THE SYNTHESIS AND IDENTIFICATION OF ISOMERIC PRODUCTS OF ENZYMATIC O-DEMETHYLATION OF THE SYMPATHOMIMETIC TETRAMINOL – *trans*-3-(2-HYDROXYETHYLAMINO)-5,8-DIMETHOXY-1,2,3,4-TETRAHYDRO-2-NAPHTHOL

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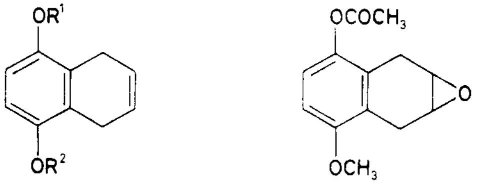
Received December 29, 1990
Accepted July 9, 1991

The structure of the positional isomers of mono-O-demethylated metabolites (*V* and *VI*) of Tetraminol — *trans*-3-(2-hydroxyethylamino)-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (*XIX*) — and the pairs of related derivatives was determined.

Studies concerning the biotransformation in vitro of *trans*-3-(2-hydroxyethylamino)-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (Tetraminol, *XIX*), a compound with α-adrenomimetic, vasoconstrictor and pressor activity$^{1-3}$, have shown the presence of a mono-O-demethylated metabolite in the incubation medium containing a post-mitochondrial fraction (10 000 g) of the liver homogenate of experimental animals, NADPH and O_2 (ref.[4]).

The aim of this study was the synthesis of both possible isomeric mono-O-demethylated analogues of Tetraminol (*V* and *VI*) and their structural characterization, so that they might be used as standards in TLC (ref.[5]).

The synthesis of epoxide *IV*, the starting substance for the preparation* of com-



I, $R^1 = H$; $R^2 = H$
II, $R^1 = H$; $R^2 = CH_3$
III, $R^1 = COCH_3$; $R^2 = CH_3$

IV

SCHEME 1

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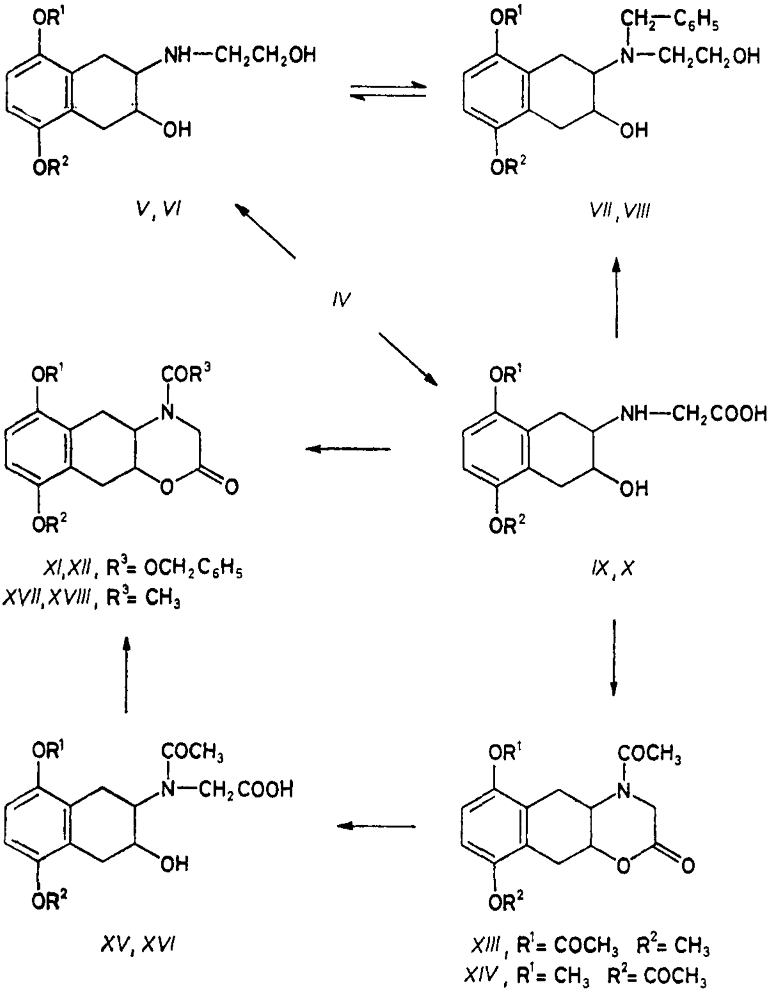
* The synthetically prepared compounds *V* and *VI*, as well as compound *XIX* and other unsymmetrically substituted compounds, are racemates.

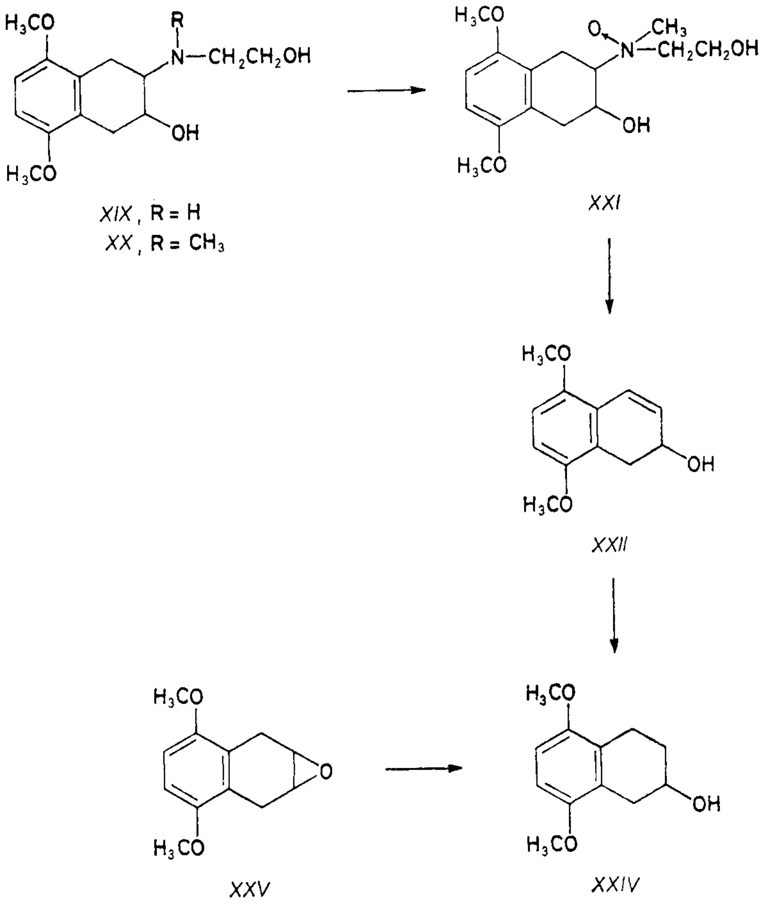
pounds *V* and *VI*, is described in Scheme 1. Compound *I* was prepared from benzoquinone and butadiene by Diels–Alder reaction[6]. Partial methylation gave compound *II*, described in literature[7]. Subsequent acetylation gave rise to compound *III*, the epoxidation[8] of which led to epoxide *IV*. Isomers *V* and *VI* (Scheme 2) were prepared by aminolysis of epoxide *IV* with 2-aminoethanol in an approximately 1 : 1 ratio. The compounds can be separated by TLC, using protracted development[5]. Further, a 1 : 1 mixture of amino acids *IX* and *X* was prepared from epoxide *IV*



