SYNTHESIS OF β-PHENYLETHYLAMINE DERIVATIVES VII [1]

The enantiomers of
erythro-1-(4'-hydroxyphenyl)-2-(1''-methyl-2''-phenoxyethylamino)-propanol-1

BY

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The resolution of racemic *erythro*-1-(4'-hydroxyphenyl)-2-(1''-methyl-2''-phenoxyethylamino)propanol-1 (Caa 40 *) is described. The absolute configuration of the three asymmetric centres of the enantiomers is established.

Introduction

In a previous publication [1] we reported on the synthesis of the four racemates of the adrenaline derivative I

$$HO-\langle\text{C}_6\text{H}_4\rangle-CHOH-CHCH_3-NH-CHCH_3-CH_2-O-\langle\text{C}_6\text{H}_5\rangle$$

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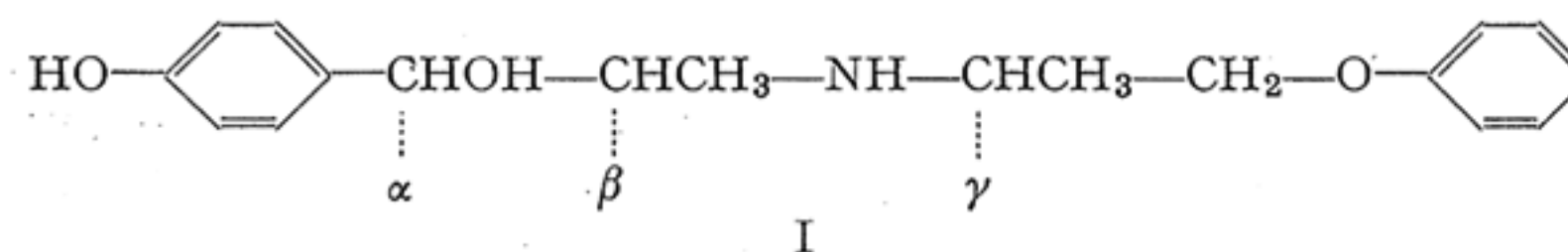
One racemate (Caa 40*), having the *erythro*-configuration [1], is a powerful vasodilator [2,3,4], which improves the peripheral circulation in patients with vascular insufficiency [5,6]. It also relaxes the uterine muscle and possesses some bronchodilator activity [7].

It is a well-known fact that the pharmacological properties of the

[1] VI. *J. van Dijk* and *H. D. Moed*, Rec. trav. chim. **78**, 22 (1959).
[2] 4th Communication; *H. D. Moed* and *J. v. Dijk*, *ibid.* **75**, 1215 (1956).
[3] *F. Brücke, G. Herting, A. Lindner* and *M. Loudon*, Wien. klin. Woch. schr. **68**, 183 (1956).
[4] *J. R. Schmid, I. W. Hillyard* and *C. B. Nash*, Federation Proc. **17**, 410 (1958).
[5] *F. Kaindl, J. Pärten* and *P. Polsterer*, Wien. klin. Wochschr. **68**, 168 (1956).
[6] *S. S. Samuels* and *H. E. Schaftel*, J. Am. Med. Assoc. **171**, 142 (1959).
[7] *K. W. Dungan* and *P. M. Lish*, Federation Proc. **17**, 365 (1958).
* Name used in the pharmacological tests. Commercial name "Duvadilan", N.V. Philips-Duphar.

mirror-image isomers of racemic adrenaline-like and ephedrine-like compounds may differ from each other [8]. Furthermore, Caa 40 differs from the other racemates of this series, which have so far been resolved, by the presence of three asymmetric centres, of which one is situated in the aryloxyalkyl side-chain. This centre might have a special effect on the difference in activity of the enantiomers. For these reasons it was of interest to resolve the racemate and to ascertain how the pharmacological properties of Caa 40 are distributed among its enantiomers.

We have also established the configuration of the enantiomers as an aid in interpreting their pharmacological properties.

