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The Steric Course of a Ketimine Reduction

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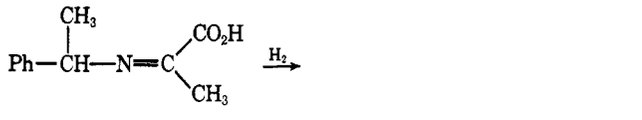
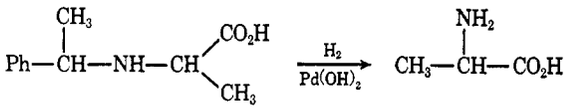
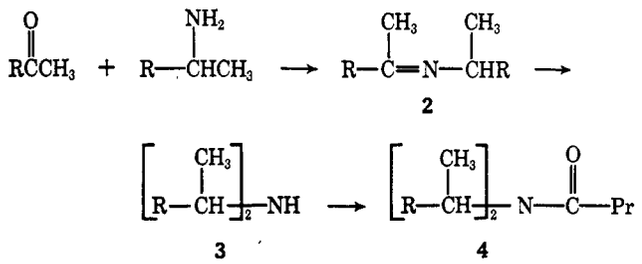
Asymmetric induction occurs when a new chiral center is formed by a reaction in which its symmetry is influenced by a second chiral center, already present in the reacting molecule. The phenomenon is most readily observed with optically active materials when the extent of asymmetric induction is evident from the optical activity of the products. For example, $R(-)$-alanine is formed in excess over the $S(+)$ enantiomer when pyruvic acid is reductively aminated with $R(+)$-α-methylbenzylamine.[2] More recently, an explanation of the stereochemistry involved has been proposed.[3] One problem, however, was the difficulty in specifying the amounts of the two geometrical isomers possible for ketimine **1**.



1



During the course of a synthesis of the amide **4**, we have observed a related case of asymmetric induction during the reduction of a ketimine with lithium aluminum hydride. In this case, the phenomenon was observed with optically inactive materials and the extent of the asymmetric induction was evident by glpc analysis of the two diastereoisomers present in the product. An explanation for the steric course of the reduction is presented which is based on the geometry of the ketimine **2**.



2

3 **4**

The ketimine **2**, resulting from condensation of 2-octanone and 2-aminooctane, was reduced with lithium aluminum hydride to give the amine **3** in 69% yield. When analyzed by glpc, the amine product showed two barely resolved peaks in a roughly 2:1 ratio on a 6 ft × $^1/_4$ in. Apiezon column. Acylation of the amine with butyryl chloride gave the amide **4**, which showed two peaks in a similar ratio. In the case of the amide, however, the two peaks were sufficiently well resolved to permit their separation by preparative glp, and in this way it was shown that the two peaks were due to diastereoisomers.

The two chiral centers in the amide **4** are probably closer to one another than are the chiral centers in the amine **3**. The greater interaction of symmetries in **4** presumably explains the ease of resolution of the diastereoisomers of **4** on a short-packed glpc column. The two isomers collected from preparative glpc were indistinguishable by ir, nmr, and tlc, while their mass spectra did show slight differences.

Before attempting to explain why the two diastereoisomers were produced in unequal amounts, it was first necessary to determine whether the major product from reduction of the ketimine **2** was the *meso* or the racemic form of the amine **3**. The racemic form should be resolvable on a glpc column containing an optically active liquid phase, and in fact Gil-Av[4] has reported the resolution of racemic amines as their trifluoroacetyl (TFA) derivatives on columns containing amino acid derivatives. Consequently, a 200 ft × 0.010 in. column was coated with the ureide of L-valine isopropyl ester. On this column, for example, the TFA derivative of 1-methylheptylamine gave two equal peaks due to the two enantiomers. However, all attempts to analyze the TFA derivative of bis(1-methylheptyl)amine (**2**) by this method were unsuccessful owing to excessive bleeding of the column above the recommended maximum temperature of 120°.

As an alternative method for distinguishing between the diastereoisomers, the amine **3** was acylated with an optically active acid chloride, N-trifluoroacetyl-L-prolyl chloride (TPC).[5] The product was analyzed on an 8 ft × $^1/_4$ in. column containing diethylene glycol succinate and showed three peaks. Two of these were equal in size and clearly resulted from the racemic diastereoisomer of the amine.

