PREPARATION OF L- AND D-1-(4'-BROMPHENYL)-2-METHYL-AMINO-PROPANE AND STUDY OF ITS CONFIGURATION

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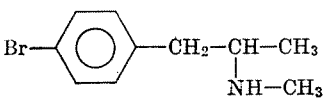
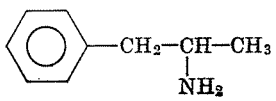
1. Preparation of L- and D-1-(4'-bromphenyl)-2-methyl-amino-propane

Introduction

1-(4'-Bromophenyl)-2-methylamino-propane (I) is a derivate of 1-phenyl-2-amino-propane (II) a well-known psychomimetic named Amphetamin, Aktedron, Benzedrin resp. Anara.



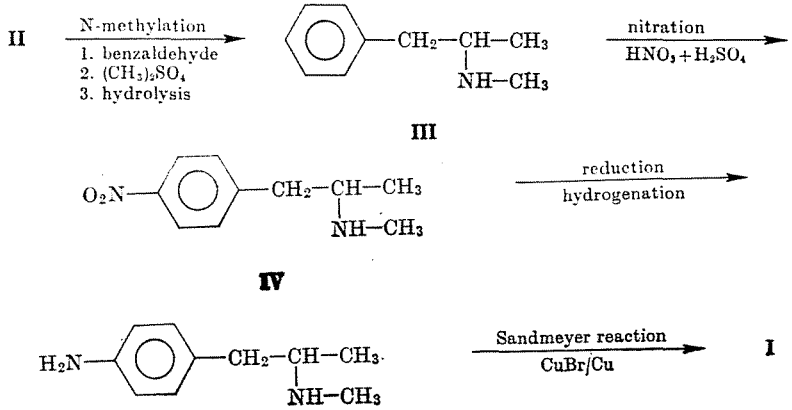
I



II

Its preparation was performed by Ecsery and co-workers [1] at the Chinoin Pharmaceutical and Chemicals Works. Pharmaceutical screening demonstrated its vasopressor and psychostimulant effect, similar to a number of other amphetamine derivatives [2].

Ecsery and co-workers synthetized I from II by the following route:



II and III are known products — they are widely used in therapy [3]. The biological effects of their optical isomers are not equal (in the case of II, the D- and DL-form, in the case of III, the L-form are commercialized), therefore the preparation of the optical isomers of the new derivatives was necessary.

Resolution should be carried out as early as possible in the interest of economic efficiency, insofar as no racemization occurs in the further of the synthesis.

II can be resolved at the earliest stage. Its optical isomers were prepared already in 1919, since it proved to be readily resolvable [5]. d-Tartaric acid [6] and various N-acyl-aminoacids [7] are suitable for its resolution.

Two methods were published for the preparation of the antipodes of III. Emde [8] and Ogota [9] prepared D- and L-forms of III from optically active ephedrine [9].

They obtained the D- and L-form of III by the resolution of the racemic form of III too with d-tartaric acid in alcohol. There is no reference in the literature concerning the resolution of IV, V and I.

Experimental

Ecsery's synthesis (1) has been reproduced in the course of our experimental work standing from optically active compounds.

We obtained the following results:

D(L)II → D(L)III → partially racemized IV → DL-V

D(L)IV → partially racemized V → DL-II

D(L)V → partially racemized II

It can be seen that partial racemisation occured in the course of the above synthesis-route in the nitration, hydrogenation and Sandmeyer reactions. Its extent still allowed to establish the absolute configuration of II, but it made the process uneconomical.

The starting materials, the intermediates and the products had to be resolved to carry out the experiments. We developed a new process [11] to resolve I, II, III and V, according to which

2 mols of the base + d-tartaric acid + HCl $\xrightarrow[\text{alcohol, or water}]{\text{aqueous alcohol or}}$ L-(D)-base-d-bitartarate $\downarrow$ + D(L) base. HCl (in solution).

