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ENANTIOMERS AS A RESULT OF RESTRICTED ROTATION ABOUT PARTIAL DOUBLE BONDS: RESOLUTION OF N-NITROSO-, (N-FORMYL)-, AND N-THIOFORMYL-4-PIPERIDINECARBOXYLIC ACIDS.

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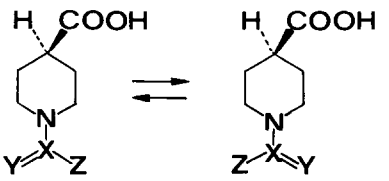
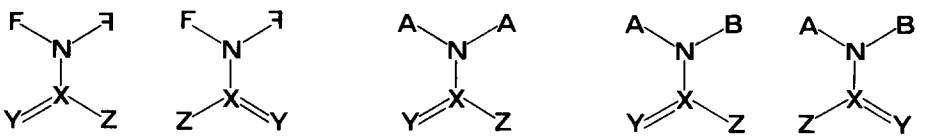
We wish to report the first separations of enantiomeric N-nitrosamines, thioamides and amides, whose chirality is the result of asymmetry caused solely by restricted rotation about partial double bonds. Specifically, compounds 1, 2 and 3 were obtained optically active.



1 Y = O, X-Z = N:
2 Y = S, X-Z = C-H
3 Y = O, X-Z = C-H

The study of these compounds was initiated to provide the following information:

(1) From the standpoint of systematic static stereochemistry, compounds 1 - 3 may be viewed as belonging to the class commonly known as geometrical enantiomers. This is readily apparent from the abstract formulae A and $\bar{A}$.



A $\bar{A}$ B C D

In general, enantiomeric moieties F and ∃ may occur in three different ways: (a) as stereogenic elements, such as chiral centers of opposite (R and S) configurations [1], (b) as enantiomeric (M and P) conformations or (c) as enantiomorphic (Re and Si) halfspaces [2]. For 1 - 3 the latter category applies [3].

(2) Compounds 1 - 3 allow the determination of activation parameters of restricted rotation about the N-X bond by conventional polarimetric kinetics, a method noted for its relatively high accuracy.

This possibility may be of value although excellent results have been achieved with the help of DNMR (compounds of type B or C and D) and conventional equilibration methods (compounds of type C and D) [5].

(3) Considerable effort has been devoted toward establishing a circular dichroism sector rule for N-nitrosamines. Due to the difficulties caused by the low local symmetry of the N-nitroso chromophore and E/Z isomerism various proposals - the first one was originated by Snatzke [6]- have been discussed without apparently reaching an unequivocal conclusion [7]. Compound 1 may contribute to the solution of this problem. It possesses the unique property that all perturbing atoms are situated on the same side of the local symmetry plane of the chromophore, and that they are arranged symmetrically to a plane passing through C-4 and the two nitrogen atoms and perpendicular to the first. This plane corresponds to the symmetry plane of 4-piperidinecarboxylic acid.

Enantiomer resolution of 1, 2 and 3 [8] was achieved via crystallization of diastereomeric salts with optically pure amines. Since similar procedures were applied to the three compounds, detailed results are reported only for the nitrosamine 1.

A mixture of equimolar solutions of quinine (in methanol) and (±)-1 (in ethyl acetate) was evaporated under reduced pressure in a rotary evaporator (bath temperature ca. 40°C) until crystals appeared. The crystallization was then allowed to proceed for ca. 1 h at ambient temperature, and the salt isolated (91 %) [9]. The acid was recovered by distribution of the salt between ethyl acetate and 1 N hydrochloric acid at 0°C, drying the organic solution and concentrating it in vacuum at 0 - 5°C (rot. evap., 1 torr). The resultant crystalline (-)-1 was chemically pure according to elemental analysis and spectral data [10] mp 137 - 139°C; $[\alpha]_{436}^{22}$ -80° (c = 2.0, methanol). Similar resolving experiments with other amines (1-phenylethylamine, ephedrine [11]) gave acids with smaller optical rotations.