In formulae *V*, *VII*, *IX*, *XI*, *XV* and *XVII* : $R^1 = H$; $R^2 = CH_3$
VI, *VIII*, *X*, *XII*, *XVI* and *XVIII* : $R^1 = CH_3$; $R^2 = H$

SCHEME 2

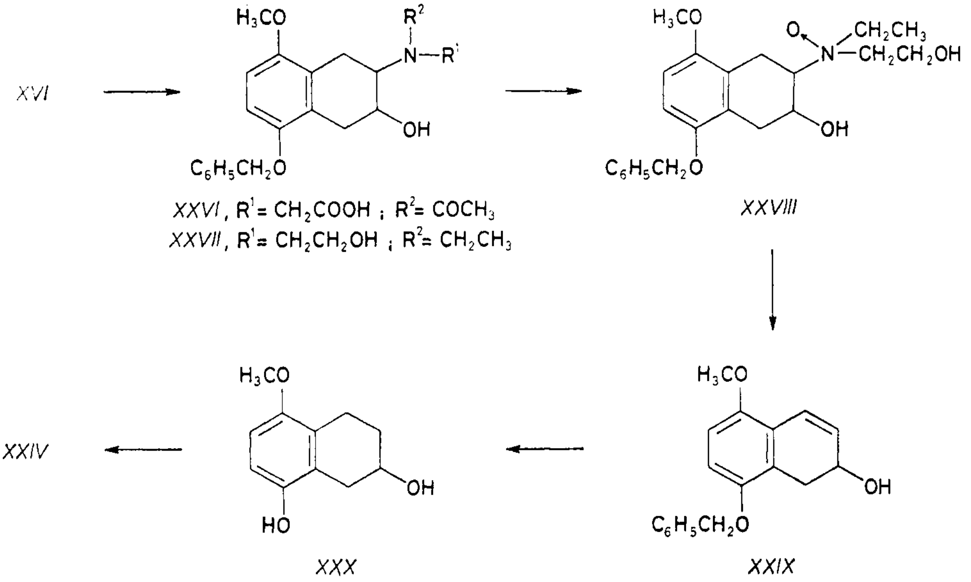
and aminoacetic acid (cf. ref.[9]), from which lactones *XI* and *XII* were prepared. Their mass[10], IR and NMR (ref.[11]) spectra confirmed their structures, but the intramolecular H-bond between the phenolic OH group and the amidic C=O group, considered in one of the two compounds, which would determine it as the isomer *XI*, was not detected. Therefore the structural characterization of compounds *V* and *VI* (or *IX*, *X* and other pairs of isomeric products from Scheme 2) was carried out by chemical correlation.



SCHEME 3

In Scheme 3 the sequence of chemical conversions is shown, carried out with Tetraminol *XIX*, which served as a model in the elaboration of this technique: N-methylation[5] from *XIX* to *XX*, oxidation of the tertiary nitrogen to N-oxide *XXI* and decomposition according to Cope (*cis*-elimination) under mild conditions[12]. Catalytic hydrogenation of the allyl alcohol *XXII* formed leads to compound *XXIV* which was also prepared by reduction of epoxide *XXV*.

Amino acids *IX* and *X* can be separated by crystallization of their mixtures from water. The better crystallizing compound *X* was gradually submitted to acetylation to compound *XIV*, hydrolysis to *XVI*, O-benzylation to *XXVI*, reduction to *XXVII*, N-oxidation to *XXVIII*, decomposition according to Cope to *XXIX* and catalytic hydrogenation during which reduction of the double bond 3(4) and hydrogenolysis of the benzyl ether took place.

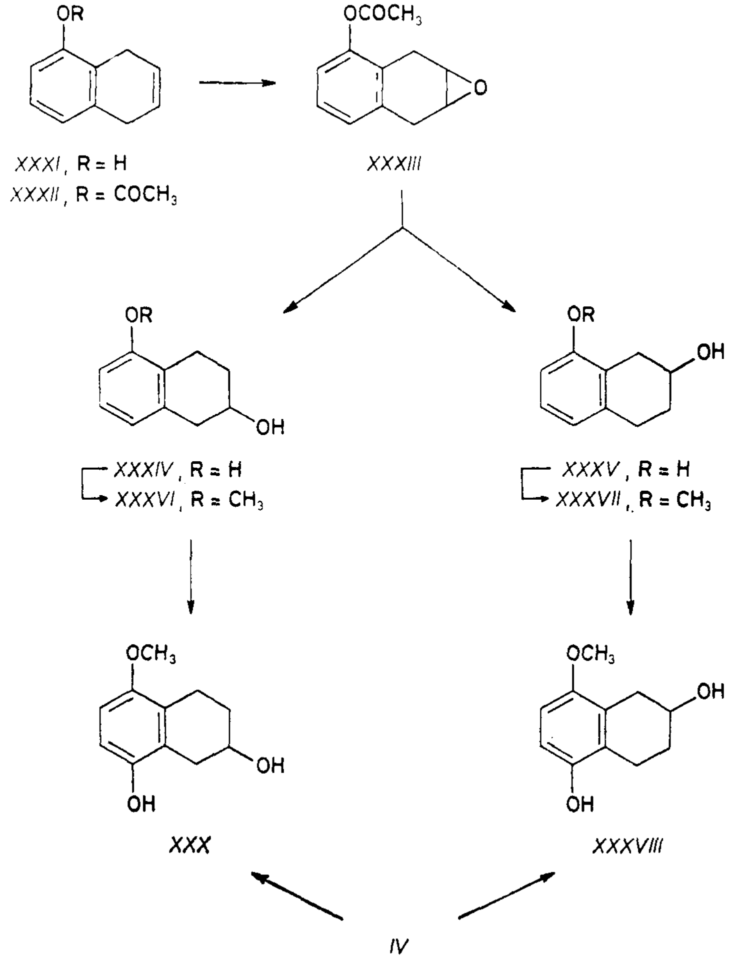


SCHEME 4

After termination of this sequence (Schemes 2 and 4) a compound was obtained which was identical with 5-methoxy-1,2,3,4-tetrahydro-2,8-naphthalenediol (*XXX*) according to its R_F value, colour reactions and melting point. The latter was synthetized (Scheme 5) from 1,2,3,4-tetrahydro-2,5-naphthalenediol (*XXXIV*), described in literature[13], by direct hydroxylation of its methyl ether (*XXXVI*) according to Hamilton and co-workers[14].

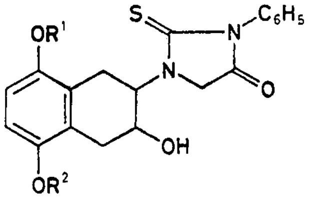
In the course of the syntheses illustrated in Scheme 5 compounds *XXXV*, *XXXVII* and *XXXVIII* were also prepared and characterized, which are isomeric to compounds *XXXIV*, *XXXVI* and *XXX*. Compounds *XXX* and *XXXVIII* were also prepared directly on reduction of epoxide *IV*. Subsequent methylation of each of them leads to *XXIV*.

