Tetrahedron. Vol. 30, pp. 3493 to 3497. Pergamon Press 1974. Printed in Great Britain

THE STEREOCHEMICAL COURSE OF FORMIC ACID REDUCTION OF ENAMINES

J. Ø. MADSEN*† and P. E. IVERSEN
Department of Organic Chemistry, Chemical Institute, University of Aarhus, DK-8000 Aarhus C, Denmark

(*Received UK* 8 *May* 1974; *Accepted for publication* 15 *May* 1974)

Abstract—Formic acid reduction of enamines derived from 2-methyl- and 2-(β-cyanoethyl)-cyclohexanone has been shown to proceed with high stereoselectivity, the *cis* to *trans* ratio of the resulting cyclohexylamines being about 9. The stereochemistry of the isomers has been established by Cope-eliminations of the corresponding N-oxides and by applying the boiling point and refractive index relations of the *Auwers-Skita rules*.

INTRODUCTION

The chemical reduction of enamines by hydride transfer agents depends upon the prior generation of an immonium salt. Reduction has been achieved with sodium borohydride[1,2] in protic solvents, whereas LAH which cannot be used in protic solvents is without action on enamines.[3] Mixed hydride reagents like aluminium chlorohydrides are electrophilic in character ane can add directly to the enamine double bond, and hydrolysis of the adduct gives the saturated amine.[4] Reduction with such agents is accompanied by hydrogenolysis of the C–N bond, producing olefins. With aluminium hydride itself hydrogenolysis is the principal reaction.[5] Reduction with formic acid has been known for a long time, even before the full chemical potentiality of enamines had been exposed by the work of Stork *et al.*[6,7] The reduction can be carried out easily since under the conditions of the reaction (i.e. formic acid) the enamine is protonated; carbon dioxide is the sole by-product. The first example involves reduction of a heterocyclic immonium salt with formate ion.[8] That the reduction proceeds by hydride transfer was proven by Leonard and Saurs in an elegant study on the reduction of $\Delta^{1(10)}$-dehydro-quinolizidine with all of the three possible deuterated formic acids.[9] The nature of the hydride transfer agent is not known, but is presumed to be a formate ion or a formate ion pair. The reduction proceeds stereoselectively, as demonstrated with heterocyclic enamines[10,11] and also with some enamines derived from 3-ketosteroids,[12] the hydride io approaches the immonium double bond from th sterically more accessible side of the molecule. Fo recent reviews on enamine chemistry see Ref 13 The present work was undertaken in order t identify and define the stereochemistry of *cis-tran* isomeric cyclohexylamines (**3c-3f**) obtained fron electrochemical reduction of heterocyclic enammonium salts (preceding paper[14]); formic aci reduction of enamines has also been of interest t us in other studies.[15]

RESULTS AND DISCUSSION

Formic acid reduction. Six enamines derived fron 2-methyl- and 2-(β-cyanoethyl)cyclohexanone an secondary amines, **1a–1f**‡ (Scheme 1), were subjected to reduction with formic acid. Yields an physical properties of the resulting saturate amines are given in Table 1.§ Yields were generall high and the products were obtained analyticall pure by simple procedures.

According to the results mentioned above immonium formates **2** are intermediates in th reductions, and hydride transfer from the les hindered side of the intermediates leads to amines of *cis* geometry. GLC analysis of the product showed the presence of both isomers in remarkabl constant ratios of about 9:1. In the cases of **3a** an **3b** the pure isomers (~100%) were isolated a follows: distillation on a spinning band column gav a *lower* boiling, enriched fraction (~90%) of th minor isomer from which the pure isomer wa obtained by preparative GLC, and a *higher* boilin fraction of the pure major isomer. The possibilit of using the Karplus equation to establish th stereochemistry of the amines was ruled ou because of badly resolved and complicated 60 MH NMR spectra, and it was then decided to tr Cope-elimination of the corresponding N-oxide The results (see below) unambiguously showed th

