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<td>Citation</td>
<td>Bulletin of the Institute for Chemical Research, Kyoto University (1976), 54(3): 119-127</td>
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<tr>
<td>Issue Date</td>
<td>1976-08-31</td>
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<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/2433/76668">http://hdl.handle.net/2433/76668</a></td>
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<tr>
<td>Type</td>
<td>Departmental Bulletin Paper</td>
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Kyoto University
Mechanism of Benzyl Migration from Nitrogen to Carbon in Enamines

Jun’ichi Oda, Takeshi Igarashi, and Yuzo Inouye

Received March 29, 1976

The rearrangement of (R)-N-isobutenyl-N-methyl-benzylamine-a-d was thermally effected to give (R)-2, 2-dimethyl-3-phenyl-propanal-3-d with over-all retention of configuration of the migrating terminus in 91% asymmetric yield. The stereochemical outcome in the present benzyl migration unequivocally established the mechanism to be the sequential N-alkylation, retrogressive dissociation and C-alkylation, with two Walden inversions involved in the process.

INTRODUCTION

In connection with our study1 on the reaction of chiral enamines, it seemed of interest to undertake the elucidation of mechanism of the thermally induced benzyl migration from nitrogen to carbon in enamines.

An example of such rearrangements was demonstrated by Brannock2 who treated N-isobutenyl-N-methyl-benzylamine (1) with methyl iodide in acetonitrile to afford N-isobutenyl-N-methyl-3-phenyl-propanal (2) after hydrolysis of the rearrangement product.

However, three different mechanisms have been proposed for the rearrangements of this category: 1) a direct intramolecular 1,3-shift of benzyl group from nitrogen to carbon (mechanism 1)3; 2) a partial retrogressive dissociation of the first formed ammonium salt into enamine and benzyl halide, followed by an intermolecular nucleophilic displacement between enamine and the ammonium salt (mechanism 2)4; 3) a prior N-alkylation of enamine and subsequent retrogressive dissociation, followed by C-alkylation of enamine with benzyl halide (mechanism 3).4 Although these proposals are all seemingly successful in explaining the rearrangement leading to the end product, no convincing evidence has been presented for each mechanism.
3) \((\text{CH}_3)_2\text{CH}=\text{CH}-\text{N}(\text{CH}_3)_2\) [I\text{---} \text{CH}_2\text{C}_6\text{H}_5] \text{CH}_2\text{C}_6\text{H}_5\text{CH}_2\text{N}(\text{CH}_3)_2\]

Should the intramolecular 1,3-shift mechanism 1 be valid for the present rearrangement, inversion of configuration at the migrating terminus would be duly expected from the Woodward-Hoffmann rule.\(^5\) The inversion would be predicted also for the intermolecular nucleophilic displacement (mechanism 2). In contrast, if the reaction should proceed through the last pathway (mechanism 3), the overall retention of configuration at the migrating terminus would result from two consecutive Walden inversions involved in the process.

In view of a priori consideration mentioned above, we preferred the stereochemical means with an optically active enamine whose chirality was due to the replacement of one hydrogen by deuterium.

RESULTS AND DISCUSSION

The chiral enamine subjected to thermal rearrangement was \((R)-\text{N}-\text{isobutenyl-N-methyl-benzylamine-}\alpha-d\ (11)\), prepared from \((R)-(\text{--})-\text{N}-\text{methylbenzylamine-}\alpha-d\ (10)\) and isobutyraldehyde according to scheme 4. For the preparation of isotopically pure benzylamine-\alpha-d (9), an enzymic process was incorporated with synthesis; 2-phenyl-2-morpholinoacetonitrile (3) was deuterated with deuterium oxide at 100°C in DMF to give the nitrile 4, which on hydrolysis, afforded nearly completely deuterated benzaldehyde (5).\(^6\) Enantiomerically pure \((S)-(\text{--})-\text{benzyl-}\alpha-d\) alcohol (6), \([\alpha]_D 1.45^\circ\), was obtained by reduction of 5 with fermenting bakers' yeast.\(^7\) The benzyl alcohol \((S)-(\text{--})-6\) was converted to the azide 8 via the thermolabile tosylate 7. The lithium aluminum hydride reduction of the azide gave \((R)-(\text{--})-\text{amine} 9, [\alpha]_D -1.7^\circ, which on N-methylation, afforded the desired N-methyl-benzylamine-\alpha-d (10), [\alpha]_D -2.88^\circ. Since it has been established\(^8\) that the reaction of azide ion proceeds with inversion of configuration, the levorotatory amine (10) can be assigned the \(R\)-configuration. The chiral enamine 11 was finally obtained by the condensation of isobutyraldehyde with \((R)-(\text{--})-10\).
The rearrangement of the chiral enamine 11 was thermally effected under the literature conditions to give (+)-2, 2-dimethyl-3-phenyl-propanal-3-d (12). Oxidation of 12 with silver oxide gave (+)-2, 2-dimethyl-3-phenylpropionic-3-d acid (13) in 43% yield, \([\alpha]_D 1.65^\circ\).