The method is extremely simple, it does not demand special conditions and special puryfying operations. The detailed resolving procedure will be reported only for III, data concerning the other three compounds are reported in tables.

I 1.) 30 g (0.2 mols) of DL-III are dissolved in the solution of 16.5 g (0.11 mols) of d-tartaric acid in 90 ml of water, and slowly, with external

cooling, 8.3 ml (37w%, d: 1.19 g/ml) 0.1 mols) of hydrochloride acid are added dropwise. Crystallization starts (effected by inoculation or scraping) after a few minutes and can be completed by cooling with ice for two hours. The precipitate is filtered, washed with water and dried under an infrared lamp.
Yield: 24.0 g (73%)
M.p.: 155—7°C
$[\alpha]_D^{20}$: +6,8° (c: 5; water)

2.) The precipitate is suspended in 50 ml of water, made alkaline with 40% aqueous NaOH (about 40 ml) to pH 13, and the free base extracted with 3×60 ml of benzene. The benzene layer is dried over anhydrous Na_2SO_4, clarified with active carbon, filtered and evaporated to dryness.
Residue: 11.3 g L-III (73)%
$[\alpha]_D^{20}$: —2,6° (c: 91.7; oil)
$[\alpha]_D^{20}$: —16.2° (c: 5; nHCl)

3.) The filtrate obtained according to 1. is made alkaline NaOH (about 40 ml) to pH 13, extracted with 3×40 ml of benzene and further processed according to 2.).
Residue: 13 g of D-III (82%)
$[\alpha]_D^{20}$: +2.5° (c: 91,7; oil)
$[\alpha]_D^{20}$: +16.1° (c: 5; nHCl)

Tabulated resolving data for the compounds II, V, I resolved by the method mentionned at I

Resolved compound	DL—II	DL—V	DL—I
Charge (g)	26.8 (0.2 mols)	32.8 (0.3 mols)	45.6 (0.2 mols)
Tartaric acid (g)	16.5 (0.11 mols)	16.5 (0.11 mols)	16.5 (0.11 mols)
Water (ml)	—	—	—
Ethanol (ml)	50	120	160
37% aqueous HCl (ml)	10.6 (0,08 mols)	12 (0.09 mols)	12 (0.09 mols)
Precipitated tartarate			
Weight (g)	24	24.2	26
Yield (%)	77	71	69
M.p. (°C)	126—135	125—128	179—181
$[\alpha]_D^{20}$ (c: 5; water)	+23.2°	20.8	+17
Processing of the precipitate			
Water (ml)	120	60	40
40% aqueous NaOH	30	40	40
Benzene (ml)	3×40	3×60	3×60
Residue (g)	7.4 of L-II	11 of L-V	15 of L-I
Yield (%)	55	67	66
$[\alpha]_D^{20}$(c: 5 MeOH)	+14°	—	—
$[\alpha]_D^{20}$(c: 5)	+18° (H_2SO_4-water)	—3.6° (MeOH)	—6.6° (HCl—MeOH)

Resolved compound	DL—II	DL—V	DL—I
Processing of the filtrate			
Evaporation	+	+	+
Water (ml)	40	40	60
40% aqueous NaOH (ml)	40	40	60
Benzene (ml)	3×40	3×60	3×100
Residue (g)	13.4 of D+DL-II	19 of D+DL-V	22 of D+DL-I
Yield (rel%)	145	117	92
$[\alpha]_D^{20}$ (c: 5)	−12° (MeOH)	+2.1° (MeOH)	−0.6° (HCl—MeOH)
$[\alpha]_D^{20}$ (c: 5)	−20° (n H_2SO_4)		

II 4.) The resolution of the p-nitro-product IV was carried out similarly utilizing dibenzoyl-d-tartaric acid. 39 g (0.2 mols) of racemic IV were dissolved in a mixture of 160 ml of water and 12 ml (0.1 mol, 37%, d: 1.19 g/ml) of hydrochloride acid. 37.6 g (0.1 mol) of dibenzoyl-d-tartaric acid monohydrate were dissolved in 80 ml of methanol. The two solutions were mixed under stirring and cooling. Precipitation of the acid L-IV-dibenzoyl-d-tartarate starts on scraping or inoculation. It is left to stand overnight filtered and washed.