---

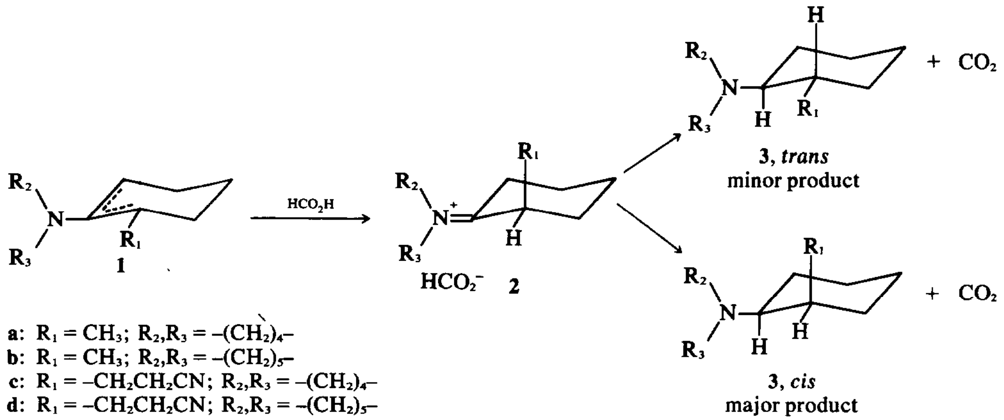
†Present address: Department of Organic Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark.

‡Enamines from 2-alkylcyclohexanones are mixtures of isomers, without consequence to the course of formic acid reduction.

§To our knowledge only the amine **3a** has been previously described, but of undefined stereochemistry.[5]

Table 1. Yields, isomer ratios and physical properties of cyclohexylamines 3

							Elemental analyses											
	%	Isomer ratio	Boiling point °C/mm Hg		Refractive index, n_D^{25}		Found% mixture			Found% *cis*			Found% *trans*			Calc.%		
Comp.	yield	*cis* : *trans*	mixture	*cis*	*cis*	*trans*	C	H	N	C	H	N	C	H	N	C	H	N
3a	87	85:15	92–94/10	118/25	1·4878	1·4768	79·05	12·65	8·46	79·06	12·60	8·51	78·73	12·63	8·31	78·98	12·65 ($C_{11}H_{21}N$)	8·37
3b	86	89:11	112–113/13	126/20	1·4860	1·4762	79·31	12·73	7·79	79·33	12·84	7·97	79·21	12·78	7·83	79·49	12·79 ($C_{12}H_{23}N$)	7·72
3c	83	88:12	106–108/0·3				75·64	10·78	13·64							75·67	10·75 ($C_{13}H_{22}N_2$)	13·58
3d	69	92:8	114–116/0·35				76·25	11·10	12·81							76·31	10·98 ($C_{14}H_{24}N_2$)	12·71
3e	12	90:10	113–118/0·1				70·38	9·97	12·19							70·23	9·97 ($C_{13}H_{22}N_2O$)	12·60
3f	59	88:12	140–142/10				73·07	11·34	15·64							73·28	11·18 ($C_{11}H_{20}N_2$)	15·54