This investigation is part of a general program comprising the study of the pharmacological properties of enantiomers and diastereo-isomers, which are formed, when one or more asymmetric centres are introduced into pharmacodynamically active compounds.
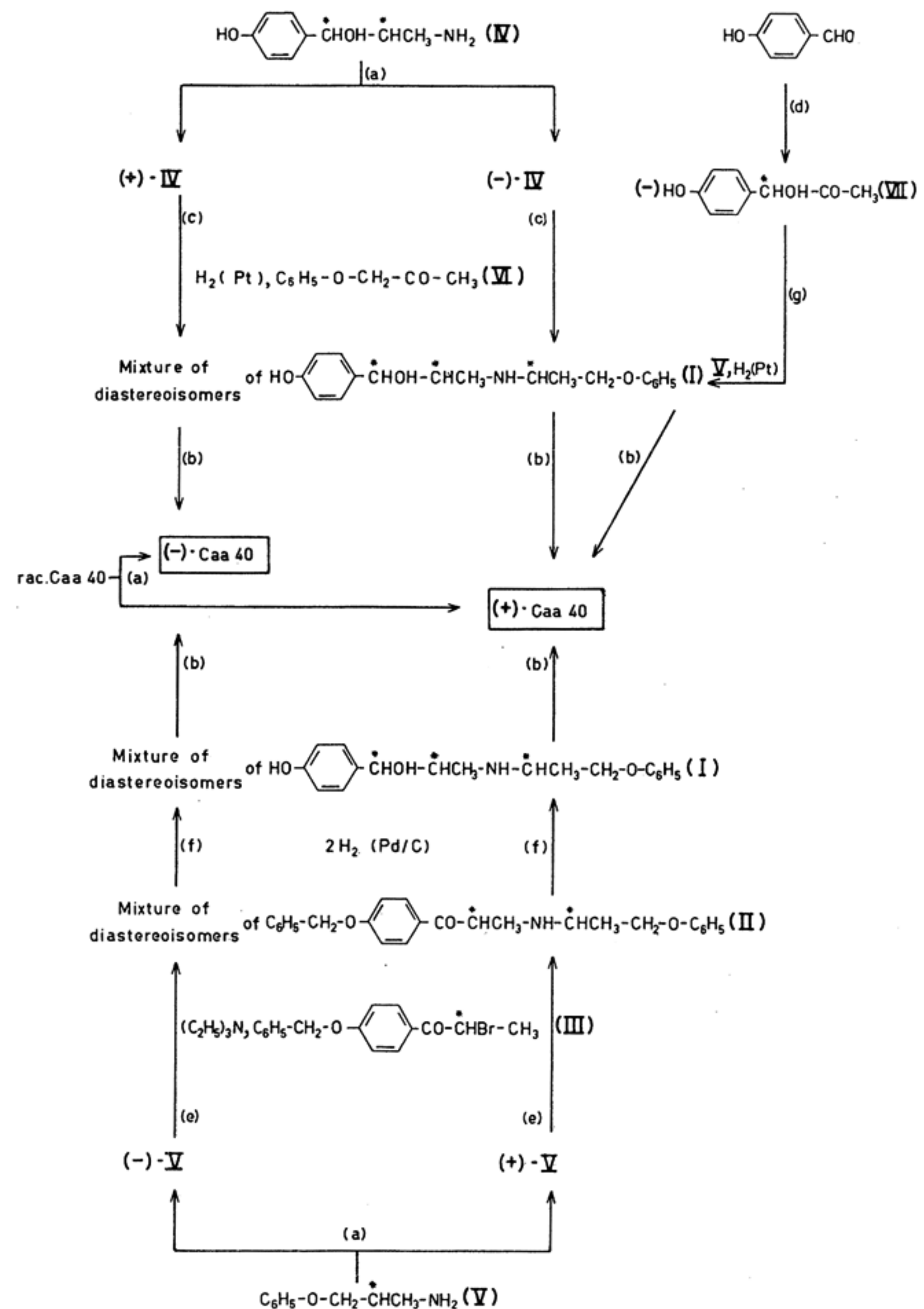
In this communication the resolution of Caa 40 and the establish-ment of the configuration of the three asymmetric centres of the enantiomers is described. The pharmacological investigation and the discussion of its results will be published later.

Chemistry

Resolution of Caa 40 (scheme I)

The racemate was resolved via its diastereomeric salts with (+)- and (—)-mandelic acid, using *Pope's* method. The laevorotatory form was obtained by combining the racemic base with half the equivalent amount of (+)-mandelic acid. After seeding a solution of these in isopropanol-ether, the crude salt crystallized. This product was purified by fractionating from the same solvent .The (+)-form was obtained by treating the mother liquors with ammonia and combining the base thus obtained with (—)-mandelic acid.

The very slight rotation value ($[M_D] = \sim 10.5°$) of the salts of the antipodes of I, and the poor solubility of several compounds, meant that the optical purity could only be concluded from the sharp melting points of some derivatives.

[8]   D. *Bovet* and F. *Bovet-Nitti,* Structure et activité pharmacodynamique des Médicaments du Système Nerveux Végétatif, 1948, p. 57-61.
M. L. *Tainter,* B. F. *Tullar* and F. P. *Ludueña,* Science **107**, 39 (1948).
A. *Lindner* and *Ch. Stumpf,* Sci. Pharm. **21**, 1 (1953).
E. *Beccari,* A. *Beretta* and J. S. *Lawendel,* Science **118**, 249 (1953).
A. M. *Lands,* F. P. *Ludueña* and B. F. *Tullar,* J. Pharmacol. **111**, 469 (1954).
A. E. *Light,* A. L. *Wnuck* and E. J. *de Beer,* Federation Proc. **18**, 415 (1959).

Scheme I

Syntheses and determination of the relative configurations.

(a)= resolution, (b)= crystallization, (c)= reductive aralkylation, (d)= fer-mentation, (e)= condensation, (f)= catalytic hydrogenation, (g)= reductive amination. C* = asymmetric centre.