Yield: 54 g (93%)

M.p.: 152°

5.) Alternatives for processing the precipitate:

a) The precipitate is suspended in 80 ml of water, alkalified with aqueous NaOH (about 40 ml) to pH 13 and extracted with 3×60 ml of benzene. Further cf. 2.

Residue: 11.2 g of L-IV; (60%)

$[\alpha]_D^{20}$: —2.0° (c: 5 HCl—MeOH)

b) The salt precipitated according to 4. is suspended in 80 ml of water and acidified with aqueous HCl to pH 1 (about 20 ml). The precipitate is filtered.

Yield: 30 g of dibenzoyl-d-tartaric acid H_2O (81%)

M.p.: 87—90°C

$[\alpha]_D^{20}$: —114.8° (c: 5 MeOH)

L-IV can be obtained from the aqueous solution according to 2. after alkalifying it with 40 ml of 40% aqueous NaOH.

Residue: 8.6 g of L-IV (44%)

$[\alpha]_D^{20}$: —0.5° (c: 5 HCl—MeOH)

6.) The filtrate obtained according to 4. is evaporated to dryness, the residue is dissolved in 40 ml of water and alkalified with 40 ml of 40% aqueous NaOH, extracted with 3×60 ml of benzene and further processed according to 2.

Residue: 18.6 g of D-IV (95%)

$[\alpha]_D^{20}$: +10.8° (c: 5 HCl-MeOH)

2. Deduction of the configuration of optically active 1-(4'-bromphenyl)-2-methylamino-propane

When both optical isomers of all the starting materials, the intermediates and the final products were at disposal, we repeated the synthesis route [1], now however, using optically active materials.

a) Preparation of D-III from D-II.

10.6 g (0.1 mol) of benzaldehyde were dissolved in 100 ml of ether and 13.5 g (0.1 mol) of D-II ($[\alpha]_D^{20}$: +17.1° [c: 5 MeOH]) were dropwise added at 0°C. The reaction mixture was cooled with salted ice to keep the temperature below +5° C. When the addition was completed, the ethereal phase was extracted with 2×10 ml of 2% acetic acid, dried over Na_2SO_4, evaporated to dryness and the residue was purified by fractional distillation.

Residue: 17.8 g (80%)
Main fraction: 13.2 g (73%)
B.p.: 130°C/0.6 Torr
$[\alpha]_D^{20}$: 1.5711

8.3 g (0.063 mols; a: 1.352 g/ml) of dimethylsulfate were dropwise added to the main fraction (13.2 g; 0.062 mols). The temperature was slowly raised to 85°C after the addition. The reaction mixture was stirred half an hour at 85—90°C. In this period the mixture thickened.

A mixture of 28 ml of water and 0.9 ml of cc. HCl was poured to the reaction mixture. After cooling to about 20°C the benzaldehyde was extracted with 2×20 ml of benzene. The organic layer was dried over $MgSO_4$ and the benzene was evaporated.

Residue: 5.1 g of benzaldehyde
n_D^{25}: 1.5405

The aqueous phase was alkalified with 10 ml of 40% NaOH and the formed D-III was extracted with 3×20 ml of benzene. The benzene solution was dried over Na_2SO_4 and the benzene was evaporated.

Residue: 7.2 g of D-III (77.5%)
$[\alpha]_D^{20}$: +2.1° (c; 91,7; oil)

b) Preparation of L-III from L-II.

Cf. 7. a
Starting compound L-II: $[\alpha]_D^{20}$: —16.8° (c: 5; MeOH)
Product L-III: $[\alpha]_D^{20}$: —1.9° (c: 91,7; oil)

8/a Preparation of D-IV from D-III.