As further confirmation of the above peak assignment, the amine **3** was converted to its hydrochloride salt, which was recrystallized several times. When the amine was regenerated from the purified salt, the ratio of the two diastereoisomers was found to be significantly altered. The TPC derivative of this refined amine was analyzed as described above, and the size of the two equal peaks had changed relative to the third peak, confirming the earlier peak assignment.

Having thus distinguished between the two isomers, it was now evident that the racemate of **3** was the major product from reduction of the ketimine **2**, and in fact the racemate made up 62% of the isomeric mixture. Any explanation of this difference in the quantity of the diastereoisomers is complicated by the existence in the ketimine itself of two geometrical isomers, which is evident from its nmr spectrum. The olefinic methyl group of **2** appears as two distinct singlets at 8.30 and 8.16 ppm. The peak at 8.30 is much larger and is probably

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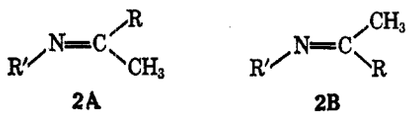
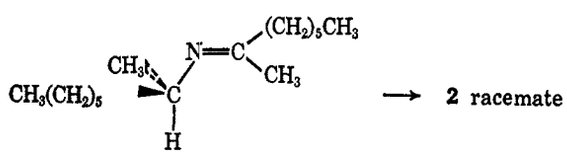
due to the more stable isomer **2A** which seems to make up 87% of the mixture.



2A **2B**

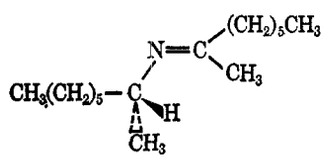
R = n-hexyl
R′ = 2-octyl

Of the various conformations which can result from rotation about the single CN bond in **2A**, the two most likely to be present in the transition state leading to reduction are shown in the diagrams below. When the tertiary hydrogen lies in the plane of the paper, the attacking hydride ion is more likely to approach the olefinic carbon from below the plane of the paper for the particular enantiomer shown. In this case, the incoming ion encounters the methyl group rather than the bulkier six-carbon chain and the amine is produced as the racemic diastereoisomer.



→ 2 racemate

A second likely conformation for this enantiomer would occur when the tertiary hydrogen and the methyl group are both staggered on either side of the plane of the paper. Then the attacking hydride ion would prefer to approach from above the plane of the paper and so encounter the hydrogen atom rather than the bulkier methyl group. Consequently, the amine would be produced in the *meso* form when the ketimine is reduced in this conformation.



→ 2 *meso*

The observation that **3** is formed as an isomeric mixture containing 62% of the racemate indicates that the first conformation is more favored than the second. Other factors, however, in addition to those described above may well be involved.

Experimental Section

N-(2-Octyl)methylhexylketimine (2).—A solution of 2-octanone (157.5 g, 1.24 mol) and 2-aminooctane (158.9 g, 1.24 mol) in toluene (1.5 l.) was refluxed overnight with a Dean–Stark trap in which water (20.2 g, 1.13 mol) was collected. The solvent was evaporated and the residue distilled under nitrogen to give a small forerun of starting materials, bp 45–95° (1 mm), followed by the ketimine (190 g, 62%): bp 96–97° (52 μ); n^{27}D 1.4414; uv max (isooctane) 245 mμ (ε 112); ir (liquid film) 1658 cm^{-1} (C=N); nmr (neat) τ 6.62 (m, 1, CH—N=C), 7.87 (t, 2, J = 6 Hz, CH_2—C=N), 8.16 and 8.30 (S, 3, CH_3=N) ppm. Analysis by glpc on several different columns showed one peak.

Anal. Calcd for $C_{16}H_{33}N$: N, 5.85. Found: N, 5.70.