The relative configuration of Caa 40 (scheme I)

The reactions establishing the relative configuration of the three asymmetric centres of (+)- and (—)-Caa 40, are illustrated in scheme I.

Reaction (c) correlates the configuration of two asymmetric centres (α and β) with those of the corresponding asymmetric carbon atoms of *p*-hydroxy-norephedrine (IV). The reductive aralkylation of (+)-IV with VI gives rise to a mixture of two diastereoisomeric aminoalcohols (I). After crystallization of both hydrochlorides from water the less soluble salt was found to be identical with (—)-Caa 40. (+)-Caa 40 was correlated with (—)-IV in the same way.

Reactions (e) *and* (f) establish the relative configuration of the third asymmetric centre (γ). The condensation of (—)-V with III gave a mixture of two optically active aminoketones in probably equal amounts. The stereospecific reduction of this mixture, as described in a previous publication [1], produced a mixture of two diastereomeric aminoalcohols (I), of which the isomer less soluble in water was shown to be identical with (—)-Caa 40. The other enantiomer of Caa 40 was identical with one of the aminoalcohols synthesized from (+)-V and III by the same series of reactions.

Reaction (g) correlates the configuration of the α-asymmetric carbon atom with that of (—)-VII. The stereospecific reductive amination of this ketol with V gave a mixture of two isomers, one of which was also identical with (+)-Caa 40.

The absolute configuration of (+)- *and* (—)-*Caa 40.* (*Scheme's II and III*)

Scheme II shows the relation of the asymmetric centres α, β and γ with those of some compounds of known configuration and with the standard substance D(+)-glyceraldehyde. This information was used to determine the absolute configuration of these centres.

The configuration of the asymmetric centres of the enantiomers of IV can be deduced from those of the optical isomers of ephedrine (C₆H₅—CHOH—CHCH₃—NHCH₃) on the basis of the following considerations. Just like this compound, IV belongs to the *erythro*-series and according to the rule of *Tschugaeff* [10], it is not to be expected that the introduction of a *p*-hydroxyl group so far from the asymmetric centres, and the absence of an N-methyl group will change the sign of the rotation. Some data from the literature support this assumption (Scheme II). *Lyle* [11] correlated (—)-phenylethanolmethyl-amine ((—)-IX) with D(—)-mandelic acid on the basis of optical

[10] L. *Tschugaeff*, Ber. **31**, 360, 1775, 2451 (1898); **34**, 606 (1901).