The absolute configuration of (+)-13 was determined by the correlation to (S)-(+)-2, 2-dimethyl-3-hydroxy-3-phenylpropionic acid (14a) of the well-defined S-configuration. According to scheme 6, (S)-(+)14a, \([\alpha]_D 8.3^\circ\), was obtained by the Reformatsky reaction of 2-bromo-isobutyric acid with benzaldehyde, followed by optical resolution with (−)-methylbenzylamine. The (+)-acid was transformed to the mesylate 15, which was then reduced with lithium aluminum deuteride to the dextro-rotatory alcohol 16, \([\alpha]_D 6.1^\circ\). Finally, the oxidation of (+)-16 with potassium bichromate afforded the (+)-acid 13, \([\alpha]_D 1.78^\circ\) which proved to be identical with that 13 derived from the rearrangement product.

On the basis of this chemical conversion, the acid (+)-13 can be assigned the R-configuration, since the S-configuration of (+)-14a has been unequivocally established and a Walden inversion at the LAD reduction step was involved in the transformation. The enantiomeric purity is assessed to be 91% based on the maximum rotation 9.02° of the starting acid 14a.

Accordingly, the chiral enamine (R)-11 rearranged on heating to the R-product, which means that the present thermal rearrangement proceeds with retention of configuration at the migrating terminus Ph-CHD, the Cahn-Ingold-Prelog sequence of ligands at the chiral centers being the same before and after the rearrangement.

The present stereochemical outcome thus argues against both intra- and intermolecular migrations of benzyl group which should have been accompanied by inversion of configuration (mechanisms 1 and 2), and cogently supports the last mechanism.
involving the prior $N$-alkylation, retrogressive dissociation, followed by $C$-alkylation.

Further support for this deduction was furnished by the following studies. The corresponding perchlorate 18, derived from the iodide salt 17 by exchange with silver perchlorate, was found completely inert to heating, no alkylated aldehyde having been detected in the hydrolyzate of the reaction mixture (scheme 7). Since no one can find apparent reason why the intramolecular $N\rightarrow C$ shift should be prohibited upon exchanging the gegen anion from iodide to perchlorate, the result, though negative, excludes a direct benzyl group migration defined as 1, 3-sigmatropic rearrangement which demands a suprafacial allylic shift.

![Chemical Structures]

To obtain more information concerning the mechanism, a crossover-recombination experiment was designed: a) an intimate mixture of 1-$N$-morpholino-isobutene-1 (19) and 1-morpholino-2-ethyl-butene-1 (20) was allowed to react with an equimolar benzyl bromide and $p$-methylbenzyl bromide. b) A mixture of the salts 21 and 22 which were readily prepared from the enamines 19 and 20 with the corresponding bromides, was heated in exactly the same manner. In both reactions, the hydrolysis of reaction mixtures resulted in the formation of four cross-hybrids, 2, 2-dimethyl-3-phenyl-propanal (2), 2, 2-dimethyl-3- $p$-xylyl-propanal (23), 2-ethyl-2-benzyl-butyraldehyde (24) and 2-ethyl-2-$p$-xylyl-butyraldehyde (25) in nearly the same distribution as proved by vpc-analysis. (Table I). The same product distribution found for these two reactions clearly shows the congruency of operating species in both systems, which again excludes the direct intramolecular migration of benzyl group and favors the retrogressive dissociation mechanism.

