

ASYMMETRIC REACTIONS. XLV.*

UTILISATION OF THE ASYMMETRIC TRANSFORMATION
TO DETERMINE THE ABSOLUTE CONFIGURATION OF AMINES

O. ČERVINKA and V. DUDEK

*Department of Organic Chemistry,
Institute of Chemical Technology, Prague 6*

Received February 8th, 1972

The reaction of (*S*)-(+)-hydratropic acid with the racemic amines I–VI in the presence of dicyclohexylcarbodiimide leads to amides which are formed preferentially with one antipode of the amines used. From the sign of the optical rotation of the unreacted amine can be judged of the absolute configuration of the carbon atom carrying the amino group.

In one of our previous papers¹ has been reported the reduction of alkylarylketimines and diarylketimines with optically active alkoxy lithium aluminium hydrides prepared by partial decomposition of lithium aluminium hydride with optically active alcohols. In order to support the results obtained by the asymmetric reduction of ketimines we have now determined the absolute conformation of the amines by the method which utilises the asymmetric transformation.

In our first paper dealing with the utilisation of the asymmetric transformation to determine the absolute configuration of organic compounds² we have studied the acylation of optically active amines with racemic hydratropic acid in the presence of dicyclohexylcarbodiimide. The isolation of the unreacted optically active hydratropic acid was explained by the formation of two energetically different transition states the decomposition of which leads to two diastereoisomeric amides in different amounts. The configuration of the isolated optically active hydratropic acid is opposite to that of the acid which is involved in the formation of the preferred amide. Already in the referred paper we have pointed out that the reaction with primary amines need not necessarily proceed unambiguously. In such cases it is of advantage to prepare a secondary amine from the primary one, usually the N-methyl derivative will do, and to compare the results of the asymmetric reaction obtained with both amines. Similar observations were made when utilising this reaction to determine the absolute configuration of acids bearing an asymmetric carbon atom at the α -position in respect to the carboxyl group^{3,4}.

In the present work we have modified this method. For the reaction we used optically active (*S*)-(+)-hydratropic acid of known absolute configuration⁵ and

* Part XIV: This Journal 38, 938 (1973).

optically inactive amines. The reduction was performed in such a manner that we first mixed the calculated amount of (*S*)-(+)-hydratropic acid with an equimolar amount of dicyclohexylcarbodiimide in tetrahydrofuran. To the thus prepared acylating agent was added the racemic amine in the same solvent. The ratio of the acid to the amine was always 1 : 1.5. After standing for 24 h, the unreacted amine was isolated and its optical rotatory power determined.

From the reaction of (\pm)- α -phenylethylamine, (\pm)-phenylbenzylmethylamine, (\pm)-phenyl-*o*-tolylmethylamine, (\pm)-methyl-1-naphthylmethylamine, (\pm)-phenyl-1-naphthylmethylamine, and (\pm)-1-amino-1,2,2,3,4-tetrahydronaphthalene with (*S*)-(+)-hydratropic acid we isolated (*R*)-(+)- α -phenylethylamine (*Ia*), $[\alpha]_D^{20} +0.67^\circ$ (*c* 3.6, ethanol), (*R*)-(-)phenylbenzylmethylamine (*II*, *R* = H), $[\alpha]_D^{20} -1.66$ (*c* 3.1, ethanol), (*S*)-(-)-phenyl-*o*-tolylmethylamine (*III*, *R* = H), $[\alpha]_D^{20} -0.82^\circ$ (*c* 4.7, ethanol), (*S*)-(-)-methyl-1-naphthylmethylamine (*IV*, *R* = H), $[\alpha]_D^{20} -1.33^\circ$ (*c* 6.1, ethanol), (*S*)-(+)-phenyl-1-naphthylmethylamine (*V*, *R* = H), $[\alpha]_D^{20} +0.67^\circ$ (*c* 5.2, ethanol), and (*S*)-(+)-1-amino-1,2,3,4-tetrahydronaphthalene (*VI*, *R* = H), $[\alpha]_D^{20} +1.60$ (*c* 4.4, ethanol). From the *N*-methyl derivatives we obtained (*S*)-(-)-methylphenylmethylaminomethane (*Ib*), $[\alpha]_D^{20} -3.50^\circ$ (*c* 4.8, ethanol), (*R*)-(-)phenylbenzylmethylaminomethane (*II*, *R* = CH₃), $[\alpha]_D^{20} -4.75^\circ$ (*c* 3.3, ethanol), (*S*)-(-)-phenyl-*o*-tolylmethylaminomethane (*III*, *R* = CH₃), $[\alpha]_D^{20} -2.6$ (*c* 6.8, ethanol), (*S*)-(-)-methyl-1-naphthylmethylaminomethane (*IV*, *R* = CH₃), $[\alpha]_D^{20} -1.53^\circ$ (*c* 4.2, ethanol), (*S*)-(+)-phenyl-1-naphthylmethylaminomethane (*V*, *R* = CH₃), $[\alpha]_D^{20} +2.90$ (*c* 6.6, ethanol), (*S*)-(+)-1-methylamino-1,2,3,4-tetrahydronaphthalene (*VI*, *R* = CH₃), $[\alpha]_D^{20} +3.9$ (*c* 4.6, ethanol).