1

2

3, *trans*
minor product

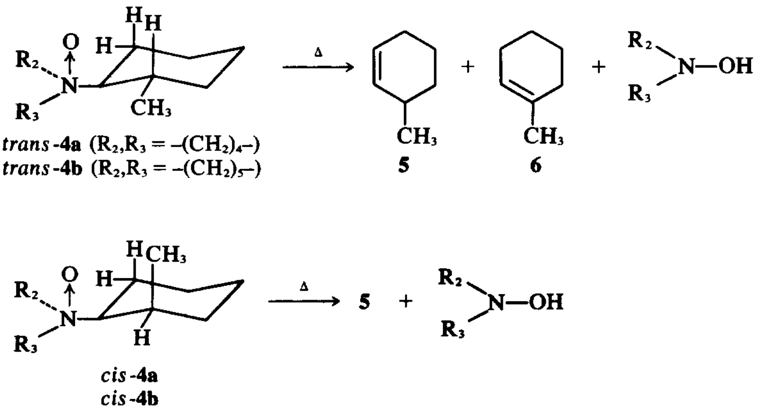
3, *cis*
major product

a: $R_1 = CH_3$; $R_2,R_3 = -(CH_2)_4-$
b: $R_1 = CH_3$; $R_2,R_3 = -(CH_2)_5-$
c: $R_1 = -CH_2CH_2CN$; $R_2,R_3 = -(CH_2)_4-$
d: $R_1 = -CH_2CH_2CN$; $R_2,R_3 = -(CH_2)_5-$
e: $R_1 = -CH_2CH_2CN$; $R_2,R_3 = -CH_2CH_2-O-CH_2CH_2-$
f: $R_1 = -CH_2CH_2CN$; $R_2 = R_3 = CH_3$

SCHEME 1

minor isomers to have *trans* geometry and the major isomers *cis* geometry for methyl compounds **3a** and **3b**. The boiling point and refractive index relations of the isomers of the amines **3a** and **3b** are in accordance with the *Auwers-Skita rules* (for a thorough discussion see Ref 16). The assignment of the isomers of **3a** and **3b** to their geometrical configurations could have been made on the basis of these rules, and quite safely because the isomers of the structurally very close dimethyl(2-methylcyclohexyl)amine have been shown to follow the rules.[16] We did not succeed in preparing N-oxides of the 2-(β-cyanoethyl)cyclohexylamines **3c-3f** (oxidation with hydrogen peroxide in aqueous methanol led to hydrolysis of the cyano group as detected by IR; oxidation in acetic acid gave very small yields as detected by TLC) and the isomers of these amines, which were separated by analytical GLC only, therefore could not be assigned to their geometrical configurations by the Cope-elimination procedure. Assignments were made on the following grounds: *firstly*, the minor isomers have lower boiling points than the major isomers (this follows from the fact that the minor isomers have the shortest retention times on the unpolar SE-30 GLC column) and according to the *Auwers-Skita rules* these isomers must be of *trans* geometry, and *secondly*, it seems hard to explain why the stereochemical course of the formic acid reduction should be precisely inverted with enamines **1c-1f**.

Cope-eliminations. The N-oxides, **4a** and **4b** (Scheme 2), of the isomers of the amines **3a** and **3b** were obtained in quantitative yields by oxidation with hydrogen peroxide in aqueous methanol Methanol solutions of the N-oxides were injected into the injection port of a gaschromatograph and analysis of the olefins formed followed directly. I is seen from Table 2 that for each pair of N-oxides one isomer gives 3-methylcyclohexene exclusively whereas the other isomer gives a mixture of 1 methyl- and 3-methylcyclohexene. Since amine oxides have been shown to undergo almos



trans-**4a** ($R_2,R_3 = -(CH_2)_4-$)
trans-**4b** ($R_2,R_3 = -(CH_2)_5-$)

5

6

cis-**4a**
cis-**4b**

SCHEME 2

Table 2. Cope-eliminations of *cis-trans* isomeric (2-methylcyclohexyl) amine N-oxides^{a} in the injection port of a gaschromatograph. Oven temperature, 60–80°

N-oxide	Injection port temp. °C.	Product distribution %		%yield^{c} **5** + **6**
		5	**6**	
cis **4a**	150	100^{b}	0	
	200	100	0	26
	270	98–99	1–2	
cis-**4b**	140	100^{b}	0	19
	190	100	0	
trans-**4a**	150	60^{b}	40^{b}	
	200	59	41	
	260	57	43	35
trans-**4b**	145	60^{b}	40^{b}	
	190	61	39	27

^{a}2·0 μl of ~50% solutions in methanol were applied.
^{b}Broad, asymmetric peaks (indicating relatively slow reactions).
^{c}Calculated with authentic samples of the olefins as external standards.

