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Thin-layer chromatography of the positional isomers of some 1,2,3,4-tetrahydro-2-naphthol and 3-amino-1,2,3,4-tetrahydro-2-naphthol derivatives

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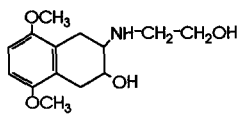
ABSTRACT

The separation of 29 isomer pairs, namely three pairs of 5- and/or 8-substituted 1,2,3,4-tetrahydronaphthols, one pair of naphthalene derivatives (naphthalene-1,7-diol and naphthalene-1,6-diol) and 25 pairs of N-substituted 3-amino-1,2,3,4-tetrahydro-2-naphthols {including their lactone derivatives, tetrahydro-4*H*-naphth[2,3-*b*][1,4]oxazin-2-ones} in TLC systems on silica or alumina was studied. The possibility of two-point contact with the adsorbent in the case of more strongly retained isomers and their edgewise orientation against its surface is discussed. Attention is also paid to the influence of substituents in position 3 of the 1,2,3,4-tetrahydro-2-naphthol ring system on the retention sequence of the respective isomers.

INTRODUCTION

trans-3-[(2-Hydroxyethyl)amino]-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol* (tetraminol, **1**) is a



Tetraminol (1)

drug exhibiting α-adrenomimetic, vasoconstrictory and pressoric effects [1–3]. In the course of a study of its biotransformation *in vitro* involving the elucidation of the structure of the isomeric products of mono-O-demethylation (**12** and **13**), three isomeric pairs of 1,2,3,4-tetrahydro-2-naphthols substituted in the aromatic nucleus (**2–7**) and nine pairs of isomeric derivatives of 3-amino-1,2,3,4-tetrahydro-2-naphthols 5,8-disubstituted in the aromatic nucleus as well as on the N-atom (**12–15**, **20/21**, **40/41**, **44–47**, **54–59**) [4,5] were prepared (Table I).

This paper is devoted to the interpretation of the retention sequence of isomers. In order to check some conclusions, N-acetyl (**18/19**) and N-benzoyl (**36/37**) derivatives of compounds **12** and **13** were prepared. For the sake of comparison, five isomeric pairs devoid of a methoxy group in the aromatic nucleus (**10/11**, **16/17**, **34/35**, **38/39**, **42/43**) were also prepared [6]. It has been found that during chromatography in basic systems S3 and S4, lactones **54–59** react with the components of the mobile phases (methanol, ethanol, ammonia). Chromatographic retention of the resulting esters **22–25**, **28–31** and **48–51** and the amides **26–27**, **32/33** and **52/53**, most of which were prepared synthetically [6], has been shown to be important for the corect interpretation

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* In agreement with standard chemical nomenclature, position of the alcohol group is indicated here as 2- and that of the amino group as 3- (*cf.*, *C.A.* code No. 64381-81-8), although the name 2-hydroxyethylamino-3-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene has been used in the chemical and pharmacological literature [1–3].

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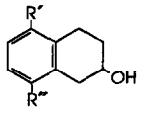
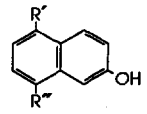
TABLE I

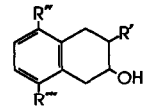
STRUCTURES OF THE COMPOUNDS



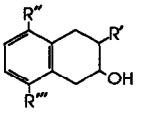
Compound No.	R′ (5)	R″ (8)
2	OH	H
3	H	OH
4	OCH_3	H
5	H	OCH_3
6	OH	OCH_3
7	OCH_3	OH



	R′	R″
8 (1,6-diol)	OH	H
9 (1,7-diol)	H	OH

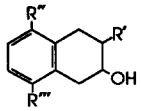
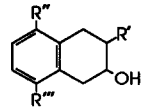
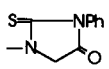
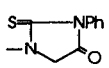