The ORD curves of the non-methylated and methylated amines obtained show that the pairs considered belong to the same steric series. The absolute configuration of the amines *Ia,b* was determined by Leithe⁶ who correlated them with L-(+)-alanine. The absolute configuration of the amines *II* (*R* = H) and *IV* (*R* = H) has been inferred by means of the analysis of their optical rotatory dispersion curves⁷⁻⁹. The ORD curves of the amines *III* (*R* = H) and *V* (*R* = H) (Fig. 1) exhibit a complicated Cotton effect. The presence of two chromophores in the molecule does

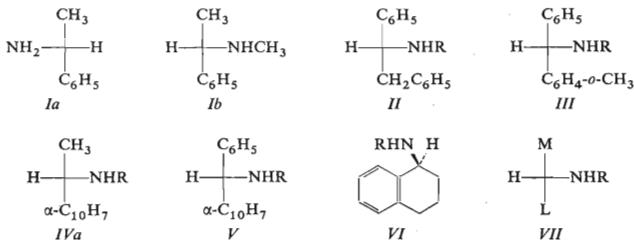


TABLE I
Derivatives of the Primary Amines

Amine R ^a	B.p., °C (yield, %)	Formula (m. w.)	Calculated/Found		
			% C	% H	% N
<i>II</i> CH ₃	157–158/16 ^b (67)	C ₁₅ H ₁₇ N (211·3)	85·26 85·20	8·11 7·98	6·63 6·64
<i>III</i> CHO	109–110 (82)	C ₁₅ H ₁₅ NO (225·3)	79·97 79·73	6·71 7·05	6·22 6·00
<i>III</i> CH ₃	112/0·01 ^b (66)	C ₁₅ H ₁₇ N (211·3)	85·26 85·19	8·11 8·10	6·23 6·24
<i>IV</i> CHO	96–97 (76)	C ₁₃ H ₁₃ NO (199·2)	78·36 78·03	6·58 6·57	7·03 7·13
<i>IV</i> CH ₃	111–112/11 ^b (56)	C ₁₃ H ₁₅ N (185·3)	84·27 84·33	8·16 8·10	7·56 7·50
<i>V</i> CHO	116–119 (81)	C ₁₈ H ₁₅ NO (261·3)	82·73 82·79	5·79 6·11	5·36 6·13
<i>V</i> CH ₃	57–58 ^c (55)	C ₁₈ H ₁₇ N (247·3)	87·41 87·11	6·93 6·89	5·66 5·74
<i>VI</i> CHO	81–82 (84)	C ₁₁ H ₁₃ NO (175·2)	75·40 75·34	7·48 7·66	7·99 7·84
<i>VI</i> CH ₃	85/0·01 ^b (63)	C ₁₁ H ₁₅ N (161·2)	81·94 82·06	9·38 9·61	8·69 8·43

^a The formyl derivatives were crystallised from acetone–ether; ^b b.p. °C/Torr; ^c m.p. of the hydrochloride of the base 231°C with decomposition.

