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# NADH MODELS XXI.[1] STEREOSELECTIVE REDUCTION OF CHIRAL IMINES WITH HANTZSCH ESTER

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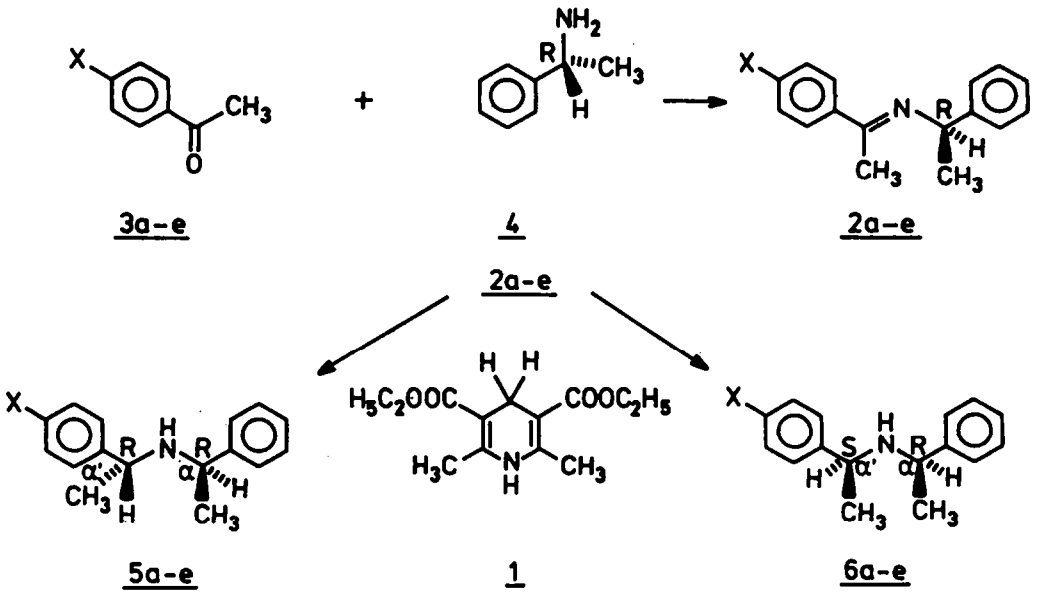
Abstract - Imines derived from p-substituted acetophenones and (+) R-1-phenylethylamine are reduced by 3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine (Hantzsch ester), in acetonitrile, in the presence of magnesium perchlorate, to diastereomeric mixtures of the corresponding N-1-arylethyl, N-1-phenylethylamines. The reduction proceeds diastereoselectivity with the R,R-diastereomer being formed predominantly. Mechanistic aspects of the selectivity of reduction are discussed.

Reductions by 1,4-dihydropyridine derivatives have been extensively studied in the last years as models of the reduced pyridine nucleotide (NADH) mediated enzymatic reactions.[3] Of the classes of compounds employed as substrates, the imines are of special interest since their reduction by 1,4-dihydropyridines is a general reaction and while requiring electrophilic catalysis, is not dependent upon special structural features inherent to the specific substrate molecule.[4] It may be recalled that in case of carbonyl and olefinic substrates, activation by electronegative substituents is an essential requirement. From the practical standpoint, the asymmetric reduction of imines by 1,4-dihydropyridine constitutes a worthwhile objective since the reaction can be utilized, amongst others, for the synthesis of optically active amino acids and useful asymmetric synthons. Several chiral dihydropyridines have been synthesized and employed for the reduction of activated carbonyl compounds.[5] Also, an example of the reduction of an iminium salt by a chiral dihydronicotinamide has been reported.[6] In view of the fact that syntheses of these reagents is not simple in practice, we have favoured the approach in which readily available dihydropyridines and chiral imines are used as reagents and substrates respectively. In this communication we describe the diastereoselective reduction of a series of such imines with Hantzsch ester (1).