exclusive *cis* elimination,[17,18] these results show that the isomers which produce 3-methylcyclohexene only must be of *cis* geometry, and the isomers which give both of the possible olefins must be of *trans* geometry, as has been depicted in Scheme 2. The yields of the eliminations are rather small, the pyrrolidine derivatives giving higher yields than the piperidine derivatives. Since large amounts, ~50%, of the starting tertiary amines were detected most of the N-oxides must be converted by some reduction process, the nature of which is not clear. Preparative elimination reactions with the neat amine oxides gave smaller yields of the olefins. Again, large amounts, ~40%, of the starting amines were isolated. In the case of the pyrrolidine N-oxide, **4a**, N-hydroxypyrrolidine was detected by anodic polarography[19] in aqueous alkaline solution, but not isolated. In the case of the piperidine n-oxide, **4b**, a small amount of N-hydroxypiperidine was isolated as the hydrochloride, and identified by comparison with an authentic sample[20] (m.p., IR, anodic polarographic wave).

EXPERIMENTAL

M.ps and b.ps are uncorrected.

The GLC analyses were carried out on an FM Model 810, equipped with a flame ionization detector, using a 6 ft × 0·125 in of 10% Se-30 on Chromosorb W column. Preparative GLC was performed on a Varian Autoprep, using a 10 ft × 0·375 in of 20% SE-30 on chromosorb W column. Spinning band distillations were carried out on a Nester-Faust instrument equipped with a teflon band.

We are indebted to Løvens Kemiske Fabrik for the microanalyses.

Starting materials. The enamines **1a** and **1b** were prepared from 2-methylcyclohexanone in the usual manner[6]. **1c**-**1f** were obtained by cyanoethylation of the corresponding enamines by standard procedures.[6] The methylcyclohexenes **5** and **6** were commercial products.

General procedure for the formic acid reduction of enamines. Excess (50–100%) of formic acid was added to the pure enamine (0·05–0·10 mole); the temp normally quickly raised and a vigorous gas evolution started. The mixture was refluxed for several hr (overnight in the cases of **1c**-**1f**) after which it was stirred with 100–200 ml of 4N HCl for several hr in order to hydrolyse possible unchanged starting material. After extraction with two 100 ml portions of ether, the acidic aqueous soln was made strongly alkaline with NaOH and extracted 3 times with 100 ml portions of ether. The combined etheral extracts were dried over KOH pellets, the solvent stripped off, and the oily residue fractionated *in vacuo* giving the saturated amines in the yields shown in Table 1.

For some of the amines the methiodides have been prepared by addition of excess MeI to an ethereal soln of the amine at room temp. The crystalline salts were obtained analytically pure in nearly quantitative yields after standing for some days and washing with dry ether on the filter.

cis-N-(2-Methylcyclohexyl)-N-methylpyrrolidinium iodide, m.p. 217–218°. (Found: C, 46·71; H, 7·87; N, 4·41; J, 41·00. $C_{12}H_{24}NJ$ requires: C, 46·65; H, 7·81; N, 4·53; J, 41·01%).

cis-N-(2-Methylcyclohexyl)-N-methylpiperidinium iodide, m.p. 220–221°. (Found: C, 48·40; H, 8·08; N, 4·22; J, 39·01. $C_{13}H_{26}NJ$ requires: C, 48·35; H, 8·11; N, 4·33; J, 39·21%).

N-*(2-Cyanoethylcyclohexyl)-trimethylammonium iodide*, prepared from **3f** with a *cis* : *trans* ratio of 88 : 12, m.p. 200°. (Found: C, 44·60; H, 7·09; N, 8·14; J, 39·38. $C_{12}H_{23}N_2J$ requires: C, 44·75; H, 7·20; N, 8·70; J, 39·40%).