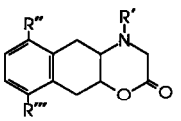
	R′ (3)	R″ (5)	R‴ (8)
10	$-NHCH_2CH_2OH$	OH	H
11	$-NHCH_2CH_2OH$	H	OH
12	$-NHCH_2CH_2OH$	OH	OCH_3
13	$-NHCH_2CH_2OH$	OCH_3	OH
14	$-NHCH_2COOH$	OH	OCH_3
15	$-NHCH_2COOH$	OCH_3	OH
16	$-NCH_2CH_2OH$ (O=CCH₃)	OH	H
17	$-NCH_2CH_2OH$ (O=CCH₃)	H	OH
18	$-NCH_2CH_2OH$ (O=CCH₃)	OH	OCH_3
19	$-NCH_2CH_2OH$ (O=CCH₃)	OCH_3	OH



Compound No.	R′ (3)	R″ (5)	R‴ (8)
20	$-NCH_2COOH$ (O=CCH₃)	OH	OCH_3
21	$-NCH_2COOH$ (O=CCH₃)	OCH_3	OH
22	$-NCH_2COOCH_3$ (O=CCH₃)	OH	OCH_3
23	$-NCH_2COOCH_3$ (O=CCH₃)	OCH_3	OH
24	$-NCH_2COOC_2H_5$ (O=CCH₃)	OH	OCH_3
25	$-NCH_2COOC_2H_5$ (O=CCH₃)	OCH_3	OH
26	$-NCH_2CONH_2$ (O=CCH₃)	OH	OCH_3
27	$-NCH_2CONH_2$ (O=CCH₃)	OCH_3	OH
28	$-NCH_2COOCH_3$ (O=CCH₃)	$-OCOCH_3$	OCH_3
29	$-NCH_2COOCH_3$ (O=CCH₃)	OCH_3	$-OCOCH_3$
30	$-NCH_2COOC_2H_5$ (O=CCH₃)	$-OCOCH_3$	OCH_3
31	$-NCH_2COOC_2H_5$ (O=CCH₃)	OCH_3	$-OCOCH_3$
32	$-NCH_2CONH_2$ (O=CCH₃)	$-OCOCH_3$	OCH_3
33	$-NCH_2CONH_2$ (O=CCH₃)	OCH_3	$-OCOCH_3$

TABLE I (*continued*)

Compound No.				Compound No.			
	R′ (3)	R″ (5)	R‴ (8)		R′ (3)	R″ (5)	R‴ (8)
34	O=CPh | –NCH$_2$CH$_2$OH	OH	H	48	O=COCH$_2$Ph | –NCH$_2$COOCH$_3$	OH	OCH$_3$
35	O=CPh | –NCH$_2$CH$_2$OH	H	OH	49	O=COCH$_2$Ph | –NCH$_2$COOCH$_3$	OCH$_3$	OH
36	O=CPh | –NCH$_2$CH$_2$OH	OH	OCH$_3$	50	O=COCH$_2$Ph | –NCH$_2$COOC$_2$H$_5$	OH	OCH$_3$
37	O=CPh | –NCH$_2$CH$_2$OH	OCH$_3$	OH	51	O=COCH$_2$Ph | –NCH$_2$COOC$_2$H$_5$	OCH$_3$	OH
38	CH$_2$Ph | –NCH$_2$CH$_2$OH	OH	H	52	O=COCH$_2$Ph | –NCH$_2$CONH$_2$	OH	OCH$_3$
39	CH$_2$Ph | –NCH$_2$CH$_2$OH	H	OH	53	O=COCH$_2$Ph | –NCH$_2$CONH$_2$	OCH$_3$	OH
40	CH$_2$Ph | –NCH$_2$CH$_2$OH	OH	OCH$_3$				
41	CH$_2$Ph | –NCH$_2$CH$_2$OH	OCH$_3$	OH				
42	S=CNHPh | –NCH$_2$CH$_2$OH	OH	H				
43	S=CNHPh | –NCH$_2$CH$_2$OH	H	OH				
44	| –NCH$_2$CH$_2$OH	OH	OCH$_3$				
45	S=CNHPh | –NCH$_2$CH$_2$OH	OCH$_3$	OH				
46		OH	OCH$_3$				
47		OCH$_3$	OH				