The substrate imines 2a-e were easily available by reaction of the appropriate p-substituted acetophenones (3a-e) with R-(α)-phenylethylamine (4). The choice of the substrates was governed by the fact that the catalytic reduction of 2a and analogous imines has been previously described in the literature.[7-10] Thus, the results of reduction by Hantzsch ester and the thereupon based ideas on the mechanism of the process could be compared with those existing in the literature.

For electrophilic catalysis of the reduction of imines, advantage was taken of the fact that in the presence of magnesium ions, a rapid equilibrium is established between the imine and its protonated form, in "wet" acetonitrile.[11] The reduction was consequently carried out by refluxing a mixture (1:1) of 1 and 2a-e in acetonitrile in the presence of $Mg(ClO_4)_2$ (1 eq.), till the Hantzsch ester was consumed (TLC, 24-48 h). In all cases the reaction led to the formation of a mixture of the diastereomeric amines (5a-e and 6a-e, Fig. 1), in which one of the diastereomers was formed predominantly (Table 1). The overall structures of the amines were established by their spectral data and comparison with their authentic samples which were prepared by sodium borohydride reduction of the starting imines (2a-e).




a X = H, b X = Cl, c X = Br, d X = $OCH_3$, e X = $NO_2$

Fig. 1

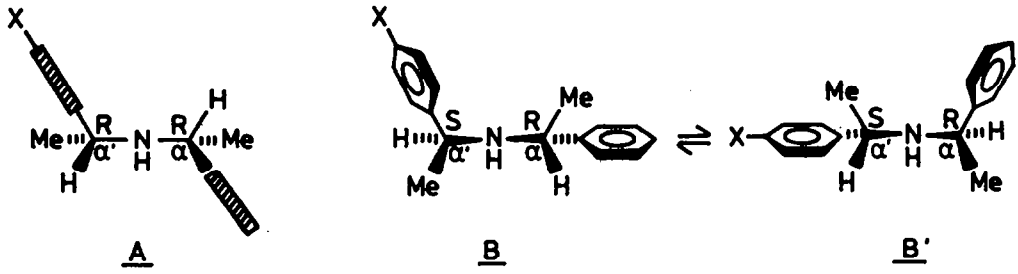



Fig. 2

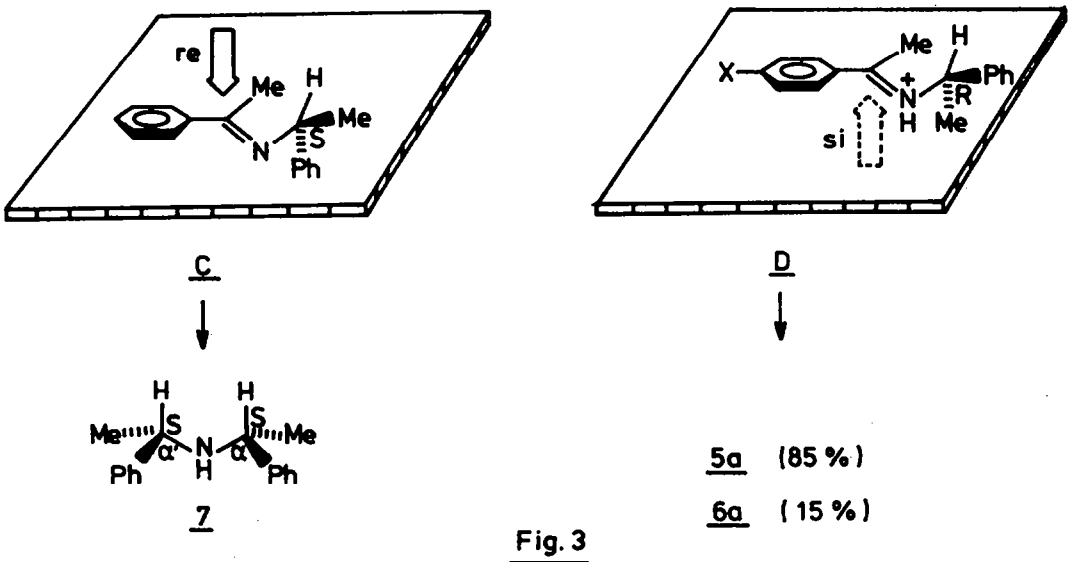



Fig. 3

The configurational assignments of the amines (Table 1) is based upon the following considerations. One type of data which provides valuable information is optical rotation measurements. Assuming that the configurational integrity of the starting chiral amine component is retained during the reaction, the diastereomers shall possess the αR,α'R and the αR,α'S configurations. In the case of reduction of 2a (X = H), the αR,α'S diastereomer possesses a meso structure and shall, consequently, not display optical activity. Since the minor product (6a) of this reaction is optically inactive, it is identified as the αR,α'S diastereomer. The αR,α'R configuration can then be assigned to the major diastereomer (5a), which exhibits a significant positive rotation value. The optical activity data of the other diastereomers allows, by analogy, their configurational assignments. The major diastereomers (5b-e) are assigned the αR,α'R structures in view of their appreciable positive rotations. The minor diastereomers, on the other hand, show very low positive rotations (6b and 6d) or a negative rotation (6e), which is consistent with their αR,α'S structures.[12]

Table 1. Diastereomeric amines 5a-e and 6a-e formed by the reduction of imines 2a-e by 3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine (1) in $CH_3CN$ (reflux), in the presence of $Mg(ClO_4)_2$.

| | Amines 5a-e (αR,α'R) | | | | | Amines 6a-e (αR,α'S) | | | |