<table>
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<tr>
<th>Products</th>
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<tr>
<td>2</td>
<td>3.0</td>
<td>2.6</td>
</tr>
<tr>
<td>23</td>
<td>3.1</td>
<td>2.7</td>
</tr>
<tr>
<td>24</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>25</td>
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Additional evidence for the mechanism was provided also by another asymmetric system, with $N$-methyl-methylbenzylamine (26) used as the chiral migrating group. When the chiral enamine 27, prepared from (R)-(±)-$N$-methyl-methylbenzylamine (122)
zylamine (26), \([\alpha]_D^{25} 54.4^\circ\) and isobutyraldehyde, was heated with methyl iodide, the aldehyde 28 was obtained after the usual work-up of the reaction mixture. This was transformed by silver oxide oxidation to the acid 29a, whose esterification with diazomethane afforded methyl 2,2-dimethyl-3-phenylbutyrate (29b), \([\alpha]_D^{25} 15.67^\circ\).

The absolute configuration of the acid 29a was correlated to the known (+)-phenylbutyric acid\(^{12}\) (30) according to scheme 9: (S)-(+) acid 30 \([\alpha]_D^{25} 52.4^\circ\) was converted into (-)-29 \([\alpha]_D^{25} 33.48^\circ\), via a-mono methylated acid 31, by means of exhaustive a-methylation with methyl iodide, sodium hydride and butyllithium. The configuration of the chiral center in (S)-(+)30 is not disturbed during this process and is retained as such in the alkylated product 29, but the sequence of ligands at the chiral center in 30 is reversed in the product 29. So that the R-configuration is assigned to (+)-29 and the enantiomeric purity is assessed to be 45% based on that of the starting acid 30.

Consequently, here again the rearrangement of 26 to 28 proceeded with retention of configuration, in conformity with the deduced mechanism. The observed lowering in asymmetric yield may probably be due to the extreme ease with which the immediately formed a-methylbenzyl iodide undergoes racemization.

In conclusion, all the experimental evidence presented in the present study supports the mechanism involving a prior N-quanternization with methyl iodide, and subsequent nucleophilic attack of iodide to the chiral benzylic carbon with liberation of benzyl iodide which in turn undergoes a nucleophilic displacement by enamine. This is consistent with the mechanism proposed by Pandit\(^{13}\) for alkylation of diazamines.
EXPERIMENTAL

The melting and boiling points were uncorrected. Ir-spectra were recorded with a Hitachi 215 spectrophotometer. Pmr-spectra were taken on a Varian EM-360 spectrometer. Elemental analyses were carried out with a Yanagimoto CHN-corder TM-1. Optical rotations were observed on a Yanagimoto OR-50 and a Perkin Elmer R-241. Gas liquid chromatography was on a Shimazu Model 4BPF and a Varian Aerograph A-700.

(R)-(—)-N-Methyl-benzylamine-α-d (10). The titled compound was prepared by the following processes. (a) (S)-(++)-Benzy1-α-d alcohol (6), [α]D5 +1.43°, (neat), was obtained by the prescribed procedure7) from benzaldehyde-α-d (5). (b) Benzyl-α-d tosylate (7). The alcohol 6 (2.1 g) was added to p-toluenesulfonyl chloride (2.9 g) in 25% aqueous sodium hydroxide with stirring at 5°C. After 1.5 hr, an equivalent amount of the chloride in 25% aq. sodium hydroxide was added to the reaction mixture, which was then stirred for further 3 hr at 5°C. The product was poured into ice-water and was extracted with ether. Removal of solvent gave the crystalline tosylate 7. (c) Benzyl-α-d azide (8). The crude tosylate 7 was added to a solution of sodium azide (2 g) in water (5.8 ml) and methanol (26 ml). After stirring at 60°C for 24 hr, the reaction mixture was treated with ice-water and was extracted with ether. Removal of solvent gave an oily product, which was unstable at room temperature, so that it was subjected to the following reduction without further purification. (d) (R)-(—)-Benzy1amine-α-d (9). The reduction of the azide 8 with LAH gave the corresponding amine as an oil in 40% yield: bp 79–81°C (20 Torr), nD5 1.5412, [α]D5 +1.79° (neat). The ir-spectrum was identical with that of the authentic sample.14) (e) (R)-(—)-N-Methyl-benzylamine-α-d (10). The methylation of the amine 9 (1 g) by treating with formic acid (0.5 ml) and formaldehyde (1.2 ml), followed by the LAD reduction, afforded the titled amine 10 in 90% yield. [α]D5 +2.88° (neat), pmr (in CDCl3): δ, 3.52 (s, 3H, N-CH3).