(2,3,4a,5,10,10a-hexahydro-4*H*-naphth[2,3-*b*] [1,4]oxazin-2-one derivatives)

	R′ (4)	R″ (6)	R‴ (9)
54	–COCH$_3$	OH	OCH$_3$
55	–COCH$_3$	OCH$_3$	OH
56	–COCH$_3$	–OCOCH$_3$	OCH$_3$
57	–COCH$_3$	OCH$_3$	–OCOCH$_3$
58	–COOCH$_2$Ph	OH	OCH$_3$
59	–COOCH$_2$Ph	OCH$_3$	OH

of some of the effects noted in the chromatography of compounds **54–59**.

EXPERIMENTAL

Materials

Kieselgel 60 F_{254} and Aluminiumoxid 60 F_{254} glass plates were obtained from Merck (Darmstadt, Germany).

Analytical-reagent grade chemicals were used unless indicated otherwise. Chloroform [stabilized with 1% ethanol (Merck), not redistilled], absolute methanol (Merck, not redistilled), 96% ethanol (chemically pure, distilled), butanol (Merck), acetic acid (Merck), 4-nitrobenzenediazonium fluoroborate (Reanal, Budapest, Hungary) and 1,7-naphthalenediol (**9**) [95% (pract.) (Fluka, Buchs, Switzerland)] were commercial products.

1,6-Napthalenediol (**8**) was prepared by heating 5-amino-2-naphthol at 180°C in 10% sulphuric acid for 4.5 h in a sealed ampoule as recommended by Dr. J. Latinák (VChZ, Pardubice-Semtín, Czechoslovakia), who also supplied the starting substance.

Compounds **2–7**, **12–15**, **20/21**, **40/41**, **44–47** and **54–59** were prepared by procedures described elsewhere [4,5].

Compounds **10** and **11** were prepared by aminolysis of 2,3-epoxy-5-acetoxy-1,2,3,4-tetrahydronaphthalene with 2-hydroxyethylamine, using a method analogous to that for the production of **12** and **13** [4,5,7].

Compounds **16–19** were prepared by N-acetylation and **34–37** by N-benzoylation of **10–13**. Compounds **38** and **39** were prepared by the reduction of **34** and **35** with lithium aluminium hydride. Compounds **42** and **43** were prepared from **10** and **11** by means of phenyl isothiocyanate [5]. Compounds **26** and **27** were prepared by heating the lactones **54** and **55** with 25% ammonia.

Compounds **22/23** and **48/49** were prepared by briefly heating methanolic solutions of the lactones **54/55** and **58/59**, respectively. Compounds **24/25** and **50/51** were similarly prepared by heating of ethanolic solutions of the respective lactones.

Methyl esters **28/29** and ethyl esters **30/31** were prepared by adding catalytic amounts of triethylamine to the solutions of the lactones **56/57** in chloroform–methanol (1:1, v/v) or chloroform–ethanol (1:1, v/v), respectively.

The amides **32/33** and **42/43** resulted during chromatography of the lactones **56/57** and **58/59**, respectively, on silica in systems S3 and S4, which contain ammonia. Chromatographic spots corresponding to the amides were identified according to their chromatographic retention and the colours of the detection reactions.

Compounds **2–7** are racemates; **10–53** are 2,3-*trans* racemates; the 2,3,4a,5,10,10a-hexahydro-4*H*-naphth[2,3-*b*] [1,4]oxazin-2-one derivatives **54–59** are 4a,10a-*trans* racemates.

Chromatographic technique

A Camag (Muttenz, Switzerland) Model 20/20 chromatographic tank was used. Equilibration was applied for 30 min before chromatography.

TLC solvent systems. The following systems were used: S1 = chloroform; S2 = chloroform–methanol (95:5, v/v); S3 = chloroform–methanol–25% (w/v) aqueous ammonia (80:10:1, v/v/v); S4 = chloroform–96% (v/v) ethanol–25% (w/v) aqueous ammonia (80:10:1, v/v/v) (turbidity is removed by filtration through cotton-wool); S5 = chloroform–methanol–acetic acid (15:5:1, v/v/v); and S6 = butanol–acetic acid–water (40:10:50, v/v/v) (the organic phase is used).