|---|---|---|---|---|---|---|---|---|---|
| X | $[\alpha]_D$[a] | $\delta CH_3$[b] | $\delta CH$[b] | % | X | $[\alpha]_D$[a] | $\delta CH_3$[b] | $\delta CH$[b] | % |
| H | +15.6 | 1.25d | 3.5 q | 85 | H | 0 | 1.35d | 3.77q | 15 |
| Cl | +19.9 | 1.22d | 3.46q | 82 | Cl | +0.3 | 1.32d | 3.74q | 18 |
| | | 1.26d | 3.50q | | | | 1.34d | | |
| Br | +12.1 | 1.24d | 3.47q | 86 | Br | - | 1.31d | 3.44q | 14 |
| | | 1.26d | 3.48q | | | | 1.33d | 3.74q | |
| OMe | +15.6 | 1.24d | 3.46q | 78 | OMe | +0.48 | 1.33d | 3.72q | 22 |
| | | 1.25d | 3.50q | | | | 1.34d | 3.76q | |
| $NO_2$ | +22.9 | 1.22d | 3.37q | 83 | $NO_2$ | -24.6 | 1.37d | 3.76q | 17 |
| | | 1.23d | 3.57q | | | | | 3.88q | |

[a] ethanol. [b] $CDCl_3$

Corroboration of the assignments is derived from the NMR spectra of the two series of diastereomers. Of particular significance are the chemical shifts of the methyls and the tertiary protons attached to the α- and the α'- carbon atoms. For the αR,α'R diastereomers, both groups of protons consistently exhibit an upfield shift compared to their signals in the αR,α'S series (Table 1). While the differences in the chemical shifts are of diagnostic value in identifying the diastereomers, their origin requires comment. Inspection of models of the two diastereomers shows that the sterically favoured conformations of the molecules are as described in A and B $\rightleftharpoons$ B' (Fig. 2) for the αR,α'R and αR,α'S configurations, respectively. In A the atoms of the extended Me-C(α)-N-C(α')-Me chain lie in the same plane with the farthest separation between the methyl groups. In this conformation, the tertiary α- and α'- hydrogens project in the shielding zones of the aromatic rings attached to the opposite (α'- and α-, respectively) carbon atoms. This would, in general, lead to an upfield shift of their signals. In case of the αR,α'S diastereomers, an extended Me-C(α)-N-C(α')-Me chain results in forbidding steric interactions between the aromatic groups. The strain-free conformations B $\rightleftharpoons$ B' (in which both the aryl rings and the methyls are well-separated and furthermore, the C-Me bonds are perpendicular to the aromatic groups attached to the same carbons) exhibit the following characteristics. The C(α)- and C(α')-hydrogens lie in the planes of the corresponding aromatic rings; in addition, one of the methyls (C(α)-Me in B) is proximate to and in the deshielding region of the C(α')-aryl substituent. Rotation (60°) about the C(α)-N and C(α')-N bonds leads to the conformation, described in B', in which the C(α')-methyl group is deshielded by the C(α)-phenyl and, once again, the C(α)- and C(α')-hydrogens reside in the planes of the aryl rings. The combined influence of these factors is to cause a deshielding of both the methyls and the tertiary hydrogens in αR,α'S diastereomers. From the fore-