The isolation of *XXX* as a product of specific degradation of the better crystallizing isomer of the amino acid pair *IX* and *X* permits the identification of this isomer as compound *X*. Total benzoylation of compound *X*, its reduction to *VIII* and catalytic hydrogenation afford the less retained (TLC) of the two isomeric mono-O-demethylated metabolites of Tetraminol, i.e. 3-(2-hydroxyethylamino)-5-methoxy-1,2,3,4-tetrahydro-2,8-naphthalenediol (*VI*) (Scheme 2). From the amino acid which

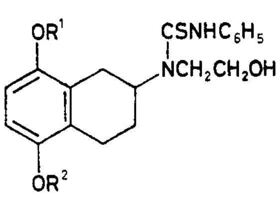


SCHEME 5

remained in the mother liquor (*IX*) the more strongly retained (TLC) 3-(2-hydroxyethylamino)-8-methoxy-1,2,3,4-tetrahydro-2,5-naphthalenediol (*V*) was prepared in the same manner via its N-benzyl derivative *VII*. Compounds *VII* and *VIII* were also prepared directly from *V* and *VI* by benzoylation and reduction.



XXXIX, $R^1 = H$; $R^2 = CH_3$
XL, $R^1 = CH_3$; $R^2 = H$



XLI, $R^1 = H$; $R^2 = CH_3$
XLII, $R^1 = CH_3$; $R^2 = H$

Phenylthiohydantoins *XXXIX* and *XL* and N-phenylthiocarbamoyl derivatives *XLI*–*XLII* may be prepared in a quantitative yield under mild conditions, and they separate well (TLC). Therefore they were used for analysing the mixtures *IX* with *X* and *V* with *VI* after derivatization with phenyl isothiocyanate.

The mechanism of the chromatographic separation of the isomeric pairs described *V*/*VI*, *VII*/*VIII*, *XI*/*XII*, *XXXIV*/*XXXV*, *XXXVI*/*XXXVII*, *XXX*/*XXXVIII*, *XXXIX*/*XL* and *XLI*/*XLII* will be discussed in a subsequent paper[15].

EXPERIMENTAL

The melting points were not corrected and they were determined in capillaries on a Büchi 510 instrument. The melting point of compound *XXVIII* was determined on a Kofler block. The IR spectra were recorded on a Specord 75 IR Carl Zeiss instrument. The frequencies are given in cm^{-1}. The mass spectra were measured using a Jeol MS D 100 instrument. Thin layer chromatography (TLC) was carried out on Silufol UV_{254} plates (Kavalier, Votice). The solvent systems for TLC were the following (volume proportions): S1 chloroform–methanol–25% ammonia (80 : 10 : 1), S2 chloroform (1% ethanol), S3 chloroform–methanol–water (80 : 8 : 0·4), S4 chloroform–methanol–acetic acid (15 : 5 : 1), S5 chloroform (1% ethanol)–methanol (9 : 1), S6 benzene, S7 chloroform, S8 chloroform–methanol (95 : 5).

Colour reactions for TLC detection were the following: D1 (ref.[16]) — A solution of $HIO_4 . 2 H_2O$ (1 g) in 10 ml ethanol is mixed with 10 ml of ether. The chromatogram was sprayed with this solution and heated at 50°C for a few minutes. A 5% aqueous solution of $HIO_4 . 2 H_2O$ may also be used. This reaction requires that the layer be neutral or acid. In cases when the layer contains bases (after chromatographing in systems with ammonia or some amine), these must be eliminated with hot air. Detection limit is 2 $\mu g/cm^2$. D2 (ref.[16]) — After treatment of the chromatogram as under D1 and appearance of a yellow (ochre) coloration the layer is sprayed with a 15% solution of morpholine in chloroform. D3 (ref.[5]) — The chromatographic layer is first saturated with ammonia vapours and then sprayed with a 5% aqueous solution of $HIO_4 . 2 H_2O$. D4 — 5 ml of a 0·1% aqueous solution of 4-nitrobenzenediazonium fluoroborate is mixed with 5 ml of a 0·1% aqueous solution of $NaHCO_3$. It should be used immediately after mixing.

8-Methoxy-1,4-dihydro-5-naphthol (*II*)

Dimethyl sulfate (22·68 g, 0·18 mol) was added dropwise and under bubbling through with nitrogen into a solution of 1,4-dihydro-5,8-naphthalenediol[6] (*I*) (20 g, 0·12 mol) in a mixture of NaOH (12 g, 0·3 mol) and water (400 ml). The temperature was maintained at 30°C. The stirring under nitrogen was continued for another 90 min at 30°C. The precipitated 5,8-dimethoxy-1,4-dihydronaphthalene was filtered off and the filtrate acidified with concentrated HCl. The precipitated product *II* was filtered off under suction and crystallized from water. Yield, 12 g (55%). M.p. 133 – 134°C; ref.[7] gives m.p. 133°C. TLC: R_F (S2) 0·46; detection: D1 – ochre, D2 – orange.

5-Acetoxy-8-methoxy-1,4-dihydronaphthalene (*III*)

A solution of compound *II* (3·6 g, 20 mmol) in a mixture of acetic anhydride (3 ml, 30 mmol), pyridine (3 ml) and benzene (40 ml) was heated under reflux for 3 h. After cooling the solution was washed with dilute HCl and water, dried over anhydrous Na_2SO_4 and evaporated in a vacuum. Yield, 4 g (90%) of a crystalline product. M.p. 89–91°C (methanol). TLC: R_F (S2) 0·9; detection by fluorescence quenching at 254 nm. For $C_{13}H_{14}O_3$ (218·3) calculated: 71·54% C, 6·47% H; found: 71·61% C, 6·52% H. IR spectrum (KBr); 2 840 (Ar—OCH_3); 1 740 (C=O, ester); 1 475, 1 375, 1 255, 1 220, 1 090, 840, 680.

5-Acetoxy-2,3-epoxy-8-methoxy-1,2,3,4-tetrahydronaphthalene (*IV*)

A solution of compound *III* in a 6% ethereal solution of a triple molar amount of monoperphthalic acid[17] was allowed to stand at room temperature for 7 days. The reaction mixture was washed with a 10% solution of Na_2CO_3 and water, dried over anhydrous Na_2SO_4 and concentrated in a vacuum. The product was crystallized first from light petroleum (60–80°C) and then from methanol. Yield, 60%. M.p. 124–126°C. TLC: R_F (S2) 0·58; detection by fluorescence quenching at 254 nm. For $C_{13}H_{14}O_4$ (234·3) calculated: 66·66% C, 6·02% H; found: 66·58% C, 5·53% H. IR spectrum (KBr): 2 840 (Ar—OCH_3); 1 755 (C=O, ester); 1 475, 1 210, 1 090, 825 cm^{-1}.

trans-3-(2-Hydroxyethylamino)-8-methoxy-1,2,3,4-tetrahydro-2,5-naphthalenediol (*V*) and *trans*-3-(2-Hydroxyethylamino)-5-methoxy-1,2,3,4-tetrahydro-2,8-naphthalenediol (*VI*)

A solution of 2-aminoethanol (0·75 g, 12 mmol) in ethanol (10 ml) was bubbled through with nitrogen for 30 min and epoxide *IV* (1 g, 4 mmol) was then added to it. The mixture was refluxed under a stream of nitrogen for another 3 h, then cooled and acidified with concentrated HCl, diluted with water (5 ml) and washed with chloroform. The aqueous phase was evaporated in a vacuum almost to dryness and the residue was diluted with ethanol (2 ml) and the mixture allowed to stand at 0°C overnight. The product was filtered off under suction, washed with ethanol and acetone and dried. This product represents, according to TLC, a mixture of isomers *V* and *VI* in an approximately 1 : 1 ratio. M.p. 250–252°C (under decomposition). For $C_{13}H_{19}.NO_4.HCl$ (289·8) calculated: 53·89% C, 6·96% H, 4·83% N; found: 53·99% C, 6·58% H, 4·81% N. IR spectrum (KBr): 3 500–3 030, 1 610–1 590 (NH); 1 490, 1 440, 1 270, 1 080, 1 050, 810, 730.