Bis(1-methylheptyl)amine (3).—N-(2-Octyl)methylhexylketimine (150.0 g, 0.772 mol) was added to a stirred solution of lithium aluminum hydride (29.3 g, 0.772 mol) in tetrahydrofuran (1 l.) at room temperature under a nitrogen atmosphere. After refluxing for 24 hr, the metal complex was decomposed by treatment with aqueous base in the usual manner,[6] the resulting suspension was filtered, and the organic layer of the filtrate was dried ($MgSO_4$) and evaporated. The residue was distilled to give bis(1-methylheptyl)amine (105.4 g, 69%), bp 102–105° (60 μ), n^{26}D 1.4363–1.4372; nmr (neat) τ 7.36 (broad, 2, CH-N) ppm.

Anal. Calcd for $C_{16}H_{35}N$: C, 79.59; H, 14.61; N, 5.80. Found: C, 80.08; H, 14.85; N, 5.79.

Treatment of a sample of the amine in hexane with aqueous hydrochloric acid gave the amine hydrochloride salt, mp 104–107°, after two recrystallizations from heptane.

Anal. Calcd for $C_{16}H_{36}NCl$: C, 69.01; H, 13.05; N, 5.04. Found: C, 68.92; 13.51; N, 4.96.

A second sample of the amine was converted to the trifluoroacetyl derivative by treatment of a 10% solution of the amine in hexane (1 ml) with trifluoroacetic anhydride (100 μl). The solution was analyzed at 200° on a 6 ft × 1/4 in. glpc column containing 15% Apiezon L and shown to contain two isomers in a 62:38 ratio.

A third sample of the amine (50 mg, 0.21 μmol) in chloroform (2 ml) was treated with a 0.1 *M* solution of N-trifluoroacetyl-L-prolyl chloride in chloroform (2.3 ml), as obtained from Regis Chemical Co. After stirring for 1 min, triethylamine (40 μl, 0.23 μmol) was added and the solution stirred for 15 min at room temperature when 6 *N* hydrochloric acid (3 ml) was added. The organic layer was washed with water, dried ($MgSO_4$), and most of the solvent evaporated in a stream of nitrogen. The remaining derivative of **3** was analyzed directly at 225° on an 8 ft × 1/4 in. column containing 10% of diethylene glycol succinate.

Bis(1-methylheptyl)butyramide (4).—Bis(1-methylheptyl)amine (85.6 g, 0.356 mol) was refluxed overnight in toluene (600 ml) containing butyryl chloride (20.6 g, 0.193 mol). The toluene was evaporated and hexane (600 ml) was added when the amine hydrochloride was removed by filtration and the filtrate washed with aqueous base and water before drying ($MgSO_4$). The hexane was evaporated and the residue distilled, giving a small forerun of bis(1-methylheptyl)amine, bp 80–83° (8 μ), followed by bis(1-methylheptyl)butyramide (38.6 g, 64%) bp, 127–130° (8 μ), n^{26}D 1.4550, ir (liquid film) 1640 cm^{-1} (C=O).

It had two broad absorptions at τ 6.09 and 6.84 ppm in the nmr. These two peaks, which are due to the tertiary hydrogens in two distinct conformations, coalesced to one broad peak on warming above room temperature. The nmr also showed a peak at τ 7.71 ppm (t, 2 CH_2CO), while the glpc analysis gave two well-resolved peaks on Apiezon L at 250°.

Anal. Calcd for $C_{20}H_{41}NO$: C, 77.10; H, 13.27; N, 4.50. Found: C, 77.21; H, 13.26; N, 4.54.

Registry No.—**2A**, 20273-75-0; **2B**, 20273-76-1; (±)-**3**, 20221-59-4; (±)-**3** HCl, 20273-77-2; *meso*-**3**, 20273-78-3; *meso*-**3** HCl, 20273-79-4; (±)-**4**, 20273-80-7; *meso*-**4**, 20273-81-8.

Acknowledgment.—The author wishes to express his gratitude to Dr. J. J. Conradi and Dr. H. A. Harris for helpful discussions.

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Alkoxyl Exchange Reactions of Naphthalene Ethers

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During the course of our work on the photooxidation of aromatic systems[2] we had occasion to prepare 1,2,4-trimethoxynaphthalene. In order to do this we hydrolyzed 1,4-diacetoxy-2-methoxynaphthalene[3] (**1**) with

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