15 g (0.1 mol) of D-III ($[\alpha]_D^{20}$: +2.52° (c: 91,7; oil)] were dissolved in a mixture of 11.4 ml of 98% H_2SO_4 and 5 ml of water in a four-necked flask provided with a stirrer, reflux condenser, dropping funnel and thermometer. The temperature must be kept below 40°C. Then 12.5 ml of 96% HNO_3 were dropwise added. The reaction mixture was kept at 50°C. After the addition

it was stirred half an hour at room temperature, and subsequently its temperature was raised to 50 °C with a thermostated water bath and left to stand overnight. Next morning the reaction mixture was poured on ice. After thawing of the ice, the undesirable by-products were extracted with 2×200 ml of benzene, and the aqueous phase was alkalified with 60 ml of 40% NaOH under permanent cooling with ice. The formed o-p-nitro-III (IV) was extracted with 3×40 ml of benzene. The benzene phase was dried over Na_2SO_4 and the benzene evaporated.

Residue: 19.0 g of D-IV (97%)

$[\alpha]_D^{20}$: +5° (c: 5; HCl—MeOH)

b) Preparation of L-IV from L-III

Cf. 8/a

Starting compound L-III $[\alpha]_D^{20}$: —2.6° (c: 91,7; oil)

Product L-IV $[\alpha]_D^{20}$: —11.2° (c: 5; HCl—MeOH)

9/a Preparation of D-V from D-IV

23.1 g (0.1 mol) of D-IV hydrochloride (($[\alpha]_D^{20}$: +5°) c: 5; MeOH)) were dissolved in 400 ml (about 16fold amount) of abs. alcohol and hydrogenates in the presence of 2.3 g (10%) of boneblack-supported Raney—Ni at atmospheric pressure. Hydrogen uptake was 8000 ml (114% of the calculated). The solution was clarified, filtered and evaporated to dryness.

Yield: 19.2 g

$[\alpha]_D^{20}$: —2.0° (c: 5; MeOH)

b) Preparation of L-V from L-IV

Cf. 9/a.

Starting compound L-IV. hydrochloride: $[\alpha]_D^{20}$: —4.0° (c: 5; MeOH)

Product L-IV. hydrochloride: $[\alpha]_D^{20}$: +2.3° (c: 5; MeOH)

10/a Preparation of D-I from D-V

The following solutions were introduced into a four-necked flask provided with a stirrer, reflux condenser, dropping funnel and thermometer:

Solution I: 18 g of $CuSO_4 \cdot 5\ H_2O$ in 120 ml of water
18 g of KBr in 43 ml of water
7.2 g of Cu powder in 65 ml of 48% aqueous HBr.

This solution was heated one hour. In the mean time solution II is being-prepared.

Solution II: 16.4 g of D-V $[\alpha]_D^{20}$: +4.0° (c: 5; MeOH) were dissolved in a mixture of 48 ml of azeotropic (48%) aqueous HBr and 90 ml of water.

Subsequently a solution of 7 g of $NaNO_2$ in 14 ml of water was dropwise added at a temperature below 0 °C.

The solution of the diazonium compound formed was then added to solution I cooled to 15 °C.

The reaction mixture was stirred on a boiling water bath one hour, then cooled to room temperature, alkalified with 98 ml of 40% aqueous NaOH

and ammonia was introduced into the solution till the precipitate dissolved completely. The clear dark blue solution was extracted with 3×80 ml of benzene, the benzene phase was dried and the benzene was evaporated.
Residue: 20.5 g of D-I (90.6%)