trans-3-Carboxymethylamino-8-methoxy-1,2,3,4-tetrahydro-2,5-naphthalenediol (*IX*) and *trans*-3-Carboxymethylamino-5-methoxy-1,2,3,4-tetrahydro-2,8-naphthalenediol (*X*)

A solution of NaOH (4 g, 0·1 mol) and aminoacetic acid (7·5 g, 0·1 mol) in water (30 ml) was heated to boiling temperature and then bubbled through with nitrogen for 30 min. Epoxide *IV* (4·7 g, 20 mmol) was then added and the mixture refluxed in a stream of nitrogen for 3 h. After cooling concentrated HCl (12 ml) was added and the mixture washed with chloroform. The aqueous phase was concentrated in vacuo to approx. a third of its volume. A part of the hydrochloride formed crystallized out and the suspension formed was alkalized to pH 9 with NaOH. The product dissolved. Immediately afterwards the mixture was acidified with concentrated HCl to pH 6·5 and allowed to stand overnight at 4°C. The separated product was filtered off under suction, washed with water and acetone and dried. Yield, 3·5 g (65%). This product represents a mixture of isomers *IX* and *X* in an approx. 1 : 1 ratio. The individual amino acids can be separated by crystallization from water (see below). M.p. (of the mixture) 257–259°C (decomp.). For $C_{13}H_{17}NO_5$ (267·3) calculated: 58·42% C, 6·41% H, 5·24% N; found: 58·19% C, 6·39% H, 5·10% N.

Separation of Isomeric Amino Acids *IX* and *X*

A mixture of isomeric amino acids *IX* and *X* (0·7 g) was dissolved in boiling distilled water (100 ml) under stirring and the solution was decolorized with active charcoal and filtered while hot. The final volume was 80 ml. The solution was allowed to stand at 4°C. Compound *X* crystallized after 15 h standing, it was filtered off, washed with acetone and dried. Yield, 260 mg. After another crystallization from a minimum amount of water 180 mg of amino acid *X* were obtained. M.p. 277–279°C (decomp.). TLC: R_F (S4) 0·31; detection: D1 – ochre, D2 – green. IR spectrum (KBr): 3 450–3 000, 1 620 (COO^-); 1 400, 1 250, 1 080, 1 050, 790, 720.

The mother liquor was concentrated on a vacuum rotatory evaporator to 60 ml, then inoculated with compound *X* and allowed to stand again at 4°C overnight. Yield, 220 mg of a mixture of both isomers (*IX* and *X*). The last mother liquor was evaporated to approximately 10 ml volume and ethanol (10 ml) was added to the solution. Cooling was continued for another night at 0°C to afford compound *IX* (130 mg), which was filtered off, washed twice with acetone and dried. M.p. 264–266°C (decomp.). TLC: R_F (S4) 0·31; detection: D1 – ochre, D2 – green. IR spectrum (KBr): 3 500–3 050, 1 625 (COO^-); 1 400, 1 260, 1 080, 1 040, 800, 730.

Analysis of Fractions Obtained by Crystallization of the Mixture of *IX* and *X* by TLC of Substituted Phenylthiohydantoins *XXXIX* and *XL* Formed by Derivatization with Phenyl Isothiocyanate

Amino acid (about 2 mg, either a mixture of *IX* and *X* or each isomer separately) was added to a mixture of water (1 ml) and methanol (3 ml) and triethylamine (2 drops) was added to it. The mixture was thoroughly shaken, until the dissolution of the amino acid was complete. Phenyl isothiocyanate (1 drop) was then added to the solution which was shaken until the dissolution of the phenyl isothiocyanate was complete. The mixture was allowed to stand at room temperature for 20 min and then acidified with concentrated HCl (3 drops). Water (3 ml) was then added and the mixture extracted with ether (3 ml). The extract was washed with water (2 × 1 ml) and chromatographed on Silufol UV_{254} in system S5. Compound *XXXIX*: R_F 0·41; detection: D1 – ochre, D2 – red. Compound *XL*: R_F 0·33; detection: D1 – ochre, D2 – red.

4-Benzyloxycarbonyl-9-methoxy-2-oxo-2,3,4a,5,10,10a-hexahydro-*trans*-4*H*-naphth[2,3-*b*]-1,4-oxazin-6-ol (*XI*) and 4-Benzyloxycarbonyl-6-methoxy-2-oxo-2,3,4a,5,10,10a-hexahydro-*trans*-4*H*-naphth[2,3-*b*]-1,4-oxazin-9-ol (*XII*)

A solution of a mixture of *IX* and *X* (134 mg, 0·5 mmol) in absolute ethanol (5 ml) containing KOH (56 mg, 1 mmol) was evaporated to dryness in a vacuum. The potassium salt obtained was suspended in acetone (5 ml) and the suspension was cooled to –5°C under stirring. Then benzyloxycarbonyl chloride (95%, 1·5 ml) was added and the stirring was continued at the same temperature for 30 min. A solution of pyridine (1 ml) in chloroform (10 ml) was added and the stirring continued for another 30 min. The mixture was washed with 10% HCl and water. The organic phase was dried over anhydrous Na_2SO_4 and evaporated in a vacuum. The residue (750 mg), dissolved in $CHCl_3$, was applied onto preparative TLC plates (silica gel UV_{254}) and chromatographed in S3. The spots corresponding to the two isomers were scratched off and the compounds eluted with methanol. The solvent was evaporated under reduced pressure. Both lactones (*XI* and *XII*) were crystallized from methanol.

Lactone XI. M.p. 185–187°C (decomp.). TLC: R_F (S3) 0·72; detection: D1 – ochre, D2 – red. Mass spectrum, *m/e*: 383 (M^+, $C_{21}H_{21}NO_6$). IR spectrum ($CHCl_3$): 3 600 (OH); 3 500 to 3 200 ($OH_{(assoc.)}$); 1 766 (C═O, lactone); 1 705 (C═O, amide); 1 486, 1 420, 1 360, 1 335, 1 270, 1 200, 1 085, 1 065, 1 055, 1 010.

Lactone XII. M.p. 191–193°C (decomp.). TLC: R_F (S3) 0·62; detection: D1 – ochre, D2 – red. Mass spectrum, *m/e*: 383 (M^+, $C_{21}H_{21}NO_6$). IR spectrum ($CHCl_3$); 3 600 (OH); 3 500 to 3 200 ($OH_{(assoc.)}$); 1 766 (C═C, lactone); 1 705 (C═O, amide); 1 490, 1 420, 1 360, 1 335, 1 265, 1 200, 1 085, 1 010.

trans-3-(N-Benzyl-N-hydroxyethylamino)-8-methoxy-1,2,3,4-tetrahydro-2,5-naphthalenediol (*VII*) and *trans*-3-(N-Benzyl-N-hydroxyethylamino)-5-methoxy-1,2,3,4-tetrahydro-2,8-naphthalenediol (*VIII*)

A suspension of compounds *IX* and *X* (200 mg, 0·75 mmol) in a mixture of acetonitrile (10 ml) and triethylamine (1 ml) was cooled to −5°C under stirring and benzyl chloride (0·5 ml) was added to it. The mixture was stirred at room temperature for another 30 min. 10% HCl (10 ml) was added to it and the mixture was extracted with chloroform. The extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (10 ml) and additioned with $LiAlH_4$ (200 mg) and the mixture was heated and refluxed for 2 h. After cooling dilute HCl (cooled at 4°C) was added and the mixture filtered and the filtrate washed with chloroform. The aqueous phase was alkalized with KOH to pH 8 and extracted with chloroform. The extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated in a vacuum. Derivatives *VII* and *VIII* were isolated by preparative TLC on plates with a layer of Kieselgel HF 254 (type 60) MERCK, 1 mm thick. Mobile phase: S1. The compounds were scraped off the zones and eluted with acetone. Compound *VII* was crystallized from acetone as a base, while compound *VIII*, to the acetone eluate of which 1–2 drops of concentrated HCl were added, crystallized as hydrochloride.