[11] G. G. *Lyle*, Abstracts of Papers of the 136th September Meeting Am. Chem. Soc. **1959**, p. 71 P (110). J. Org. Chem. **25**, 1779 (1960).
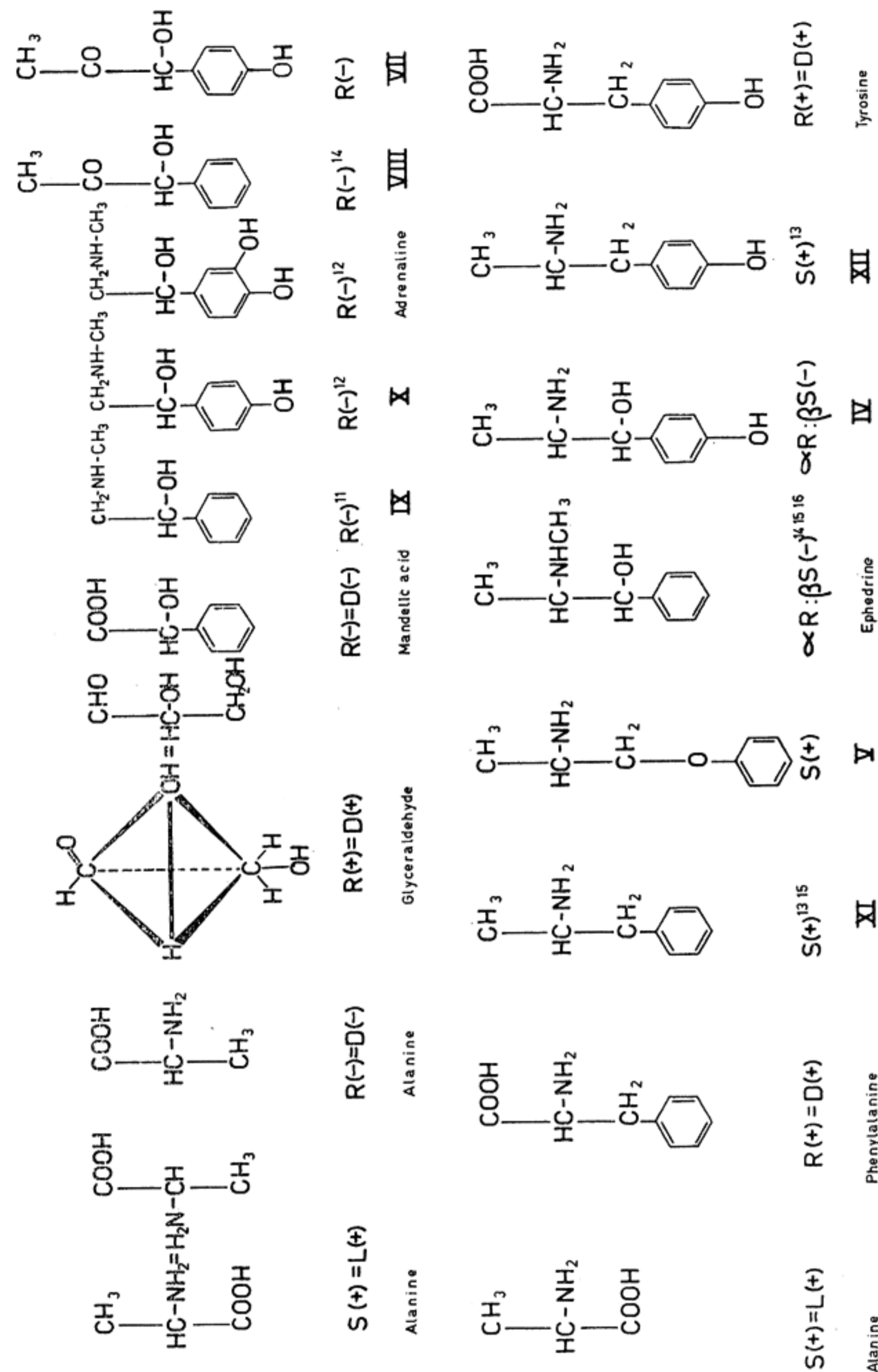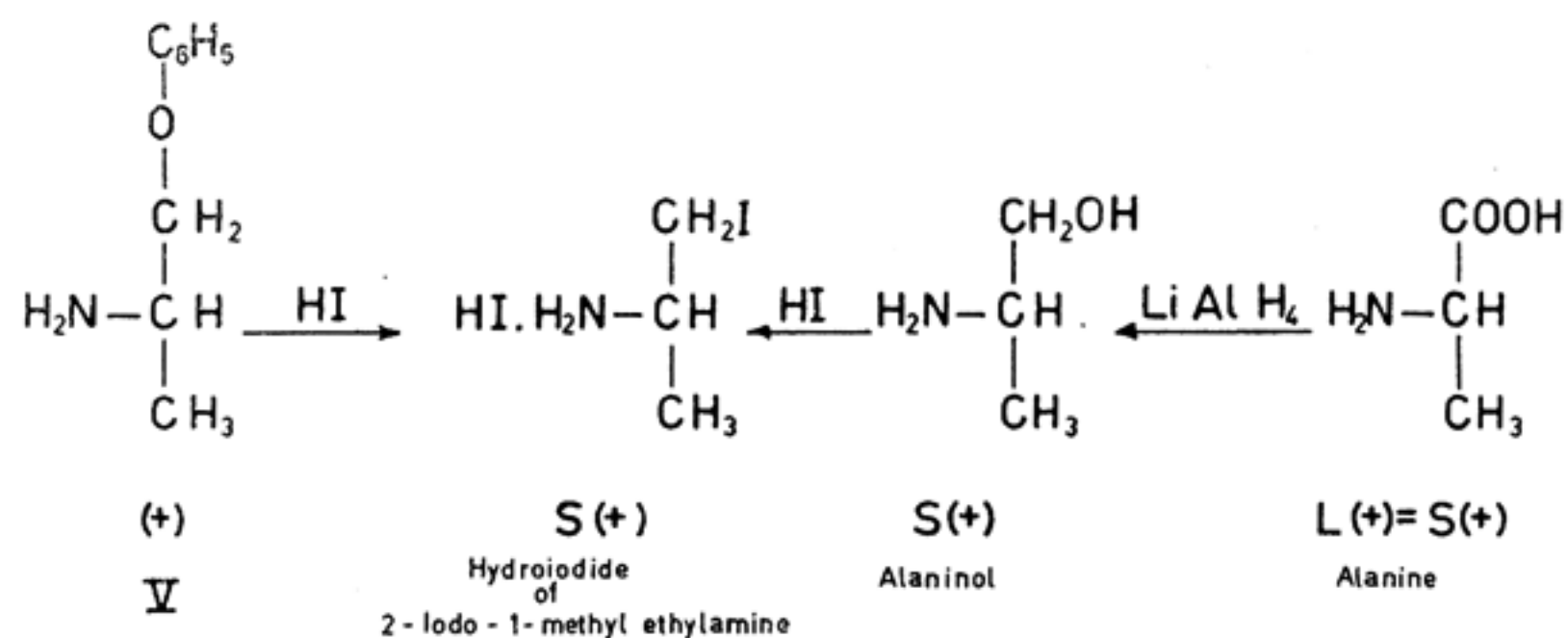
Scheme II

Relation of the enantiomers of IV, V and VII with compounds of known configuration and with D(+)-glyceraldehyde [9].