General procedure for preparation of N-*oxides.* The amine was dissolved in MeOH and excess 30% aqueous H_2O_2 added. With piperidine derivatives it was not always possible to obtain a homogenous soln from the beginning, even with addition of more MeOH, but the oily ppt dissolved during the oxidation process. The mixture was left at room temp for 3–4 days with occasional shaking after which the amine could no longer be detected by phenolphthalein-paper. A little (5–10 mg) platinum-black was cautiously added to destroy excess H_2O_2 which could no longer be detected by lead sulphide paper after 1–2 days. The platinum was then filtered off, washed with a little MeOH, and the combined filtrates evaporated *in vacuo* on a water bath at 30–40° leaving a pale-yellow oil which in some cases crystallized on standing. A crystalline N-oxide of definite composition could not be obtained, and the amount of oily product generally corresponded to slightly more than the theoretical yield for an N-oxide monohydrate. However, crystalline N-oxide picrates were precipitated in nearly quantitative yield by addition of an aliquot to excess saturated picric acid soln.

cis - N - (2 - *Methylcyclohexyl)pyrrolidine* - N - *oxide picrate*, m.p. 146–147°. (Found: C, 49·36; H, 5·82; N, 13·64. $C_{17}H_{24}N_4O_8$ requires: C, 49·51; H, 5·87; N, 13·59%).

cis - N - (2 - *Methylcyclohexyl)piperidine* - N - *oxide picrate*, m.p. 167–168°. (Found: C, 50·51; H, 6·08; N, 13·21. $C_{18}H_{26}N_4O_8$ requires: C, 50·70; H, 6·15; N, 13·14%).

REFERENCES

[1] J. A. Marshall and W. S. Johnsson, *J. Org. Chem.* **28**, 421 (1963)

[2] J. Schmitt, J. J. Panouse, A. Hallot, P.-J. Cornu, P. Comoy and H. Pluchet, *Bull. Soc. Chim. Fr.* 798 (1963)

[3] N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.* 77, 439 (1955)

[4] J. Sansoulet and Welvart, *Bull. Soc. Chim. Fr* 77 (1963)

[5] J. M. Coulter, J. W. Lewis and P. P. Lynch, *Tetrahedron* **24**, 4489 (1968)

[6] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.* **85**, 207 (1963)

[7] J. Szmuszkovicz, *Advances in Organic Chemistry, Methods and Results* Vol. 4; pp. 1,113. Interscience, New York (1963)

[8] R. Lukeš, *Collection Czech. Chem. Commun.* **10**, 66 (1938)

[9] N. J. Leonard and R. R. Sauers, *J. Am. Chem. Soc.* **79**, 6210 (1957)

[10] N. J. Leonard, P. D. Thomas, and V. W. Gash, *Ibid.* **77**, 1552 (1955)

[11] R. Bonnett, V. M. Giddey, and A. Todd, *J. Chem. Soc.* 2087 (1959)

[12] J. J. Panouse, J. Schmitt, P. J. Cornu, A. Hallot, H. Pluchet, and p. Comoy, *Bull. Soc. Chim. Fr* 1767 (1963) and the foregoing papers of this series

[13] *Enamines: Synthesis, Structure, and Reactions*, (Edited by A. G. Cook) Marcel Dekker, New York (1969)

[14] P. E. Iversen and J. Ø. Madsen, *Tetrahedron* **30** 3477 (1974)

[15] J. Ø. Madsen and S.-O. Lawesson, forthcoming paper.

[16] H. Feltkamp and K. D. Thomas, *Lieb. Ann.* **685**, 148 (1965)

[17] A. C. Cope, N. A. LeBel, H.-H. Lee, and W. R. Moore, *J. Am. Chem. Soc.* **79**, 4720 (1957) and refs therein

[18] E. S. Gould, *Mechanism and Structure in Organic Chemistry* pp. 500, 504. Holt, Rinehart and Winston, New York (1959)

[19] P. E. Iversen and H. Lund, *Anal. Chem.* **41**, 1322 (1969)

[20] C. Schöpf, A. Komzak, F. Braun, and E. Jacobi, *Lieb. Ann.* **559**, 40 (1948)