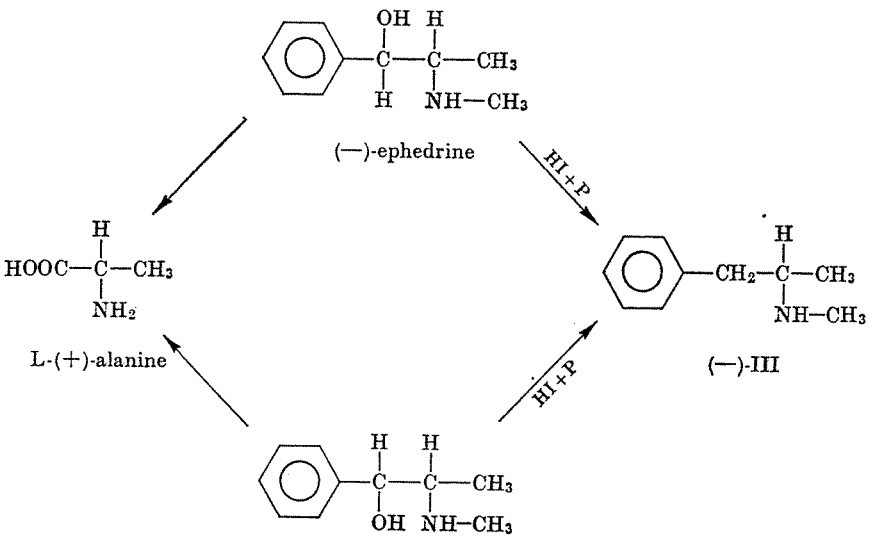
The residual oil was subjected to fractional distillation. Main fraction 15.4 g D-I (69%)
B.p.: 100 °C/0.6 Torr
n_{20}^{D}: 1.5450
$[\alpha]_D^{20}$: —0.7° (c: 113; oil)
$[\alpha]_D^{20}$: +2.3° (c: 5; MeOH)

b) Preparation of L-I from L-V
Starting compund L-V: $[\alpha]_D^{20}$: —4.0° (c: 5; MeOH)
Product L-I: $[\alpha]_D^{20}$: —2.0° (c: 5; MeOH)
$[\alpha]_D^{20}$: +0.6° (c: 113; oil)

It can be seen from the foregoings that the configuration of I can unambigous by be related to that of III (cf. Table I.). (The asymmetric carbon atom is not involved, nor does complete racemization take place.)

The absolute configuration of III was proved by Emde [8] and Ogota [9]. (+)-Pseudoephedrine and (—)-ephedrine, resp., were reduced with hydroiodic acid in the presence of red phosphorus and (—)-II·hydrochloride was obtained (the reaction did not involve the remaining asymmetry centre).

The asymmetric carbon atom attached to the N atom of (—)-ephedrine can be brought into configurative correlation with the asymmetric carbon atom of L-(+)-alanine (12). Hence the configuration of III·hydrochloride rotating to the left in methanolic solution is L.



Note: Specific rotation was measured using a Zeiss visual polarimeter whose accuracy was $\pm 0.05°$. Taking into account the low specific rotation value of the compounds in question and the fact that the determination of total proposed by Fredga [4] could not been carried out (except for II and III) it had no sense to calculate optical purity. We checked the qualitative accuracy of our data in the case of I and IV (V is not liquid) by utilizing Kirkwood's formula. (The formula can be applied with an error of about 20%).

Calculated and measured maximum values of specific rotation are:

Compound	Calculated	Measured	Calculated	Measured
IV	−1.9°	−0.7°	+1.9°	+0.5°
I	+1.0°	+2.0°	−1.7°	−1.4°
	D-isomer		L-isomer	

The compounds obtained in resolution and synthesis, resp., could not be purified neither by distillation, nor by recrystallization of their salts.

Summary

Optical isomers of amphetamine derivatives can be prepared with d-tartaric acid and its derivatives in aqueous, aqueous-alcoholic and alcoholic solutions. The configurations of the new derivatives (L and D isomers) substituted on the phenyl group with Br, NH_2 or NO_2 can be deduced from the configuration of methamphetamine (III).

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