Compound VII. M.p. 179–180°C. TLC: R_F (S1) 0·57; detection: D1 – ochre, D2 – red. For $C_{20}H_{25}NO_4$ (343·4) calculated: 69·95% C, 7·34% H, 4·08% N; found: 69·55% C, 7·62% H, 3·89% N. IR spectrum (KBr): 3 500–3 100 ($OH_{(assoc.)}$); 2 820 (Ar—OCH_3); 1 610, 1 505, 1 455, 1 390, 1 280, 1 110–1 090 doublet, 1 050, 820, 750–755, 710.

Compound VIII *hydrochloride*. M.p. 235–237°C (decomp.). TLC: R_F (S1) 0·49; detection: D1 – ochre, D2 – red. For $C_{20}H_{25}NO_4.HCl$ (379·9) calculated: 63·23% C, 6·9% H, 3·69% N; found: 63·35% C, 6·72% H, 3·83% N. IR spectrum (KBr): 3 500–3 100 ($OH_{(assoc.)}$); 2 830 (Ar—OCH_3); 1 600, 1 490, 1 460, 1 430, 1 260, 1 080, 1 050–1 040 doublet, 1 000, 790, 745, 730, 700.

Catalytic Hydrogenolysis of Base *VII* to Compound *V*

The 10% Pd/C catalyst (50 mg) was added to a solution of compound *VII* (150 mg of base) in methanol (25 ml) and the mixture was hydrogenated under constant stirring under normal pressure and room temperature for 2 h. The reaction mixture was filtered and the filtrate evaporated to dryness in a vacuum. An ethanolic solution of hydrogen chloride was added to the residue and the hydrochloride of product *V* crystallized out. Yield, 113 mg (90%). M.p. (hydrochloride) 280—282°C (decomp.) TLC: R_F (S1) 0·1*; detection: D1 — ochre, D3 — blue-violet.

Catalytic Hydrogenolysis of the Hydrochloride of Compound *VIII* to *VI*

Palladium on charcoal (10% Pd/C, 50 mg) was added to a solution of hydrochloride of compound *VIII* (271 mg) in methanol (25 ml) and the mixture was stirred under nitrogen at atmospheric pressure and room temperature for 2 h. The reaction mixture was filtered and the filtrate concentrated in vacuo tc a volume of about 2 ml. After addition of acetone (5 ml) the product crystallized out. Yield, 130 mg of hydrochloride of *VI*. M.p. (hydrochloride) 224—226°C (decomp.). TLC: R_F (S1) 0·1*; detection: D1 — ochre, D3 — blue-gray.

trans-3-(N-Phenylthiocarbamoyl-N-hydroxyethylamino)-8-methoxy-1,2,3,4-tetrahydro-2,5-naphthalenediol (*XLI*) and *trans*-3-(N-Phenylthiocarbamoyl-N-hydroxyethylamino)-5-methoxy-1,2,3,4-tetrahydro-2,8-naphthalenediol (*XLII*)

A mixture of hydrochlorides of compounds *V* and *VI* (289 mg, 1 mmol) was dissolved under mild heating in a mixture of triethylamine (3 ml) and acetonitrile (7 ml). The solution was cooled to 15°C under stirring and a solution of phenylisothiocyanate (140 mg, 1 mmol) in acetonitrile (1 ml) was added to it dropwise. The mixture was stirred at room temperature for 2 h and a mixture of water (10 ml) and concentrated HCl (3 ml) was then added to it. The product was extracted with ethyl acetate and the extract washed with water and dried over Na_2SO_4. The separation and isolation of compounds *XLI* and *XLII* was carried out by preparative TLC on Silufol UV_{254} with the system S3. The respective zones were eluted with acetone.

Compound XLI. M.p. 153—154°C (aqueous ethanol). TLC: R_F (S3) 0·18; detection: D1 — ochre, D2 — red. For $C_{20}H_{24}N_2O_4S$ (388·5) calculated: 61·83% C, 6·23% H, 7·21% N; found: 61·67% C, 6·52% H, 6·83% N.

Compound XLII. M.p. 135—137°C (aqueous ethanol). TLC: R_F (S3) 0·10; detection: D1—ochre, D2 — red. For $C_{20}H_{24}N_2O_4S$ (388·5) calculated: 61·83% C, 6·23% H, 7·21% N; found: 62·30% C, 6·15% H, 7·35% N.

6-Acetoxy-4-acetyl-9-methoxy-2,3,4a,5,10,10a-hexahydro-*trans*-4*H*-naphth[2,3-*b*]-1,4-oxazin-2-one (*XIII*) and 9-Acetoxy-4-acetyl-6-methoxy-2,3,4a,5,10,10a-hexahydro-*trans*-4*H*-naphth[2,3-*b*]-1,4-oxazin-2-one (*XIV*) (ref.[18])

A mixture of amino acids *IX* and *X* (2·7 g, 10 mmol) was suspended in a mixture of acetic anhydride (10 ml), pyridine (10 ml) and chloroform (10 ml) and the suspension allowed to stand at room temperature for 48 h. After addition of chloroform (30 ml) the solution was washed with 10% HCl, an $NaHCO_3$ solution and water. The organic phase was dried over anhydrous

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* Compounds *V* and *VI* do not separate in the mentioned chromatographic system (S1) if the running distance of the solvent was 10 cm. Continuous elution for 3 h separates both isomers (on S1). Compound *VI* is less retained, compound *V* is more strongly retained (ref.[5]).

Na_2SO_4 and evaporated under reduced pressure. The product was washed with methanol and ether, and dried. Yield, 70% of a mixture of compounds *XIII* and *XIV*, m.p. 175 – 178°C. For $C_{17}H_{19}NO_6$ (333·3) calculated: 61·25% C, 5·74% H, 4·2% N; found: 61·37% C, 5·62% H, 4·14% N. IR spectrum ($CHCl_3$): 2 843 ($Ar—OCH_3$); 1 755 (C=O, lactone); 1 730 (C=O, ester); 1 650 (C=O, amide); 1 480, 1 445, 1 375, 1 255, 1 235, 1 200, 1 190, 1 095, 1 025, 1 000, 960, 900, 820.

From amino acid *IX* compound *XIII* was obtained using the same procedure. M.p. 177 to 178°C. TLC: R_F (S2) 0·07; detection by fluorescence quenching at 254 nm.