going discussion it follows that the preferred conformations of the two series of diastereomers adequately explain the significant differences in their NMR spectra.

In order to support the correlation of configurations of the ring substituted diastereomers 5b-e with that of the unsubstituted parent compound 5a, in one case (presumed 5b), the product was reductively dehalogenated ($H_2$, Pd/C). The resulting amine was shown to be identical (NMR, MS, GLC) to the αR,α'R diastereomer 5a.

Stereochemistry of Reduction

The stereochemical course of the reduction of imines derived from alkyl phenyl ketones and S--phenylethylamine was initially studied by Overberger and coworkers.[7] Their explanation of the observed stereoselectivity -based upon the higher reactivity of the less stable imine isomer- has been criticized by Harada et al.[8] The latter authors suggest that in the catalytic reduction of N--(α-methylbenzylidene)-S-1-phenylethylamine, the substrate predominantly assumes an E-configuration on the catalyst (structure C, Fig. 3) and is reduced from the less hindered re-side of the molecule. This accounts for the formation of the αS,α'S-diastereomer 7, as the major product. Factors such as steric requirements, solvent, amount of catalyst and temperature have been shown to influence the selectivity in a predictable manner.[8]

The model represented by substrate conformation C (Fig. 2) has also been employed to explain the stereochemical results of the reduction of related imines by $LiAlH_4$.[13] The analogy to the catalytic reduction consists in the fact that complexation of the imine nitrogen with the metal (Al) and delivery of the hydride can occur from the same (re-)side of the molecule. Prior to the experiments of the current study, it was not obvious that the mechanistic model represented by C could be applied to the homogeneous reduction of imines 2a-e -present in their protonated form- by Hantzsch ester (1). Since the amine component of 2a-e possesses the R-configuration, operation of the mechanism embodied in C would lead to a transition state in which the hydride equivalent is transferred from the si-face of the substrate (structure D). This would favour the formation of the αR,α'R diastereomers. The fact that in all cases the latter diastereomer is indeed the predominant product, implies that the stereochemical course (of the reaction) is importantly determined by the conformation of the substrate in the transition state. Furthermore, as the Hantzsch ester is a bulky hydride-donating reagent, its approach from the less hindered face of the imine, leading to αR,α'R--diastereomers, is fully in accord with expectation. A complete picture of the transition state requires a description of the relative locations of the Hantzsch ester and the imine. Recent MNDO calculations on hydride transfer between pyridinium ion and 1,4-dihydropyridine suggest a linear transition state (C-H-C axis) with a continuum of structures varying between endo- and exo-alignments of the donor and acceptor molecules.[14] While the present study did not specifically address itself to the detailed nature of the transition state, we believe that the conclusions of the MNDO study also apply to the (protonated) imine reductions by Hantzsch ester.