Solutions for spotting. These were freshly prepared, as some of the compounds are not stable. Volumes of 2–3 μl of 1% solutions of the compounds tested were spotted in the following solvents: chloroform, **4/5**, **28/31**, **42–45**, **56/57**; chloroform–ethanol (4:1, v/v), **2/3**, **6–9**, **22–25**, **48–51**, **54/55**, **58/59**; chloroform–ethanol (1:1, v/v), **38–41**, **46**, **47**; ethyl acetate, **16–19**, **34–37**; methanol, **20/21**, **26/27**; and methanol–25% (w/v) aqueous ammonia (8:2), **10–15**.

Detection. Method D1 was as follows: 5 ml of an aqueous solution of 2-nitrobenzene diazonium fluoroborate (0.2%, w/v) was mixed with 3 ml of aqueous $NaHCO_3$ (1%, w/v). This mixture was immediately used for spraying of the chromatogram. Detection limits were *ca.* 0.1 μg/cm^2 on silica and 0.5 μg/cm^2 on alumina (Table II). For alternative detection of the compounds, see ref. 8.

Compounds **4/5** are detected by quenching of fluorescence excited at 254 nm.

RESULTS AND DISCUSSION

The results for all the compounds under study are given in Table III.

It should be realized that when lactones **54–59** are chromatographed in S3 or S4, which contain ammonia and methanol or ethanol, they undergo alcoholysis to give esters as indicated in Table III. In addition to the esters indicated in Table III, certain amounts of amides are produced from the lactones **54–59** in system S3 or S4 on silica.

Systems S5 and S6 usually did not resolve the isomer pairs, with the exception of **12** which is more strongly retained than **13** in S5.

With respect to the resolution of the isomer pairs, the compounds under study can be grouped into three classes: in (a) and (b) the retention sequence can be predicted on simple assumptions, whereas in (c) the prediction is difficult.

(a) In the case of isomeric 1,2,3,4-tetrahydronaphthalenediols **2/3** and **6/7**, a stronger retention corresponds to a shorter distance between the OH groups. This also applies to the pair of isomeric naphthalenediols **8/9**.

The stronger retention of **8** and **9** in the basic system S3, especially on alumina, is probably due to their biphenolic nature compared with **2/3** and **6/7**.

The stronger retention of isomers with a shorter distance between the OH groups could be explained by their capacity to form two-point contacts with the adsorbents in the case of edgewise orientation with respect to the adsorbent surface. This hypothesis is also applicable to the methoxyhydroxy isomers **4** and **5** in system S1. A weaker interaction of the methoxy groups with the adsorbent in **4** and **5**, when compared with phenolic OH groups in the remaining isomer pairs (**2/3**, **6–9**), may explain the loss of separation of **4** and **5** in the more polar systems S2 and S3.

With all the other compounds, nitrogen occurs in position 3 of the tetrahydronaphthalene or in the oxazine ring.

(b) In all instances in which a bulky substituent is bound to this nitrogen (compounds **34–53** and **58/59**), compounds with OH or $OCOCH_3$ in position 8 of the tetrahydronaphthalene or in position 9 of the hexahydronaphthoxazinone are more strongly retained. Here again, one would postulate the formation of two-point contacts of the analyte with the adsorbent in the case of edgewise orientation with respect to the adsorbent surface. Such an orientation involving OH (or $OCOCH_3$) in position 5 (or 6) would be prevented by the bulky substituent on the nitrogen.

(c) With the remaining compounds (**10–33** and **54–57**), it is difficult to establish whether the nitrogen- or the oxygen-containing grouping is more polar and to predict whether the isomer with OH (or $OCOCH_3$) in position 5 or 8 of the tetrahydronaphthalene (or 6 or 9 of the hexahydronaphthoxazinone) would be more strongly retained.

Primary alcohols **16/17** and **18/19** and the esters **22/23** and **24/25** resemble the groups discussed under (a) and (b) by their stronger retention of the 8-OH isomers.