N-Isobutenyl-N-methyl-benzylamine-α-d (11). (R)-(—)-N-Methyl-benzylamine-α-d (10, 1.2 g) was allowed to react with an equimolar isobutyraldehyde (0.6 g) in benzene according to the procedure of Benzing.15) The product was purified by distillation under reduced pressure; bp 54–56°C (1 Torr) yield 2 g (90%), ir: no absorption band at 1700 cm−1 due to νC=O, νν=ω at 1620 cm−1.

(+)-2, 2-Dimethyl-3-phenylpropionic-3-d acid (13). The thermal rearrangement of the enamine 11 (2 g) was effected by the literature procedure to give 2, 2-dimethyl-3-phenylpropanal-3-d (12) in 43% yield: The silver oxide oxidation of the aldehyde 12 afforded the acid 13, whose specific rotation did not alter on repeated recrystallizations from benzene. Yield 300 mg: mp 46–48°C: [α]D8 +1.65° (c, 1.0, MeOH), ir: νν=ω 3000 and 1710 cm−1. pmr (CDCl3): δ, 1.26 (s, 6H, 2CH3), 2.56 (broad s, s, H, CH), 7.27 (s, 5H, aromatic protons) and 10.33 (s, 1H, COOH). Found: C, 73.74; H, 8.16. Calcd for C11H15O2D: C, 73.71; H, 7.94%.
Benzyl Migration from N to C

Absolute assignment of configuration to (+)-2, 2-dimethyl-3-phenylpropionic-3-d acid (13). (S)-(+)3-Hydroxy-2, 2-dimethyl-3-phenylpropionic acid9) (14a, \([\alpha]_D^3 +8.3^\circ (c, 2.88, \text{AcOH})\) prepared by resolution of the racemate10) with (S)-(-)-methylbenzylamine, was esterified with diazomethane to the methyl ester 14b, \([\alpha]_D^3 +27.2^\circ (c, 2.2, \text{chloroform})\). The methyl ester (1 g) was allowed to react with mesyl chloride (2.4 g) in pyridine (25 ml) at −5°C for 3 days to give the mesylate 15. The completion of reaction was checked by the disappearance of OH signal in pmr spectrum. Subsequent reduction of the mesylate with LAD (700 mg) afforded the corresponding alcohol 16, \([\alpha]_D^3 +6.10^\circ\), which was further oxidized with potassium bichromate to the acid (+)-13, yield 210 mg, mp 46-48°C, \([\alpha]_D^3 +1.78^\circ\). The ir and pmr spectra were superimposable with those obtained from the rearrangement. Found: C, 73.73; H, 8.23. Calcd for C11H13O2D: C, 73.71; H, 7.94%.

(R)-(+)3-N-Isobutenyl-methyl-methylbenzylamine (27). This enamine was obtained by the reaction of N-methyl-methylbenzylamine (26, 10 g) with isobutrylaldehyde (20 g) in benzene according to the Benzing's procedure;15) bp 125-8°C (25 Torr), \(n_D^0 1.4852\), yield 13.8 g, ir: va-c 1635 cm\(^{-1}\).

(R)-(+)3-2, 2-Dimethyl-3-phenylbutyric acid (29a) and its methyl ester (29b). Methyl iodide (19 g) was added to the chiral enamine (27, 20 g) in acetonitrile (50 ml) with cooling. The mixture was heated under reflux for 20-24 hr. The usual work up gave the crude aldehyde 28, bp 104-105°C (10 Torr), yield 6.51 g (34%), \([\alpha]_D^3 +20.58^\circ (c, 1.0, \text{MeOH})\). The crude aldehyde 28 was oxidized with silver oxide to give the corresponding acid 29a, which was esterified with diazomethane. The analytical sample of methyl ester was obtained by preparative vpc (5% PEG, column length 2m, oven-temperature 180°C, He 1.2 kg/cm\(^2\)); \([\alpha]_D^5 15.67^\circ (c, 1.0, \text{MeOH})\), pmr (CDCl\(_3\)): \(\delta, 1.05 (d, 3H, \text{CHCH}_3), 1.20 (d, 6H, \text{C(CH}_3)_2), 3.05 (m, 1H, \text{CH}), 3.51 (s, 3H, \text{COOCH}_3)\) and 7.25 (s, 5H, aromatic protons).

