3ONa in dimethyl sulfoxide (*R*)(−)-XV, showing bp 120—124° (3 mmHg) (bath temp.) and $[\alpha]_D^{24}$ −22.9° (*c*=1.135, $CHCl_3$), was obtained as a colorless oil in a 71% yield. This oil appeared to be 29% optically pure,[15] and to contain a small amount of impurity based on gas chromatographic analysis (B; 190°).[25]

However, when the same reaction was examined using *t*-BuOK in *t*-BuOH, (*R*)(−)-XV was obtained in a 73% yield, showing a bp of 123—126° (3.5 mmHg) (bath temp.) and $[\alpha]_D^{32.5}$ −19.6° (*c*=1.646, $CHCl_3$). Gas chromatographic analysis[25] (B; 190°) of this sample clearly demonstrated the presence of a small amount of impurity (retention time, 9.0 min).

Reduction of (±)- and (*R*)(−)-N-benzyl-1-methyl-N-nitroso-1-phenylpropylamine ((±)- and (*R*)(−)-XVI) with $Na_2S_2O_4$——a) Reduction of (±)-XVI: $Na_2S_2O_4$ (40.0 g, 0.23 mole) was added to a mixture of (±)-XVI (6.0 g, 0.022 mole) and 20% NaOH solution (60 ml) in EtOH (60 ml) under stirring in a N_2 atmosphere at 60—65° for 15 min. The whole was stirred at the same temperature for 5 hr, followed by the treatment used with (±)-XII, giving a neutral fraction (4.5 g) as a pale yellow oil. Column chromatography with silica gel (180 g, solvent hexane) gave the starting material (1.9 g, 32%) and (±)-XVIII. This (±)-XVIII underwent fractional distillation, to give a colorless oil (2.5 g, 46%), bp 131—133° (3 mmHg). Gas chromatographic analysis[25] (A; 220°) of this sample showed the presence of a small amount of impurity (retention time, 7.3 min) other than (±)-XVIII (retention time, 6.7 min). Further purification of crude (±)-XVIII with column chromatography using Al_2O_3 (500 g, solvent hexane) afforded pure (±)-XVIII (0.54 g, 10%) as a colorless oil. This was confirmed with infrared spectrum and gas chromatography.

b) Reduction of (*R*)(−)-XVI: The same treatment of (*R*)(−)-XVI (5.0 g, 0.019 mole) as for (±)-XVI, gave crude (*S*)(+)-XVIII (1.6 g, 36%) as a colorless oil, bp 133—135° (4 mmHg), α_D^{20} +1.885° (*l*=0.1, neat). This sample appeared to be 28% optically pure.[21] Gas chromatographic analysis[25] (A; 220°) demonstrated a presence of a small amount of impurity (retention time, 7.3 min) other than (*S*)(+)-XVIII. Further purification was carried out with column chromatography using Al_2O_3 (320 g, solvent hexane), giving pure (*S*)(+)-XVIII (0.35 g, 7.9%) as a colorless oil, bp 145—148° (4 mmHg) (bath temp.), α_D^{20} +2.130 (*l*=0.1, neat). This sample appeared to be 32% optically pure,[21] and showed only one peak (retention time, 6.7 min) on gas chromatographic analysis[25] (A; 220°), whose retention time was identical with that of the authentic (±)-XVIII. The infrared spectrum of (*S*)(+)-XVIII in capillary was superimposable on that of the authentic sample. In this reaction, recovery of the starting material (1.5 g, 30%) was also observed.

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