From amino acid *X* compound *XIV* was obtained as above. M.p. 149 – 150°C. TLC: R_F (S2) 0·13; detection by fluorescence quenching at 254 nm.

trans-3-(N-Acetyl-N-carboxymethylamino)-8-methoxy-1,2,3,4-tetrahydro-2,5-naphthalenediol (*XV*) and *trans*-3-(N-Acetyl-N-carboxymethylamino)-5-methoxy-1,2,3,4-tetrahydro-2,8-naphthalenediol (*XVI*)

A suspension of a mixture of compounds *XIII* and *XIV* (0·5 g) in a solution of KOH (0·5 g) in water (4 ml) was allowed to stand at 0°C for 1 h and the solution was acidified with conc. HCl (2 ml). The mixture was allowed to stand at 0°C for another 30 min and the separated product (a mixture of compounds *XV* and *XVI*) was filtered off under suction and dried. M.p. 144 to 145°C. For $C_{15}H_{19}NO_6$ (309·3) calculated: 58·25% C, 6·19% H, 4·53% N; found: 58·52% C, 6·26% H, 4·21% N. IR spectrum (KBr): 3 600 – 3 100 ($OH_{(assoc.)}$); 1 690 (C=O, carboxyl); 1 590 (C=O, amide); 1 450, 1 350, 1 255, 1 180, 1 080, 1 000, 800.

Using the same procedure compound *XV* was obtained from compound *XIII*. M.p. 202 to 204°C. TLC: R_F (S4) 0·8; detection: D1 — ochre, D2 — red.

Using the same procedure compound *XVI* was prepared from compound *XIV*. M.p. 135 to 137°C. TLC: R_F (S4) 0·8; detection: D1 — ochre, D2 — red.

4-Acetyl-9-methoxy-2-oxo-2,3,4a,5,10,10a-hexahydro-*trans*-4*H*-naphth[2,3-*b*]-1,4-oxazin-6-ol (*XVII*) and 4-Acetyl-6-methoxy-2-oxo-2,3,4a,5,10,10a-hexahydro-*trans*-4*H*-naphth[2,3-*b*]-1,4-oxazin-9-ol (*XVIII*)

a) N,N′-Dicyclohexylcarbodiimide (0·5 g, 2·4 mmol) was added to a solution of compound *XV*, *XVI* or a mixture of *XV* and *XVI* (0·3 g, 0·96 mmol) in N,N-dimethylformamide (5 ml) under constant stirring. After 30 min stirring of the reaction mixture it was allowed to stand overnight at room temperature. The separated N,N′-dicyclohexylurea was filtered off and water (30 ml) was added to the filtrate. The aqueous phase was separated and extracted with chloroform and the extract washed with water and evaporated in a vacuum. The residue was dissolved in methanol and the product was precipitated with water, filtered and suction dried.

b) A mixture of N-acetylamino acids *XV* and *XVI* (0·1 g) was heated at 160°C for 15 min. The melted substance was dissolved in acetone and the solution was applied onto a preparative TLC plate (silica gel UV_{254}). Development was carried out in chloroform–methanol (20 : 1). The zones containing the products were eluted with acetone, the solvent was evaporated and the residue dissolved in methanol and precipitated with water. The product was filtered and dried, representing a mixture of compounds *XVII* and *XVIII*. For $C_{15}H_{17}NO_5$ (291·3) calculated: 61·85% C, 5·88% H, 4·81% N; found: 62·02% C, 6·10% H, 4·50% N.

Compound XVII. M.p. 242 – 244°C (decomp.). TLC: R_F (S3) 0·27; detection: D1 — ochre, D2 — red. IR spectrum (KBr): 3 400 – 3 000 ($OH_{(assoc.)}$); 2 830 ($Ar—OCH_3$); 1 770 (C=O, lactone); 1 615 (C=O, amide); 1 500, 1 460, 1 435, 1 305, 1 270–1 260 doublet, 1 200, 1 070, 1 045, 970, 835–830 doublet, 670, 610.

Compound XVIII. M.p. 277–279°C (decomp.). TLC: R_F (S3) 0·36; detection: D1 – ochre, D2 – red. IR spectrum (KBr): 3 500–3 100 ($OH_{(assoc.)}$); 2 835 (Ar—OCH_3); 1 770 (C=O, lactone); 1 635 (C=O, amide); 1 500, 1 470, 1 440, 1 275, 1 200, 1 085, 820.

N-Oxide of *trans*-3-(N-Hydroxyethyl-N-methylamino)-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (*XXI*)

A solution of hydrochloride of compound[5] *XX* (800 mg) in a mixture of methanol (20 ml), 25% ammonia (10 ml) and 30% H_2O_2 (10 ml) was allowed to stand at room temperature for 20 h. The reaction mixture was evaporated under reduced pressure (the temperature of the water bath was maximum 40°C). The residue was dissolved in methanol, causing crystallization of NH_4Cl, which was filtered off. The filtrate was evaporated almost to dryness and the residue dissolved in acetone. The product which crystallized out was filtered off, washed several times with acetone and suction dried. M.p. 135–138°C (decomp.). TLC: R_F (S1) 0·3; detection: D1 – yellow, D2 – red. For $C_{15}H_{23}NO_5$ (297·4) calculated: 60·59% C, 7·8% H, 4·71% N; found: 61·20% C, 7·51% H, 4·53% N. IR spectrum (KBr): 1 475, 1 450, 1 430, 1 250, 1 110, 1 090, 1 075, 1 040, 930, 775, 705.

Decomposition of N-Oxide *XXI* according to Cope

A solution of N-oxide *XXI* (80 mg) in dimethyl sulfoxide (3 ml) and 25% NH_3 (2 drops) was heated at 70°C on a water bath for 10 h. The reaction mixture was diluted with 5% ammonia (5 ml) and extracted with diethyl ether which was previously shaken with 25% NH_3. The extract was washed with 5% ammonia and evaporated on a vacuum evaporator at room temperature. The residue was dissolved in methanol (2 ml) and applied on preparative TLC plates Kieselgel HF 254 MERCK which were previously exposed to ammonia vapours. The plates were developed in system S2. The zones containing strongly fluorescence quenching compounds were combined and put into a small vessel for catalytic hydrogenation, containing 10% Pd/C (100 mg) in methanol (20 ml) additioned with 25% NH_3 (2 drops). The mixture was stirred under hydrogen at normal pressure and room temperature for 3 h. The mixture was filtered and the filtrate evaporated in a vacuum. The product was dissolved in acetone, applied onto Silufol UV_{254} plates and developed in S2. The required compound was eluted with acetone and the eluate evaporated under reduced pressure. A substance crystallized out (31 mg) which corresponded to 5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (*XXXIV*) according to its R_F value and detection on TLC, melting point and mixture melting point (128–130°C). The same compound was also obtained on reduction of epoxide *XXV*.