The enantiomeric purity of 1 was assessed by the amide method recently developed by us [12]. For this purpose optically active 1 was converted to the acyl-imidazole (with N,N'-carbonyldiimidazole) at -30°C. The latter reacted in situ with (+)-(R)- or (-)-(S)-2-amino-1,1-diphenylpropane to give mixtures of diastereomeric amides 4a,b. These are separable by low temperature TLC, preparative column chromatography or HPLC. The latter method allowed determination of diastereomeric composition from which enantiomeric purity ep = 25±2% follows for the above specimen of (-)-1. This value is a lower limit estimate since some racemization or epimerization may have occurred during sample processing.

Compounds 1, 4a and 4b racemize or epimerize, respectively, [13]in solution at room temperature, the rates (polarimetry) excellently fit first order kinetics. As may be seen from the data summarized in the table a small but distinct dependence on the solvent is observed. Addition of formic or acetic acid has no effect on the racemization rate.

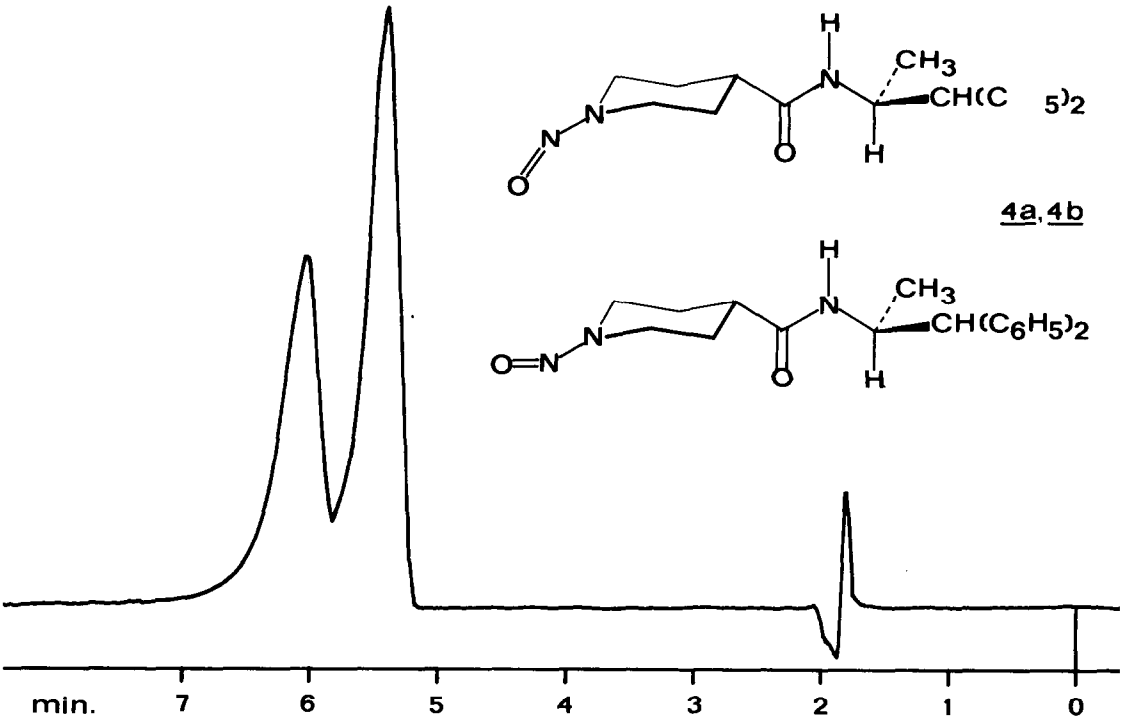


Figure. High performance liquid chromatographic separation of 4a and 4b. (Silica gel, eluent chloroform-tetrahydrofuran 96+4, UV detection, 254 nm).