[9] All structures are in *Fischer* projection formulae. Configurations are indicated according to the convention of *Cahn* et al. [18] and some of them also by the designation D- and L- (*E. Fischer*).

rotation data, confirming this by synthesis, while *Pratesi* et al. [12] established the same relationship for its *p*-hydroxy analogue (X). In addition *Karrer* and *Ehrhardt* [13] correlated the optical isomers of α-methylphenethylamine (XI) and its *p*-hydroxy analogue (XII), which have the same direction of rotation. These facts permit the conclusion, on the basis of analogous rotation, that (—)-IV has the same configuration as (—)-ephedrine. As the absolute configuration of this alkaloid has been established from its relationship to D(—)-mandelic acid [14,15,16] and L(+)-alanine [15,16], substances which have been related to D(+)- and L(—)-glyceraldehyde [17], the absolute configuration of the α- and β-asymmetric centres must be αD : βL for (+)-Caa 40 and αL : βD for its enantiomer or rather αR : βS and αS : βR, respectively, according to the unequivocal convention of *Cahn* et al. [18].

The establishment of the absolute configuration of the third asymmetric centre from known facts cannot be done on the basis of optical data alone, for instance, by comparing (+)-V with (+)-α-methylphenethylamine (XI) whose configuration is known [13,15,16], since the insertion of an O-atom between the benzene nucleus and the aminoalkyl group of XI may alter the spatial orientation of the chromophoric phenyl and phenoxy groups, which probably make a large and different contribution to the molecular rotation. For these reasons we correlated the compound V with L(+)-alanine, as shown in scheme III. On the basis of this relation the γ-C-atom of (+)-Caa 40 must have the S-configuration and the opposite configuration must be ascribed to that of (—)-Caa 40.

Reaction (g) confirms some of the above conclusions. This reductive amination correlates (+)-Caa 40 with (—)-VII. *Freudenberg* et al. [14] established the configuration of the asymmetric centre of (—)-phenylacetylcarbinol (VIII) by synthesis from D(—)-mandelamide. Therefore, on the basis of analogous rotation and particularly because the biochemical synthesis is similarly stereospecific for both ketols, (—)-VII must also have this configuration. It was also shown that the reductive amination of (—)-VIII is stereospecific [14] and gives rise to the formation of (—)-ephedrine. Assuming that reaction (g) has the same steric course, this reductive amination again correlates (+)-Caa 40 with (—)-ephedrine a second time.

Summarizing we give the symbols for the configuration of the three asymmetric centres of the enantiomers of Caa 40 according to the sequence rule of *Cahn, Ingold* and *Prelog* [18]: (—)-Caa 40 has the configuration αS : βR : γR and the configuration of its (+)-enantiomer is represented by the symbols αR : βS : γS.

Pharmacology

The pharmacological investigations were carried out by Dr. *V. Claassen* et al. (pharmacological laboratory, N.V. Philips-Duphar, Weesp) and Prof. Dr. *E. J. Ariëns* et al. (pharmacological laboratory, University of Nijmegen) and will be published later.

Scheme III

Correlation of (+)-V with L (+)-alanine [9]

Experimental Part

in collaboration with Messrs. *J. F. Peelen* and *V. G. Keizer*

Reaction (a)
Resolution of racemic Caa 40, IV and V.
Caa 40

A solution of 15.0 g (0.050 mole) of the racemic base [1] and 3.4 g (0.022 mole) of (+)-mandelic acid [19] in 65 ml of isopropanol and 100 ml of diethyl ether was seeded with the pure (+)-mandelate of the (—)-enantiomer obtained by synthesis. The salt crystallized slowly and, after occasionally shaking the mixture, the crystallized product was collected by filtration with suction, washed with ether and dried. The substance (7.95 g = 0.018 mole = 35% of the racemate)

[12] P. *Pratesi, A. La Manna, A. Campiglio* and *V. Ghislandi*, J. Chem. Soc. **1958**, 2069.

[13] P. *Karrer* and *K. Ehrhardt*, Helv. Chim. Acta **34**, 2202 (1951).

[14] K. *Freudenberg, E. Schoeffel* and *E. Braun*, J. Am. Chem. Soc. **54**, 234 (1932).

[15] W. *Leithe*, Ber. **65**, 660 (1932).

[16] K. *Freudenberg* and *F. Nikolai*, Ann. **510**, 223 (1934).

[17] W. *Klyne*, Progress in Stereochemistry, **1954**, Vol.l.p. 177-187.

[18] R. S. *Cahn* and *C. K. Ingold*, J. Chem. Soc. **1951**, 612.

     R. S. *Cahn, C. K. Ingold* and *V. Prelog*, Experienta **12**, 81-94 (1956).

[19] A. *Skita, F. Keil* and *H. Meiner*, Ber. **66**, 979 (1933).

Table I. Melting points * and mixed melting points ** of derivatives of Caa 40 obtained by synthesis and resolution (Scheme I).