With the **10/11** and **12/13** [9] pairs, the 8-isomer is distinctly more strongly retained in S3 on alumina; electrostatic attraction might increase the adsorption of the $-NHCH_2CH_2OH$ group on silica, but not on alumina.

Of the N-acetylated compounds **16–33**, amides **26** (with 5-OH) and **32** (with 5-$OCOCH_3$) and the O-acetylated esters **28** and **30** (with 5-$OCOCH_3$) show stronger retentions than their isomers. Similarly, in the **54/55** and **56/57** pairs, those with 6-OH (**54**) or 6-$OCOCH_3$) (**56**) are more strongly retained.

Amino acids **14/15** and **20/21** are not resolved; in both instances, system S6 gave the best shape of the spots.

TABLE II

DETECTION OF THE COMPOUNDS ON SILICA WITH 4-NITROBENZENEDIAZONIUM FLUOROBORATE

For alternative detection of the compounds, see ref. 8.

Compounds	D1
2/3, **10/11**, **16/17**, **34/35**, **38/39**, **42/43**	Yellow-orange
6/7, **12–15**, **18–27**, **28–33**[a], **36/37**, **40/41**, **44/45**, **48–55**, **56/57**[a], **58/59**	Red-purple
8	Ochre
9	Crimson
46/47	Brownish red

[a] The chromatogram is first enclosed in an atmosphere of ammonia in order to liberate the phenolic group by ammonolysis.

TABLE III

TLC RETENTION DATA

Compound	$R_F \times 100$						
	Silica						Alumina
	S1	S2	S3	S4	S5	S6	S3
2	6	20	38				46
3	5	16	32				40
4	19	47	66				71
5	17	47	66				71
6	6	19	38				49
7	5	14	32				42
8	7	22	32				28
9	5	17	26				18
10	0	0	7 (26)[a]		32	51	15
11	0	0	7 (27)[a]		32	51	8
12	0	0	7 (28)[a]		33	51	15
13	0	0	7 (30)[a]		36	51	10
14	0	0	0		14[b]	44	0
15	0	0	0		14[b]	44	0
16	0	8	25		94		36
17	0	6	20		94		26
18	0	7	24		94		38
19	0	6	21		94		31
20	0	0	0		42[b]	48	0
21	0	0	0		42[b]	48	0
22	7	29	53	49			62
23	5	27	49	43			55
24	7	33	58	53			65
25	5	29	52	46			57
26	0	3	14	6			14
27	0	4	16	8			14
28	8	55	74	73			81
29	10	59	76	75			81
30	11	58	76	75			81
31	12	61	78	77			81
32	–	–	33	25			–
33	–	–	36	29			–
34	0	14	35				42
35	0	12	29				34
36	0	14	35				46
37	0	12	32				39
38	0	19	52				63
39	0	14	39				50
40	0	18	51				63
41	0	14	40				53
42	0	19	40				56
43	0	13	29				42
44	0	19	42				56
45	0	13	30				44
46	0	33	56				65
47	0	20	41				53

TABLE III *(continued)*

Compound	R_F × 100						
	Silica						Alumina
	S1	S2	S3	S4	S5	S6	S3
48	10	44	65	61			70
49	7	37	57	51			63
50	13	51	66	63			70
51	12	46	58	53			63
52	–	–	30	21			–
53	–	–	27	18			–
54[c]	6	26	53 (**22**)	53 (**24**			62 (**22**)
55[c]	8	33	49 (**23**)	45 (**25**)			55 (**23**)
56[c]	13	59	74 (**28**)	75 (**30**)			81 (**28**)
57[c]	15	62	76 (**29**)	77 (**31**)			81 (**29**)
58[c]	12	48	65 (**48**)	63 (**50**)			70 (**48**)
59[c]	11	44	57 (**49**)	53 (**51**)			63 (**49**)

[a] Fivefold elution.
[b] Diffuse spots.
[c] Numbers in parentheses refer to esters into which the lactones have been converted in the respective solvent systems.

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