Table. Kinetic data [a] for the equilibration of N-nitrosamines 1 and 4a,b.

	solvent	c $[mol^{-1}]$	temp. [°C]	$\Delta G^{\neq}$ [kcal mol^{-1}]	$\tau_{1/2\ rac.}$ [min]
1	CH_3OH	0.125	22.0 ± 0.1	22.30	32
1	CH_3CN	0.125	22.0 ± 0.1	22.86	82
4a [b]	CH_3OH	0.052	22.0 ± 0.1	22.38	37

[a] Polarimetry on a Perkin Elmer 141 polarimeter.
[b] The composition of the equilibrium mixture was determined as 1:1 (HPLC ; estimated precision 5 %).

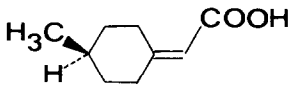
Similar results were obtained for 2. The 1-phenylethylammonium salt of 3 shows fast mutarotation. Isolation of 3 itself has been achieved by low temperature chromatography ($\tau_{1/2}$ of racemization ca. 1.5 min at 23.5°C). The method needs improvement, however.

Currently the determination of the absolute configuration of 1 and 2 is under active investigation. Our approach to the solution of this difficult problem is based on ^{1}HNMR spectral differences of 4a and 4b [14], and the corresponding derivatives of 2.

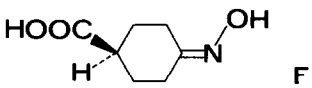
[1] R.E. Lyle, G.G. Lyle, J. Org. Chem. 22, 856 (1957); 24, 1679 (1959).

[2] V. Prelog, G. Helmchen, Helv. Chim. Acta 55, 2581 (1972).

[3] Earlier examples of this type of stereoisomers, E and F, are known: W.H. Perkin, W.F. Pope, O. Wallach, Liebigs Ann. Chem. 371, 180 (1909) and W.H. Mills, A.M. Bain, J. Chem. Soc. 97, 1866 (1910), respectively.



E



F

A detailed discussion of the rather intriguing problem of stereochemical specification of these compounds will be presented elsewhere [4].

[4] G. Helmchen, V. Prelog, C. Wintner, to be published.

[5] Equilibration methods: A. Mannschreck, H. Münsch, A. Mattheus, Angew. Chem. 78, 751 (1966) (nitrosamines); T.H. Siddall III, Inorg. Nucl. Chem. Letters 1, 155 (1965) (amides); W. Walter, G. Maerten, H. Rose, Liebigs Ann. Chem. 691, 25 (1966) (thioamides). A combination of DNMR and an equilibration method was first applied by A. Jaeschke, H. Münsch, H.G. Schmid, H. Friebolin, A. Mannschreck, J. Mol. Spectr. 31, 14 (1969); literature cited therein.

[6] G. Snatzke, H. Ripperger, Chr. Horstmann, K. Schreiber, Tetrahedron 22, 3103 (1966).

[7] T. Polonski, K. Prajer, Tetrahedron 32, 847 (1976); B. Liberek, J. Ciarkowski, K. Plucinska, K. Stachowiak, Tetrahedron Lett. 1407 (1976).

[8] Racemic 1, 2 and 3 were prepared according to standard procedures; for 2 Walter's method proved especially convenient: W. Walter, G. Maerten, Liebigs Ann. Chem. 669, 66 (1963).

[9] Since the acid had an enantiomeric purity of ca. 25 %, the yield of 91 % indicates that 2nd order asymmetric transformation had occurred.

[10] All new compounds described in this report were characterized in the same way.

[11] With (+)- and (-)-ephedrine both acids, (-)- and (+)-1, respectively, can be obtained, $|[\alpha]_{436}^{22}| \sim 50°$.

[12] G. Helmchen, W. Strubert, Chromatographia 7, 713 (1974); G. Helmchen, H. Völter, W. Schühle, Tetrahedron Lett. 1417 (1977).

[13] In the crystalline state, these compounds can be stored for several months without apparent loss of enantiomeric purity even at ambient temperature.

[14] According to investigations in our laboratory the absolute configuration of carboxylic acids $R^1R^2HCCOOH$ can be determined by methods analogous to those described in [15].

[15] G. Helmchen, R. Ott, K. Sauber, Tetrahedron Lett. 3873 (1972); see also the second reference of [12].