From the data presented in Table 1, it is clear that p-substituents in the benzylidene moiety of the substrates (2a-e) do not significantly affect the ratio of diastereomers (5a-e / 6a-e) in the mixture of reduction products. These results can be understood in terms of the mechanistic model presented in Fig. 3. According to this, the stereochemical course of the reaction is determined by two factors, namely, the configuration of the imine about the C=N linkage (or the corresponding protonated system, D in Fig. 2) and the direction of entry of the hydride species. Since both these factors have their origin in steric considerations, the introduction of groups at a position which is remote from the site of reduction cannot be expected to influence either of them. The insensitivity of the selectivity of reduction of (p)alkyl-$C_6H_4$-$C(CH_3)$=N-$\overset{*}{C}H(CH_3)C_6H_5$ to the presence of the p-alkyl substituent has been demonstrated by Gracheva et al.[15] The results of the present study establish that, not unexpectedly, electronic effects at the reaction centre are of no consequence to the diastereoselectivity of Hantzsch ester mediated reductions of imines 2a-e. In complete accordance with the expected influence of the substituents, on the other hand, a Hammett treatment of the rates of reductions of X-$C_6H_4$-CH=$\overset{+}{N}H$-(n)-$C_4H_9$, by Hantzsch ester, gives a sensitivity factor (ρ-value) of +1.83.[16]

In the context of the preceding discussion it is relevant to mention that imines 2a-e have been

observed to exist as two configurational isomers, according to their PMR spectra (vide experimental). The ratios of these isomers need not, however, bear any correlation with the diastereomeric distribution of the end products, since the configurational isomers are interconvertible and at the time of the reaction, their precise ratio will depend upon the reaction conditions.

Reduction of the imines 2a-e by sodium borohydride was carried out in order to prepare authentic samples of the product amines (5a-e, 6a-e). The diastereoselectivity of this reaction was slightly higher than that of the Hantzsch ester reduction. These results are not surprising in the light of the fact that the sodium borohydride reduction is carried out at a lower temperature (0°). There is ample evidence that an increase in reaction temperature results in the lowering of stereoselectivity of the reduction process.

## EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 257 spectrometer. PMR spectra were run on a Varian Associates Model A-60D, XL 100-12, XL 100-15 FT or a Bruker WM 250 instruments, in $CDCl_3$, using TMS as an internal standard. Mass spectra were obtained with a Varian Matt-711 spectrometer. Gas chromatographic analyses were carried out on a Varian Aerograph 200 instrument using a TC detector and coupled to a Philips PM 8000 recorder.

### Synthesis of imines 2a-e

A mixture of R-1-phenylethylamine (2 g, 1.7 mmoles), an equimolar amount of the acetophenone, 7 g of activated (300°, 3 hr) 4 Å molecular sieves and a catalytic amount of p-toluenesulphonic acid, in 50 ml of toluene was refluxed for 8 hr. At this stage, the molecular sieves were filtered off, a second 7 g portion of freshly activated molecular sieves added to the filtrate and the mixture refluxed for a further period of 48 hr. The mixture was then filtered and the solvent removed from the filtrate under reduced pressure. Distillation of the residue 200-250°C/.005 mm (bulb to bulb distillation apparatus) gave the imines 2a-e in yields ranging from 70-90%. The purity of the compounds was checked by GLC (12% NPGS on Chromosorb W-AW, 300x0.5 cm, 175°C, Helium flow 60ml/min). Relevant data are presented in Table 2.

Table 2. Relevant data on imines 2a-e.