Form	Method	M.P.	Nitrate (−) (c—b)	Nitrate (+) (e—f—b)	Nitrate (−) (e—f—b)	Nitrate (+) (g—b)	Nitrate rac.	Hydrochl. (−) (e—f—b)	Base (+) (e—f—b)
(pure m.p.)			178.5-9	178-9	178.5-9	178-9	165-5.5	199-201	130-2
Nitrate rac.	From rac. prod. (a)	165 - 5.5							
	(a)	178 - 9		178-9		178-9			
	(c—b)	178.5- 9	161-6		178.5-9.5	163-5			
	(c—b)	177 - 8.5	161-5	177-8.5	177 -8				
	(e—f—b)	178.5- 9	177-8	161-5	162 -5	178-9			
	(e—f—b)	178 - 9		162-4	163 -9	163-9			
	From (+) and (—) (g—b)	178.5- 9		178-9					
		178 - 9							
		164.2- 4.8					164-5.5		
Hydrochloride rac.	(a)	202 - 3							
	(a)	195 - 6							
	(c—b)	195.- 6.5							
	(c—b)	197.5- 8.5							
	(e—f—b)	196 - 8						200- 1.5	
	(e—f—b)	196 - 7						198-200	
	(g—b)	199 -201							
		196 - 7.5							
Base rac.	(a)	114 - 5							
	(a)	132.5- 3.5							
	(c—b)	131.5- 2.5							
	(c—b)	129.5- 30.5							
	(e—f—b)	130 - 1.5							129-30
	(e—f—b)	130 - 2							114-21
	(g—b)	131.5- 2.5							
		128.5- 9.5							
Benzoate rac.	(a)	176 - 7							
		139 - 40(anh)							
Nicotinate rac.	(a)	175 - 6							
		159.5- 60.5							
(+)-Mandelate rac.	(a)	147 - 8							
	(e—f—b)	163.5- 4.5							
		163 - 4.5							
(−)-Mandelate (+)	(a)	164.5- 4.8							

* : Melting points are uncorrected. Many compounds melted with decomposition.

** : Mixed melting points of products obtained by mixing about equal amounts of both components.

was recrystallized by dissolving in 90 ml of hot isopropanol and adding 100 ml of ether to the cooled solution. Yield 5.75 g of pure (+)-mandelate of (—)-Caa 40.

By adding 3 ml of concentrated ammonia and 50 ml of water to the first filtrate, the remaining base was liberated. It was extracted with ether, the extract washed with water, dried over anhydrous sodium sulphate and concentrated. This base was dissolved again in 50 ml of isopropanol with 3.70 g (0.024 mole) of (—)-mandelic acid [19] and 80 ml of ether were added. After seeding, 8.30 g (0.018 mole = 37% of the racemate) of almost pure (—)-mandelate of (+)-Caa 40 crystallized and were collected in the way described above.

By combining with (+)-mandelic acid an additional amount of the (—)-form may be obtained from the filtrate in the same way.

The corresponding hydrochlorides were obtained by shaking the mandelates with a slight excess of dilute hydrochloric acid, extracting the liberated mandelic acids with ether and concentrating the aqueous solution in vacuo.

Some melting and mixed melting points are given in table I.

Sometimes, in spite of seeding with the pure enantiomer, this method gave a sharp-melting salt of the racemic base with the active acid which could not be resolved by recrystallization.

erythro-2-Amino-1-(4-hydroxyphenyl)propanol (*p*-hydroxy-norephedrine, formula IV)

The racemic base [1] (13.4 g = 0.080 mole) was dissolved with 12.6 g (0.084 mole) of (+)-tartaric acid by heating in 10 ml of water. After standing for 20 hrs at 0°, the crystalline cake formed was separated from the liquid by filtration with suction, washed with isopropanol and ether and dried. The product (22.6 g) was recrystallized from a mixture of water and isopropanol (1 : 10) by dissolving the crystals in water and diluting the solution thus obtained with isopropanol. The pure (+)-tartrate of (+)-IV was obtained by repeating this twice. Yield 6.9 g (0.022 mole = 28% of the racemate) with a molecular rotation of + 101°, m.p. 184-185° (decomp.).

The combined filtrates were concentrated in vacuo, the residue (15 g) dissolved in 10 ml of water and the solution diluted with 20 ml of isopropanol. After about one week the crystallized impure (+)-tartrate of (—)-IV (10.0 g) was collected on a Büchner funnel and recrystallized from isopropanol-water as described before, until the melting point and the rotation were constant. After four recrystallizations 4.0 g of the (+)-tartrate of the pure (—)-enantiomer (0.013 mole = 16% of the racemate) were obtained, m.p. 184-184.5° (decomp.), molecular rotation — 23°.

The bases were obtained by adding an equivalent amount of sodium hydroxide to an aqueous solution [1].

The (—)-form of IV may also be obtained by combining a solution of 1.44 g (0.0095 mole) of (—)-mandelic acid in 2.7 ml of absolute ethanol with a solution of 1.46 g (0.0087 mole) of racemic IV in 1.8 ml of ethanol. After some days 0.8 g (0.0025 mole = 26% of the racemate) of almost pure (—)-mandelate of (—)-IV had crystallized; one recrystallination from ethanol containing some ether gave an absolutely pure product.

Some properties are given in table II.