5,8-Dimethoxy-1,2,3,4-tetrahydro-2-naphthol (*XXIV*)

Lithium aluminum hydride (0·2 g, 5 mmol) was added to a solution of epoxide *XXV* (ref.[1]) (0·618 g, 3 mmol) in ether (20 ml) and the suspension was refluxed for 1 h. After addition of dilute HCl the ethereal phase was separated and the aqueous phase extracted with ether (2 × 50 ml). The combined ethereal extracts were washed with water, dried over Na_2SO_4 and evaporated in vacuo. Yield, 0·5 g (80%) of product *XXIV*. M.p. 128–130°C. TLC: R_F (S2) 0·2; detection: D1 – yellow, D2 – red. For $C_{12}H_{16}O_3$ (208·3) calculated: 69·21% C, 7·74% H; found: 69·98% C, 7·57% H. IR spectrum (KBr): 3 450–3 100 ($OH_{(assoc.)}$); 2 833 (Ar—OCH_3); 1 600, 1 477, 1 433, 1 257, 1 117, 1 090, 1 073, 1 030, 1 000, 960, 937, 783, 713.

trans-3-(N-Acetyl-N-carboxymethylamino)-8-benzyloxy-5-methoxy-1,2,3,4-tetrahydro-2-naphthol (*XXVI*)

A solution of sodium (50 mg) in ethanol (10 ml) and benzyl chloride (0·44 g, 3·5 mmol) were added to a solution of compound *XVI* (300 mg, 0·97 mmol) in ethanol (10 ml) and the mixture was refluxed for 1 h. The reaction mixture was diluted with water (50 ml) and the separated product was filtered off, washed with dilute HCl and water, and dissolved in acetone (50 ml). Water (50 ml) was added to the solution and the mixture evaporated on a vacuum rotatory evaporator. After evaporation of acetone the compound crystallized out. Another 50 ml of water were added and the evaporation continued until the volume in the flask was 50 ml. The suspension was filtered off, washed with water and a small amount of methanol, and suction-dried. Yield, 240 mg (62%). M.p. 190—191°C (decomp.). TLC: R_F (S1) 0·06; detection: D1 — yellow, D2 — red. For $C_{22}H_{25}NO_6$ (399·4) calculated: 66·15% C, 6·31% H, 3·51% N; found: 65·85% C, 6·51% H, 3·79% N. IR spectrum (KBr): 3 550—3 100 ($OH_{(assoc.)}$); 1 695 (C=O, carboxyl); 1 620 (C=O, amide); 1 475, 1 440, 1 250, 1 180, 1 090, 1 060, 780, 735.

trans-3-(N-Ethyl-N-hydroxyethylamino)-8-benzyloxy-5-methoxy-1,2,3,4-tetrahydro-2-naphthol (*XXVII*)

$LiAlH_4$ (300 mg) was added to a solution of compound *XXVI* (300 mg) in tetrahydrofuran (50 ml) and the suspension was refluxed for 3 h. The reaction mixture was poured into cold water (4°C), alkalized with a conc. solution of NaOH and extracted with chloroform. The extract was washed with water and evaporated on a vacuum evaporator. The residue was dissolved in dilute HCl and washed with ether. The aqueous phase was alkalized with an NaOH solution and refluxed for 20 min. After cooling the base *XXVII* crystallized out, it was filtered off and dried. Yield, 190 mg (68%). M.p. (base) 140—143°C (decomp.). TLC: R_F (S1) 0·88; detection: D1 — yellow, D2 — red. For $C_{22}H_{29}NO_4$ (371·5) calculated: 71·13% C, 7·87% H, 3·77% N; found: 70·92% C, 7·60% H, 3·81% N. IR spectrum (KBr): 3 500—3 100 ($OH_{(assoc.)}$); 2 825 (Ar—OCH_3); 1 475, 1 440, 1 430, 1 250, 1 110, 1 075, 1 060, 1 030, 775, 730.

N-Oxide of *trans*-3-(N-Ethyl-N-hydroxyethylamino)-8-benzyloxy-5-methoxy-1,2,3,4-tetrahydro-2-naphthol (*XXVIII*)

A solution of *XVII* (500 mg) in a mixture of ethanol (20 ml), 25% ammonia (10 ml) and 30% H_2O_2 (10 ml) was allowed to stand at room temperature for 20 h. After evaporation to dryness on a vacuum evaporator (the temperature of the water bath did not exceed 40°C) the residue was dissolved in a minimum amount of ethanol and applied onto preparative thin-layer plates with Kieselgel HF 254, type 60 MERCK. The developing solvent was S1. The zones containing compound *XXVIII* were combined and eluted with acetone, and the solvent evaporated. The residue was suspended in water, the product filtered off and washed with water and dried. M.p. 145—147°C (decomp.). TLC: R_F (S1) 0·57; detection: D1 — yellow, D2 — red. For $C_{22}H_{29}NO_5$ (387·4) calculated: 68·20% C, 7·54% H, 3·61% N; found: 67·77% C, 7·11% H, 3·70% N.

Decomposition of N-Oxide *XXVIII* according to Cope

A solution of compound *XXVIII* (80 mg) in dimethyl sulfoxide (3 ml) additioned with 25% NH_3 (2 drops) was heated at 70°C for 7 h. The mixture was diluted with 5% ammonia (5 ml) and extracted with ether, which was previously shaken with 5% ammonia. The extract was washed with 5% ammonia and evaporated in a vacuum (bath tempeiature maximum 35°C). The residue was dissolved in methanol (2 ml) containing NH_3 (2 drops of 25% ammonia per 10 ml methanol), and the solution applied onto preparative chromatographic Kieselgel HF 254 MERCK plates. These were developed in chloroform–methanol–25% ammonia (20 : 1·25 : 0·125). The strongly fluorescence quenching zones were combined, put into a vessel for catalytic hydrogenation already containing methanol (20 ml), 25% ammonia (2 drops) and 10% Pd/C catalyst (100 mg). The mixture was stirred under hydrogen at room temperature for 3 h, then filtered and the filtrate evaporated on a vacuum rotatory evaporator at room temperature. The residue was dissolved in acetone and applied onto Silufol UV_{254} plates and developed in chloroform–methanol (80 : 4). The zones containing compound *XXX* were combined and eluted with acetone. After evaporation of acetone the product crystallized out. According to its R_F value, coloured TLC detection and melting point (185—188°C) the obtained product *XXX* was identical with 5-methoxy-1,2,3,4-tetrahydro-2,8-naphthalenediol (*XXX*), which was also obtained by reduction of epoxide *IV*.

5-Methoxy-1,2,3,4-tetrahydro-2,8-naphthalenediol (*XXX*) and 8-Methoxy-1,2,3,4-tetrahydro-2,5-naphthalenediol (*XXXVIII*)

$LiAlH_4$ (0·3 g, 8 mmol) was added to a solution of epoxide *IV* (0·5 g, 2 mmol) in tetrahydrofuran (25 ml) and the suspension was refluxed for 1 h and acidified with dilute HCl. The product was extracted with chloroform, the extract washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The product consisted of a mixture of compounds *XXX* and *XXXVIII* (in about 1 : 1 ratio) which was separated by preparative TLC in chloroform–methanol (80 : 4). The compounds were eluted from the respective zones with acetone. After working up and evaporation of the solvent the compounds crystallized out.

Compound XXX. M.p. 185—188°C. R_F (S8) 0·17; detection: D1 — ochre, D2 — red, D4 — violet. For $C_{11}H_{14}O_3$ (194·2) calculated: 68·02% C, 7·27% H; found: 67·95% C, 7·52% H. IR spectrum (KBr): 3 500—3 100 ($OH_{(assoc.)}$); 2 830 (Ar—OCH_3); 1 613, 1 500, 1 473, 1 440, 1 373, 1 340, 1 287, 1 273, 1 207, 1 150, 1 083, 1 050, 1 017, 987, 950, 873, 800, 733.

Compound XXXVIII. M.p. 168—169°C. R_F (S8) 0·23; detection: D1 — ochre, D2 — red, D4 — violet. For $C_{11}H_{14}O_3$ (194·2) calculated: 68·02% C, 7·27% H; found: 68·13% C, 7·15% H. IR spectrum (KBr); 3 450—3 100 ($OH_{(assoc.)}$); 2 837 (Ar—OCH_3); 1 613, 1 493, 1 480, 1 473, 1 450, 1 377, 1 357, 1 343, 1 313, 1 283, 1 267, 1 250, 1 087, 1 063, 1 040, 1 000, 793, 727.