| Imine, X | IR | PMR | | | | | | | MS | | $[\alpha]_D$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | (C=N) | N-CH$\underline{CH_3}$ | | N=CC$\underline{H_3}$ | | N=CH | | Ar-H | Found | Calc. | (Ph) |
| 2a, H | 1630 | 1.52 | 3H | 2.24 | 3H | 4.83 | 1H | 7.28-7.84 | 223.135 | 223.136 | -8.47 |
| | | 1.38 | 2xd | 2.29 | 2xs | | q | 10H, m | | | C=4.19 |
| 2b, Cl | 1632 | 1.52 | 3H | 2.24 | 3H | 4.83 | 1H | 7.28-7.84 | 257.094 | 257.095 | -8.09 |
| | | 1.38 | 2xd | 2.29 | 2xs | | q | 9H, m | | | C=8.52 |
| 2c, Br | 1632 | 1.52 | 3H | 2.23 | 3H | 4.81 | 1H | 7.38-7.75 | 301.045 | 301.045 | -15.58 |
| | | 1.38 | 2xd | 2.28 | 2xs | | q | 9H, m | | | C=4.48 |
| 2d, MeO | 1630 | 1.53 | 3H | 2.23 | 3H | 4.82 | 1H | 6.91-7.42 | - | - | -10.86 |
| | | 1.32 | 2xd | 2.25 | 2xs | | q | 9H, m | | | C=4.96 |
| | | | | 3.83 | 3H, s | $OCH_3$ | | | | | |
| 2e, $NO_2$ | 1632 | 1.57 | 3H | 2.32 | 3H | 4.87 | 1H | 7.38-8.25 | - | - | -15.43 |
| | | 1.39 | 2xd | | 2xs | | q | 9H, m | | | C=3.41 |

### Reduction of imines 2a-e.

A. By Hantzsch ester (1).
A mixture of equimolar amounts of the imine, Hantzsch ester and magnesium perchlorate, in acetonitrile, was refluxed (24-48 hr) till no Hantzsch ester could be detected (TLC). The mixture was analyzed by comparing the PMR and GLC data with that obtained by reducing imines 2a-e by sodium borohydride. Small amounts of diastereomers 5a-e and 6a-e were isolated by preparative gas chromatography and used for PMR and optical activity measurements.
B. By sodium borohydride.
Sodium borohydride (60 mg) was added in small amounts to a cooled (0°C) solution of the imine (0.5 g) in ethanol and the mixture stirred for 16 hr, during which period it was allowed to attain room temperature. Water was carefully added to the mixture (with cooling), the bulk of the solvents was removed by evaporation under reduced pressure and the residue treated with dil. HCl and subsequent-

ly made basic with conc. NaOH. The resulting mixture was extracted with dichloromethane, the organic layer separated and dried over anhyd. $MgSO_4$. Removal of the solvent gave a mixture of the amines 5a-e and 6a-e. Gas chromatographic analysis was carried out using two different stationary phases (Table 3).

Table 3. Gas chromatographic analysis of amines 5a-e and 6a-e.

| Amine | Column: 12% NPGS on Chromosorb W-AW | | Column: 15% DC550 on Chromosorb W-AW | |
|---|---|---|---|---|
| | temp °C | retention time, min | temp °C | retention time ,min |
| 5a | 155 | 67 | 175 | 66 |
| 6a | 155 | 78 | 175 | 76 |
| 5b | 175 | 80 | 175 | 162 |
| 6b | 175 | 93 | 175 | 180 |
| 5c | 175 | 109 | 175 | 197 |
| 6c | 175 | 117 | 175 | 214 |
| 5d | 200 | 41 | 200 | 89 |
| 6d | 200 | 49 | 200 | 100 |
| 5e | 200 | 109 | 200 | 370 |
| 6e | 200 | 117 | 200 | 388 |

Data which allows a distinction between the two sets of diastereomers has been already discussed (Table 1). Additional data are tabulated in Table 4.

Table 4. Additional spectral data on amines 5a-e and 6a-e.

| Amine | X | Ar (H) | N-H | Found | Calc. |
|---|---|---|---|---|---|
| 5a | H | 7.24 m 10H | 1.42 | 225.152 | 225.152 |
| 6a | H | 7.27 m 10H | 1.72 | | |
| 5b | Cl | 7.32 m 9H | 1.56 | 259.114 | 259.113 |
| 6b | Cl | 7.28 m 9H | 1.68 | | |
| 5c | Br | 7.08-7.48 m 9H | 1.64 | 303.061 | 303.061 |
| 6c | Br | 7.30 m 9H | 1.76 | | |
| 5d | OMe | 6.84-7.26 m 9H | 1.80 | 255.162 | 255.162 |
| 6d | OMe | 6.83-7.27 m 9H | 1.76 | | |
| 5e | $NO_2$ | 7.21-8.11 m 9H | 2.10 | 270.136 | 270.136 |
| 6e | $NO_2$ | 7.23-8.11 m 9H | 1.70 | | |