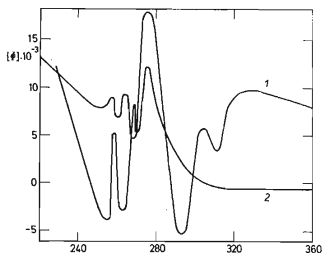


FIG. 1
ORD Curves 1 of (*S*)-(+)-Phenyl-1-naphthylmethylaminomethane (*V*, R = CH₃) and 2 of (*S*)-(-)-Phenyl-*o*-tolylmethylaminomethane (*III*, R = CH₃)

TABLE II
Amines I–VI from the Reaction of (S)-(+)-Hydrotrropic Acid with Racemic Amines

Amine	B.p., °C/Torr (literature)	Formula (m. w.)	Calculated/Found		
			% C	% H	% N
<i>Ia</i>	78–80/13	C ₈ H ₁₁ N	79.29	9.15	11.56
	77/10 (13)	(121.2)	79.36	9.30	11.22
<i>Ib</i>	80/12	C ₉ H ₁₃ N	79.95	9.69	10.36
	—	(135.2)	79.92	9.50	10.54
<i>II</i> (R = H)	110–113/0.4	C ₁₄ H ₁₅ N	85.23	7.66	7.10
	142–143 (14)	(197.3)	85.15	7.54	6.98
<i>II</i> (R = CH ₃)	157–158/16	C ₁₅ H ₁₇ N	85.26	8.11	6.63
	160–161/8	(211.3)	85.16	8.18	6.35
<i>III</i> (R = H)	113/0.2	C ₁₄ H ₁₅ N	85.23	7.66	7.10
	229/721 (15)	(197.3)	85.24	7.55	7.10
<i>III</i> (R = CH ₃)	135–138/0.2	C ₁₅ H ₁₇ N	85.26	8.11	6.63
	—	(211.3)	85.34	8.28	6.43
<i>IV</i> (R = H)	98/0.2	C ₁₂ H ₁₃ N	84.17	7.65	8.18
	153/11 (7)	(171.2)	84.17	7.85	8.32
<i>IV</i> (R = CH ₃)	111–112/1	C ₁₃ H ₁₅ N	84.27	8.16	7.56
	—	(185.3)	84.28	8.02	7.36
<i>V</i> (R = H)	77–78 ^a	C ₁₇ H ₁₅ N	87.51	6.48	6.00
	—	(233.3)	87.72	6.33	6.10
<i>V</i> (R = CH ₃)	57–58 ^a	C ₁₈ H ₁₇ N	87.41	6.93	5.66
	—	(247.3)	87.12	7.03	5.77
<i>VI</i> (R = H)	128/16	C ₁₀ H ₁₃ N	81.58	8.90	9.52
	120/12 (16)	(147.2)	81.58	9.12	9.51
<i>VI</i> (R = CH ₃)	109–111 ^a	C ₁₁ H ₁₅ N	81.94	9.38	8.69
	—	(161.2)	81.78	9.36	8.69

^a M.p., °C.

not at present allow a more detailed analysis, however the positive Cotton effect at 275 nm indicates that they possess the same absolute configuration. The comparison of the ORD curves of the amines *VI* (R = H, CH₃) with those of (S)-(+)-1-indamine and its N-methyl derivative of known absolute configuration¹⁰ confirms their absolute configuration.

On the basis of already earlier derived configurational relations belongs to the secondary amines the absolute configuration expressed by the general formula *VII*

($R = CH_3$) $L > M$, under the assumption that in this type of reactions phenyl and 1-naphthyl behave in steric respect as bulkier groups than methyl, and similarly also benzyl $>$ phenyl, *o*-tolyl $>$ phenyl, and 1-naphthyl $>$ phenyl. The analogue primary amines fit all this scheme with the only exception of amine *Ia*, as has already been pointed out in our previous papers^{2,4}.

EXPERIMENTAL

Melting and boiling points are uncorrected. Samples for analysis were dried in an oil-pump vacuum at room temperature for 8 h.