Conversion of (S)-(+)3-phenylbutyric acid (30) to (+)-2, 2-dimethyl-3-phenylbutyric acid (29). (a) 2-Methyl-3-phenylbutyric acid (31). (S)-(+)3-Phenylbutyric acid12 (30, 8.2 g), \([\alpha]_D^0 52.4^\circ\), was added to the solution of sodium hydride (12 g) and diisopropylamine (5.05 g) in absolute THF (50 ml). After heating for 5 min., n-butyl lithium (16 g) was added with external cooling and the whole was stirred for additional 3 hr at 30°C. After warming the reaction mixture for 5 min., methyl iodide (7.1 g) was added with external cooling and the whole was stirred for additional 3 hr at 30°C. By a usual work-up, the methylated acid 31 was recovered (9 g). Colorless needles, mp 126-8°C. Found: C, 74.37; H, 8.14%. Calcd for C\(_{11}\)H\(_{14}\)O\(_2\): C, 74.13; H, 7.92%. b) 2, 2-Dimethyl-3-phenylbutyric acid (29a). The treatment of the mono-methylated acid 31 in the same manner as described above afforded 2, 2-dimethylated acid 29a, bp 154-156°C (6 Torr). The pmr spectrum was consistent with that of the rearrangement product. Found: C, 74.64; H, 8.20%. Calcd for C\(_{12}\)H\(_{16}\)O\(_2\): C, 74.97; H, 8.39%. The pmr spectrum of the methylester 29b, \([\alpha]_D^6 33.48^\circ (c, 2.03, \text{MeOH})\), was identical with that of the sample derived from the rearrangement product.
Crossover-recombination experiment. Materials: 1-N-Morpholino-2-methyl-1-propene (19), bp 97-98°C (30 Torr), \( n^\circ \) 1.4193 and 1-N-morpholino-2-ethyl-1-butene (20), bp 103–105°C (40 Torr), \( n^\circ \) 1.4310 were prepared according to the literature. Ir spectra of these enamines were identical with those reported in the literature. The salts 21 and 22 were prepared from enamines and the corresponding bromides, i.e. benzyl bromide and \( p \)-methylbenzyl bromide in chilled ether solution. The structures were fully substantiated by their pmr spectra. Salt 21; mp 185°C (decomp.), pmr (CDCl₃): \( \delta \) 1.25 (d, 6H, C(CH₃)₂), 4.61 (s, 2H, CH₂), 7.50 (s, 5H, aromatic protons). Salt 22; mp 190°C (decomp.), pmr (CDCl₃): \( \delta \) 1.15 (m, 6H, C(CH₃)₂), 2.40 (s, 3H, Ph-CH₃), 2.60 and 3.75 (m, 4H, (CH₂)₂), 4.46 (s, 2H, Ph-CH₂) and 7.30 (m, 5H, aromatic protons).

Products. Aldehydes 2, 23, 24 and 25 were obtained in the crossover-recombination experiments. The ir spectra and the retention times of the glc peaks (5% PEGS, 2 m, 180°C, He 1.0 atm/cm²) of these cross hybrids were coincident with those of the authentic samples.

3-Phenyl-2,2-dimethylpropanal (2): bp 103–105°C (10 Torr.), retention time, 7 min., 2,4-dinitrophenylhydrazone, mp 154–155°C. Found: C, 59.71; H, 5.36; N, 16.18%. Calcd for C₁₇H₁₈N₄O₄: C, 56.64; H, 5.30; N, 16.37%.

3-p-Xylyl-2,2-dimethylpropanal (23), bp 115–117°C (10 Torr.), retention time, 9.4 min., 2,4-dinitrophenylhydrazone; mp 158–160°C. Found: C, 60.45; H, 5.31; N, 15.61%. Calcd for C₁₈H₂₂N₄O₄: C, 60.67; H, 5.62; N, 15.17%.

2-Benzyl-2-ethylbutyraldehyde (24): bp 124–126°C (10 Torr.), retention time, 12 min., 2,4-dinitrophenylhydrazone, mp 122–123°C. Found: C, 61.37; H, 5.84; N, 15.07%. Calcd for C₁₉H₂₂N₄O₄: C, 61.61; H, 5.99; N, 15.13%.

2-p-Methylbenzyl-2-ethylbutyraldehyde (25): bp 135–137°C (10 Torr.), retention time, 16.4 min, 2,4-dinitrophenylhydrazone, mp 135–136°C. Found: C, 62.30; H, 6.15; N, 14.62%. Calcd for C₂₀H₂₄N₄O₄: C, 62.50; H, 6.25; N, 14.60%.

REFERENCES

Benzyl Migration from N to C