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REFERENCES

* To whom correspondence should be addressed.
1. Part XX. L.H.P. Meijer and U.K. Pandit, Tetrahedron 41, 467 (1985).
2. Taken in part from the doctorate dissertation of J.C.G. van Niel, "Redukties van imines met NADH-Modellen", University of Amsterdam, 1985.
3. A survey of the nonenzymatic reductions by 1,4-dihydropyridines is given in ref. 2. Chap. 1, pp. 7-14.
4. (a) J.B. Steevens and U.K. Pandit, Tetrahedron 39, 1395 (1983); (b) R. Srinivasan, R.T. Medary, H.F. Fisher, D.J. Norris and R. Stewart. J. Am. Chem. Soc. 104, 807 (1982); (c) U.K. Pandit, H. van Dam and J.B. Steevens, Tetrahedron Letters 913 (1977); (d) S. Shinkai and T. Kunitake, Chem. Letters 1113 (1976); (e) M.J. de Nie-Sarink and U.K. Pandit, Recl. Trav. Chim. Pays-Bas 98, 162 (1979); (f) N. Baba, K. Nihiyama, J. Oda and Y. Inouye Agr. Biol. Chem. 40, 1441 (1975); (g) U.K. Pandit, R.A. Gase, F.R. MasCabré and M.J. de Nie-Sarink, J. Chem. Soc. Chem. Commun. 211 (1975).
5. (a) A. Ohno, M. Ikeguchi and S. Oda, J. Am. Chem. Soc. 101, 7036 (1979); (b) H.J. van Ramesdonk, J.W. Verhoeven and Th.J. de Boer, Bioorg. Chem. 6, 403 (1977); (c) P.C. Kaijzer, A. Oudeman, A.M. van der Burg and U.K. Pandit, Heterocycles 16, 1687 (1981); (d) R.M. Kellogg, Angew. Chem. 769 (1984); (e) N. Baba, M. Amano, J. Oda and Y. Inouye, J. Am. Chem. Soc. 106, 1481 (1984).
6. N. Baba, T. Makino, J. Oda and Y. Inouye, Can. J. Chem. 58, 387 (1980).
7. G.C. Overberger, N.P. Marullo and R.G. Hiskey, J. Am. Chem. Soc. 83, 1374 (1961).
8. T. Yoshida and K. Harada, Bull. Chem. Soc. Jap. 45, 3706 (1972).

9. K. Harada, "Chemistry of the carbon nitrogen double bond", Ed. S. Patai, Wiley, London, 1970, pp. 285-298.
10. W.H. Pirkle and J.R. Hauske, J. org. Chem. 42, 2436 (1977).
11. J.C.G. van Niel, U.K. Pandit, D.J. Stufkens and G.C. Schoemaker, Tetrahedron 41, 2745 (1985).
12. The meso (R,S) amines 6a, 6b and 6d have, as anticipated, almost no rotation. The high rotation of 6e is related to the strongly polar character of the nitro group.
13. J.-P. Charles, H. Christol and G. Solladie, Bull. Soc. Chim. Fr. 4439 (1970).
14. S.M. van der Kerk, W. van Gerresheim and J.W. Verhoeven, Recl. Trav. Chim. Pays-Bas 103, 143 (1984).
15. R.A. Gracheva, L.I. Budanova, E.A. Vasemirnova and V.M. Potapov, Zhur. Org. Khim. 9, 1235 (1973); Eng. translation.
16. Ref. 2, Chap. 4. The results of this study will be reported elsewhere.