Chemicals: (*S*)-(+)-hydratropic acid was prepared by resolving the racemic acid with strychnine, b.p. 146–148°C/13 Torr, $[\alpha]_D^{20} -90.6^\circ$ (*c* 3.51, benzene). Literature¹¹ gives b.p. 143°C/13 Torr; $[\alpha]_D^{20} +92.5$ (benzene). The following racemic amines were prepared from ketones by the Wallach-Leuckart reaction: α -phenylethylamine, phenylbenzylmethylamine, phenylbenzylmethylaminomethane, phenyl-*o*-tolylmethylamine, methyl-1-naphthylmethylamine, phenyl-1-naphthylmethylamine, 1-amino-1,2,3,4-tetrahydronaphthalene, and 1-methylamino-1,2,3,4-tetrahydronaphthalene. The formyl derivatives were prepared from the primary amines by reaction with formyl acetate in benzene. By their reduction with lithium aluminium hydride in tetrahydrofuran were obtained the corresponding N-methyl derivatives (Table I).

(+)-Phenyl-1-naphthylmethylamine (*V*, $R = H$)

The racemic amine was prepared by reaction of phenyl magnesium bromide with 1-naphthonitrile and subsequent reduction of the formed addition compound with lithium aluminium hydride. Acid tartrate m.p. 205–208°C (ethanol); literature¹² gives m.p. 190–207°C. Free base m.p. 77–78°C, $[\alpha]_D^{20} +65.5^\circ$ (*c* 4.23, benzene).

Reaction of (*S*)-(+)-Hydratropic Acid with the Amines *I–VI*

A solution of dicyclohexylcarbodiimide (1.03 g; 5 mmol) in tetrahydrofuran (2 ml) was added to (*S*)-(+)-hydratropic acid (0.75 g; 5 mmol) in tetrahydrofuran (1 ml). Into the cooled, almost solidified mixture was poured a solution of the amine (7.5 mmol) in tetrahydrofuran (10 ml). After standing overnight, dicyclohexylurea and the amide were filtered off with suction and the tetrahydrofuran layer was shaken with 10 ml of 2M acetic acid. From the acid solution the amine was liberated by alkalis and then taken up in ether. The product was distilled and crystallised. Optical rotations were measured in ethanol. The results of the experiments are summarized in Tables I and II.

Reaction of (+)-Phenyl-1-naphthylmethylamine with Racemic Hydratropic Acid

(+)-Hydratropic acid (1.15 g; 7.67 mmol) was mixed with dicyclohexylcarbodiimide (1.05 g; 5.11 mmol) and subsequently with (+)-phenyl-1-naphthylmethylamine (1.9 g; 5.11 mmol), and the mixture was set aside for 24 h. After filtering off dicyclohexylurea and the amide, the acid was taken up in 10 ml of 2M-NaOH. The alkaline solution was acidified with 1M-H₂SO₄ to afford 0.45 g of (*S*)-(+)-hydratropic acid, b.p. 138°C/10 Torr, $[\alpha]_D^{20} +2.13$ (*c* 10.1, ethanol).

The analyses were carried out in the Central Analytical Laboratories, Institute of Chemical Technology, Prague, headed by Dr L. Helešič.

REFERENCES

1. Červinka O., Suchan V., Kotýnek O., Dudek V.: *This Journal* 30, 2484 (1965).
2. Červinka O.: *This Journal* 31, 1371 (1966).
3. Červinka O., Hub L.: *Chem. Commun.* 1966, 761.
4. Červinka O., Hub L.: *This Journal* 32, 2295 (1967).
5. Bernstein H. J., Whitmore F. C.: *J. Am. Chem. Soc.* 61, 1324 (1939).
6. Leithe W.: *Ber.* 64, 2827 (1931).
7. Warren M. E. jr, Smith H. E.: *J. Am. Chem. Soc.* 87, 1757 (1965).
8. Wolf H., Bunnenberg E., Djerassi C.: *Chem. Ber.* 97, 533 (1964).
9. Smith H. E., Records R.: *Tetrahedron* 22, 813 (1966).
10. Brewster J. H., Buta J. G.: *J. Am. Chem. Soc.* 88, 2233 (1966).
11. Arcus C. L., Kenyon J.: *J. Chem. Soc.* 1939, 916.
12. Berlingozzi S.: *Gazz. Chim. Ital.* 50, 56 (1920).
13. Holmberg B.: *Ber.* 45, 997 (1912).
14. Baumgarten H. E., Peterson J. M.: *J. Am. Chem. Soc.* 82, 459 (1960).
15. Ingersoll A. W., Brown J. H., Kim C. H., Beauchamp W. D., Jennings G.: *J. Am. Chem. Soc.* 58, 1808 (1936).

Translated by R. Wicks.