1-Acetoxy-5,8-dihydronaphthalene (*XXXII*)

A solution of 5,8-dihydro-1-naphthol[19] (*XXX*; 1·2 g, 8 mmol) in a mixture of acetic anhydride (2 ml, 20 mmol) and pyridine (2 ml) was allowed to stand at room temperature for 24 h.The mixture was diluted with chloroform (10 ml), washed with dilute HCl and water. The organic phase was dried over anhydrous Na_2SO_4 and the solvent evaporated in vacuo. The product was dissolved in a minimum amount of benzene and filtered through a small column of silica gel. The column was washed with benzene and the benzene eluates were evaporated to afford a liquid product, *XXXII*; b.p. 170—171°C/3·07 kPa (cf. ref.[13]). TLC: R_F (S6) 0·6; detection by fluorescence quenching at 254 nm.

2,3-Epoxy-5-acetoxy-1,2,3,4-tetrahydronaphthalene (*XXXIII*)

Epoxide *XXXIII* was prepared from olefin *XXXII* in the same manner as epoxide *IV* from olefin *III*. M.p. 102—104°C (methanol). R_F (S6) 0·12; detection by fluorescence quenching at 254 nm. For $C_{12}H_{12}O_3$ (204·2) calculated: 70·57% C, 5·92% H; found: 70·89% C, 5·64% H. IR spectrum ($CHCl_3$): 1 760 (C═O, ester); 1 467, 1 380, 1 200, 1 033, 826.

1,2,3,4-Tetrahydro-2,5-naphthalenediol (*XXXIV*) and 1,2,3,4-Tetrahydro-2,8-naphthalenediol (*XXXV*)

$LiAlH_4$ (2·5 g, 66 mmol) was added to a solution of epoxide *XXXIII* (2·7 g, 13 mmol) in ether (150 ml) and the suspension was refluxed for 1 h. After addition of dilute HCl the ethereal layer was separated and the aqueous layer extracted with ether (2 × 50 ml). The combined ethereal extracts were washed with water and dried over anhydrous Na_2SO_4. The ether was evaporated in a vacuum evaporator. After addition of benzene to the residue the product (a mixture of compounds *XXXIV* and *XXXV* in an approx. 1 : 1 ratio) crystallized out. Yield, 1·8 g. Compounds *XXXIV* and *XXXV* were separated on preparative thin-layer plates Kieselgel HF 254 MERCK in chloroform–methanol (80 : 5; triple development). From the combined zones the compounds were eluted with acetone.

Compound XXXIV. M.p. 129—130°C (benzene); ref.[13] gives m.p. 127—128°C. TLC:R_F(S8) 0·25; detection: D1 — brown-yellow, D2 — red, D4 — orange. For $C_{10}H_{12}O_2$ (164·2) calculated: 73·15% C, 7·37% H; found: 73·25% C, 7·50% H. IR spectrum (KBr): 3 450—3 300 ($OH_{(assoc.)}$); 1 580, 1 463, 1 270, 1 033, 760.

Compound XXXV. M.p. 148—150°C (benzene). TLC: R_F (S8) 0·19; detection: D1 — brown-yellow, D2 — red, D4 — orange. For $C_{10}H_{12}O_2$ (164·2) calculated: 73·15% C, 7·37% H; found: 73·54% C, 7·20% H. IR spectrum (KBr): 3 550—3 350 ($OH_{(assoc.)}$); 1 583, 1 460, 1 333, 1 266, 1 080, 1 046, 1 000, 973, 773.

5-Methoxy-1,2,3,4-tetrahydro-2-naphthol (*XXXVI*)

Dimethyl sulfate (0·15 ml, 1·6 mmol) was added, under stirring, to a solution of compound *XXXIV* (0·2 g, 1·2 mmol) in a solution of KOH (0·12 g) in water (3 ml) and stirred at room temperature for 30 min. The product was extracted with chloroform. The extract was washed with water and then filtered through a dry column of silica gel (100—200 µm). The column was washed with chloroform containing 1% of ethanol. The eluate was evaporated and the product crystallized from octane. M.p. 70—71°C; ref.[13] gives 73—74°C. TLC: R_F (S7) 0·09; detection: D1 — brown-yellow, D2 — red. For $C_{11}H_{14}O_2$ (175·2) calculated: 75·41% C, 6·33% H; found: 75·52% C, 6·21% H. IR spectrum (KBr): 3 500—3 200 (OH); 2 840 ($Ar—OCH_3$); 1 590, 1 470, 1 440, 1 260, 1 084, 1 063, 1 033, 950, 760, 710.

M.p. of the benzoate of compound *XXXVI*, 110—111°C; ref.[13] gives 111—112°C.

8-Methoxy-1,2,3,4-tetrahydro-2-naphthol (*XXXVII*)

Methyl derivative *XXXVII* was prepared from compound *XXXV* using the same procedure as in the preparation of compound *XXXVI* from *XXXIV*. M.p. 102—103°C (octane). TLC: R_F (S7) 0·07; detection: D1 — brown-yellow, D2 — red. For $C_{11}H_{14}O_2$ (175·2) calculated: 75·41% C, 6·33% H; found: 75·35% C, 6·10% H. IR spectrum (KBr): 3 500—3 200 ($OH_{(assoc.)}$); 2 835 ($Ar—OCH_3$); 1 580, 1 465, 1 430, 1 250, 1 113, 1 090, 1 035, 753, 700.

Hydroxylation of Compound *XXXVI*

A solution of L-ascorbic acid (18 mg) and $FeCl_2$ (8 mg) in 0·2M acetate buffer of pH 4·6 (5 ml) was added to a solution of compound *XXXVI* (5 mg) in methanol (0·5 ml) and the mixture was slowly stirred in air at room temperature for 20 h. It was then extracted with ether (3 × 2 ml) and the combined extracts were washed with 0·3M phosphate buffer of pH 7·4 and water, and evaporated under reduced pressure. The residue was dissolved in chloroform (0·5 ml). An amount of 10 µl of this solution was applied onto the start of a chromatogram along with the pairs of compounds *XXXI*/*VXXXV* and *XXX*/*XXXVIII* as standards. The chromatogram was developed twice in chloroform–methanol–water (95 : 5 : 0·1), to a distance of 15 cm.

In the ethereal extract of the reaction mixture the product of O-demethylation of the starting compound *XXXVI* may be detected with D4, i.e. compound *XXXIV* and another product which according to its chromatographic behaviour and colour reaction with diazotized 4-nitroaniline (violet) is identical with compound *XXX*, prepared from epoxide *IV*.

Hydroxylation of Compound *XXXVII*

The hydroxylation of compound *XXXVII* was carried out using the same method as for compound *XXXVI*. In the ethereal extract of the reaction mixture the product of O-demethylation of the starting compound *XXXVII* may be detected with D4, i.e. *XXXV*, and a hydroxylated product identical with compound *XXXVIII* prepared from epoxide *IV*.

The author thanks Prof. I. M. Hais for valuable advice during all stages of this investigation. The author also thanks Dr V. Hanuš for the measurement and the interpretation of the mass spectra and Dr J. Holubek for the IR spectra.

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Translated by Ž. Procházka.