No resolution was obtained with (—)-malic acid and (+)-camphorsulphonic acid, possibly because of no pure seeding material being available.

1-Methyl-2-phenoxyethylamine (phenoxyisopropylamine, formula IX)

A solution of 30.0 g (0.200 mole) of racemic V [2] in 25 ml of diethyl ether was

added to a solution of 20 g (0.08 mole) of (+)-camphorsulphonic acid in 30 ml of ethanol. The solution was diluted with 200 ml of ether and seeded with pure (—)-V(+)-camphorsulphonate obtained from previous experiments. After 24 hours the crystallized material was collected and washed with ether. Yield 13.0 g (0.034 mole = 17% of the racemate) of optically pure product, m.p. 178-180°. The product was recrystallized from 14 ml of water, yielding 9.4 g, m.p. 183-184° and of constant rotation.

An additional amount was obtained from the first filtrate by adding more ether.

After removing all crystalline material from the etheral filtrate, an excess of aqueous potassium hydroxide solution was added. The etheral solution of V thus obtained was separated from the aqueous phase, washed with water and concentrated. The residual amine was dissolved in 135 ml of isopropanol with the equivalent amount of (—)-mandelic acid. After seeding, fairly pure (—)-mandelate of (+)-V crystallized, m.p. 144,5-146°. One recrystallization from isopropanol gave an absolutely pure product.

A considerable amount of the (+)-camphorsulphonate of (—)-V may again be obtained by treating the filtrates with sodium hydroxide and (+)-camphorsulphonic acid respectively.

After adding an excess of sodium hydroxide to an aqueous solution, the bases of the enantiomers were obtained by extraction with ether etc. The hydrochloride was precipitated from an etheral solution by adding an alcoholic solution of hydrogen chloride.

Some physical constants are given in table II.

Attempts to resolve V with the aid of (+)-tartaric acid proved unsuccesful.

Reaction (d)

Asymmetric synthesis of (-)-1-hydroxy-1-(4-hydroxyphenyl)propanone-2 * (Formula VII)

Fresh baker's yeast (4%) was added as a thick suspension to an aqueous 10% molasses solution (5% sugars) of pH 5.3. The temperature was 20° and a finely divided air stream was bubbled through the solution. After the fermentation was started a concentrated alcoholic solution of *p*-hydroxybenzaldehyde (max. 2% of the culture) was continuously added during 4 to 8 hrs.

After the aldehyde had been added and the fermentation stopped, the mixture was continuously extracted with ether. The ethereal solution was shaken with 10% sodium bicarbonate solution in order to remove acid by-products and with concentrated sodium bisulphite solution in order to extract a mixture of VII and *p*-hydroxybenzaldehyde. The bisulphite washings were decomposed with solid sodium bicarbonate and extracted with ether.

About 10% (calculated on the basis of added aldehyde) of impure (—)-VII was obtained by crystallization of the combined extracts from an ethereal solution. This product was recrystallized from a mixture of ether and petroleum ether or from a mixture of dioxane and cyclohexane. After a few recrystallizations well shaped crystals were obtained, m.p. 148-9°. The compound showed a characteristic U.V. absorption spectrum with maxima at $\lambda = 2310$ Å ($\varepsilon = 7230$) and $\lambda = 2785$ Å ($\varepsilon = 1920$) and a molecular rotation of $-384°$ (1% in absolute ethanol at 22°).

Found   : C 65.1 ; H 6.2
Calc. for $C_9H_{10}O_3$ (166.18): ,, 65.03; ,, 6.06.

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* The fermentation was carried out by Ir. *Visser* and co-workers.

Table II

Melting points * and molecular rotations ** of the reference compounds IV, V, VII and of the intermediate II

Form	Melting Points			Molecular rotations			
				Salt of		Calculated for the amine component from the salt	
	(+)	(—)	rac.	(+)	(—)	(+)	(—)
erythro-VIII							
base	165 -6	165 - 6	164 -4.5				
hydrochloride	171.5-2	172 -2.5	194 -5	+68	— 68	+68	—68
benzoate	197 -8	198 - 9	182.5-3.5				
(—)-mandelate		180 -80.5			—235		—58
(+)-tartrate	184 -5	184 - 4.5		+101	— 23	+57	—67
Product IX							
hydrochloride	193.6-4.1	193.5- 4	145.5-6.5		— 47		—47
hydroiodide	145 -7		155.5-6.5				
(+)-camphorsulphonate		183 -4			+ 5		—49
(—)-mandelate	147 -8			—126		+51	
Product XI		148 -9			—384 (1% in ethanol)		
Product VI							
hydrochloride	208 -10		190 -5	+130 3% in 50% ethanol	—102 1%		

* Melting points are uncorrected; many compounds melted with decomposition.
** Estimated from an aqueous solution ($\sim$ 10%) at room temperature ($\sim 22°$) for sodium light ($[M]_D$). The calculated values are estimated by subtracting the rotatory value of the ammonium salt of the opt. active acid measured in comparative concentration from that of the salt.

Reaction (c — b)

(—)- and (+)-Caa 40 from (+)- and (—)-IV, respectively

A solution of 1.76 g (0.0105 mole) of the base of (+)-IV and 3.14 g (0.0209 mole) of 1-phenoxypropanone-2 in 20 ml of ethanol and 0.65 ml of acetic acid was hydrogenated in the presence of an Adams platinum catalyst at room temperature and 1.1 atm. pressure. When the reduction was complete, the catalyst was filtered off with suction and washed with ethanol and water. The filtrates were collected and concentrated in vacuo to give a residue of 19 g. Then 4.30 ml of 2.5 N hydrochloric acid were added and the mixture again concentrated. The acid solution (12 g) was shaken with 40 ml of ether and, after standing for half an hour at room temperature, the crystallized product was isolated by filtration with suction. The material was washed with 15 ml of water

for a shorter time gave incomplete fission of the ether bond. The reaction mixture was evaporated to dryness in vacuo, the residue treated with ethanol and re-concentrated. The residual crystalline mass was washed with much ether until a white product was obtained. This was recrystallized three times by dissolving in ethanol and adding ether until crystallization started. Yield 1.36 g (0.0043 mole = 27%) of 2-iodo-1-methylethylamine hydroiodide, m.p. 153-156° (decomp.) and with a molecular rotation of +21° (5% aqueous solution).
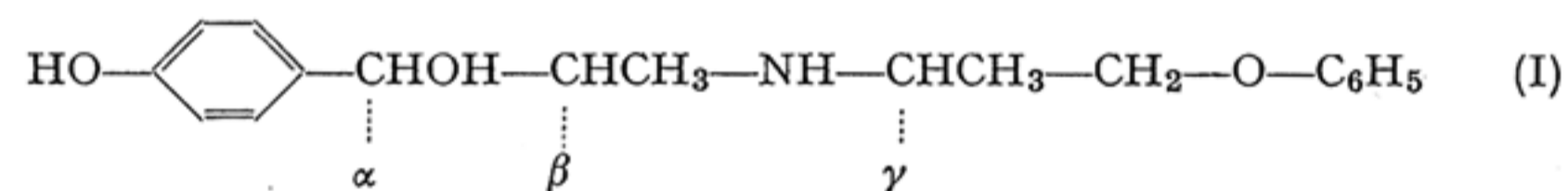
Starting from the same amount of the hydroiodide of (—)-V, 1.51 g (0.0048 mole = 30%) of a laevorotatory product was obtained, m.p. 153-156.5 (decomp.) with molecular rotation $([M]_D^{23}) = -22°$ (5% aqueous solution).

In the same way 3.25 g of the racemate of V yielded 1.64 g of scission product m.p. 128-9° (decomp.); iodide content 40.6% [calculated for $C_3H_8NI.HI$ (312.9) 40.56%].

Correlation

The relations between these substances may already be concluded from the rotation values of the products obtained above. This was corroborated by some mixed melting points. Mixing the hydroiodide synthesized from (+)-alaninol with that from the scission of (—)-V gave a pronounced depression: 127-132° (decomp.), mixing with that from (+)-V gave none: 147-150° (clear melt at 157°, decomp.). Mixing equal parts of both scission products gave the same m.p. as that of the racemate: 130-132°.

Summary

$$HO-\langle\!\!\!\bigcirc\!\!\!\rangle-CHOH-CHCH_3-NH-CHCH_3-CH_2-O-C_6H_5 \qquad (I)$$

$$\qquad\qquad\qquad \alpha \qquad\quad \beta \qquad\qquad\quad \gamma$$

1. One racemate of 1-(4'hydroxyphenyl)-2-(1″-methyl-2″-phenoxy-ethylamino)propanol-1 (Caa 40) was separated into its enantiomers by means of (+)- and (—)-mandelic acid (scheme I).
2. The relative configuration was established by synthesizing (+)- and (—)-Caa 40 from one of the enantiomers of *p*-hydroxy-norephedrine and from one of the optical isomers of phenoxy-isopropylamine (scheme I).
3. The configuration of two asymmetric centres (α- and β-) of (+)-Caa 40 is the same as that of both asymmetric carbon atoms of (—)-*p*-hydroxynorephedrine. The third asymmetric centre in the side chain (γ-C-atom) was correlated with that of (+)-phenoxy-isopropylamine. (+)-Caa 40 was also synthesized from (—)-*p*-hydroxyphenylacetylcarbinol and phenoxyisopropylamine.
4. (—)-Caa 40 was similarly related to (+)-*p*-hydroxynorephedrine and (—)-phenoxyisopropylamine.
5. The absolute configuration was determined by correlating (—)-*p*-hydroxynorephedrine with D(—)-mandelic acid and L(+)-alanine on the basis of data from the literature (scheme II) and (+)-phenoxyisopropylamine with L(+)-alanine as the result of experimental work (scheme III).
6. (—)-Caa 40 has the absolute configuration αS : βR : γR.
7. (+)-Caa 40 has the absolute configuration αR : βS : γS.