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N-Desmethyl Analogues of (+)-4-Dimethylamino-2,α-dimethylphenethylamine. Synthesis and Configurational Relationships

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The resolution of 4-dimethylamino-2,α-dimethylphenethylamine (*1*) and the synthesis of the 4-methylamino- and 4-amino-analogues *2* and *8* are described. The dextrorotatory isomer *(+)2* was prepared from *(+)1* by oxidative *N*-monodemethylation. The configurational relationships of *(+)2* and the dextrorotatory isomer of *8* was established from the corresponding carbamates, which both on reduction yielded an identical compound, (+)-4-methylamino-2,α,*N*-trimethylphenethylamine dihydrochloride [*(+)3*]. In connection with the preparation of *(+)3*, the synthesis and selective ethoxycarbonylating properties of a new type of mixed anhydride agent, are reported.

Recently the title compound, 4-dimethylamino-2,α-dimethylphenethylamine, has been shown to be a reversible and selective inhibitor of the A form of the enzyme monoamine oxidase (MAO).[1] In the course of the pharmacokinetic investigation of the dextrorotatory enantiomer of this compound it was found that the main metabolic pathway was *N*-demethylation at the aniline nitrogen.[2] At that time access to the optical isomers of these metabolites became desirable. The sequences of reactions leading to the synthesis of the target compounds are presented in Scheme 1.

The preparation of racemic 4-dimethylamino-2,α-dimethylphenethylamine was readily effected by a standard procedure involving reduction of the corresponding nitrostyrene with lithium aluminum hydride.[1] The racemic amine was conveniently resolved by use of L(+)-tartaric acid. The optical purity of the obtained isomer *(+)1* was checked by GLC analysis of the (−)-camphanic amide. Oxidative *N*-monodemethylation of *(+)1* by means of lead tetraacetate in acetic anhydride yielded *(+)2*. The method has been used previously for the selective *N*-demethylation of simple substituted *N*,*N*-dimethylanilines *e.g.* *N*,*N*-dimethyl-*p*-toluidine.[3]

In the work on the synthesis of (+)-4-methylamino-2,α,*N*-trimethylphenethylamine *(+)3* from *(+)2*, it was found that the potential intermediate, ethyl *N*-(4-methylamino-2,α-dimethylphenethyl)-carbamate, could be obtained by selective ethoxycarbonylation of *(+)2* with a new mixed anhydride, *S*-ethoxycarbonyl 4-methyl-1-piperazinecarbodithioate. The carbamate was then converted to the required amine *(+)-3* by the reduction with lithium aluminum hydride (Method A). The mixed anhydride used was initially prepared in connection with a study on biologically active dithiocarbamates, but was rejected owing to its instability.[4] The compound is easily prepared from sodium or potassium 4-methyl-1-piperazinecarbodithioate and ethyl chloroformate. The synthesis of some *S*-alkoxycarbonyl analogues is described. Examples of related anhydrides are reported in the literature, but no references were found to the potential alkoxycarbonylating properties of these compounds.[5,6] In an attempt to prepare thiosemicarbazides from *S*-ethoxycarbonyl *N*,*N*-dimethyldithiocarbamate and hydrazines only hydrazinium dimethyldithiocarbamates could be isolated.[7]

The key intermediate to compound *8*, 4-amino-2-methylbenzaldehyde (4), was prepared essentially as described in the literature from 1,2-dimethyl-4-nitrobenzene by the reaction with aqueous alcoholic sodium polysulfide.[8] The previous procedure involving steam distillation was simplified in that the compound was isolated by means of extraction. Initial attempts to condense aldehyde *4* with nitro-

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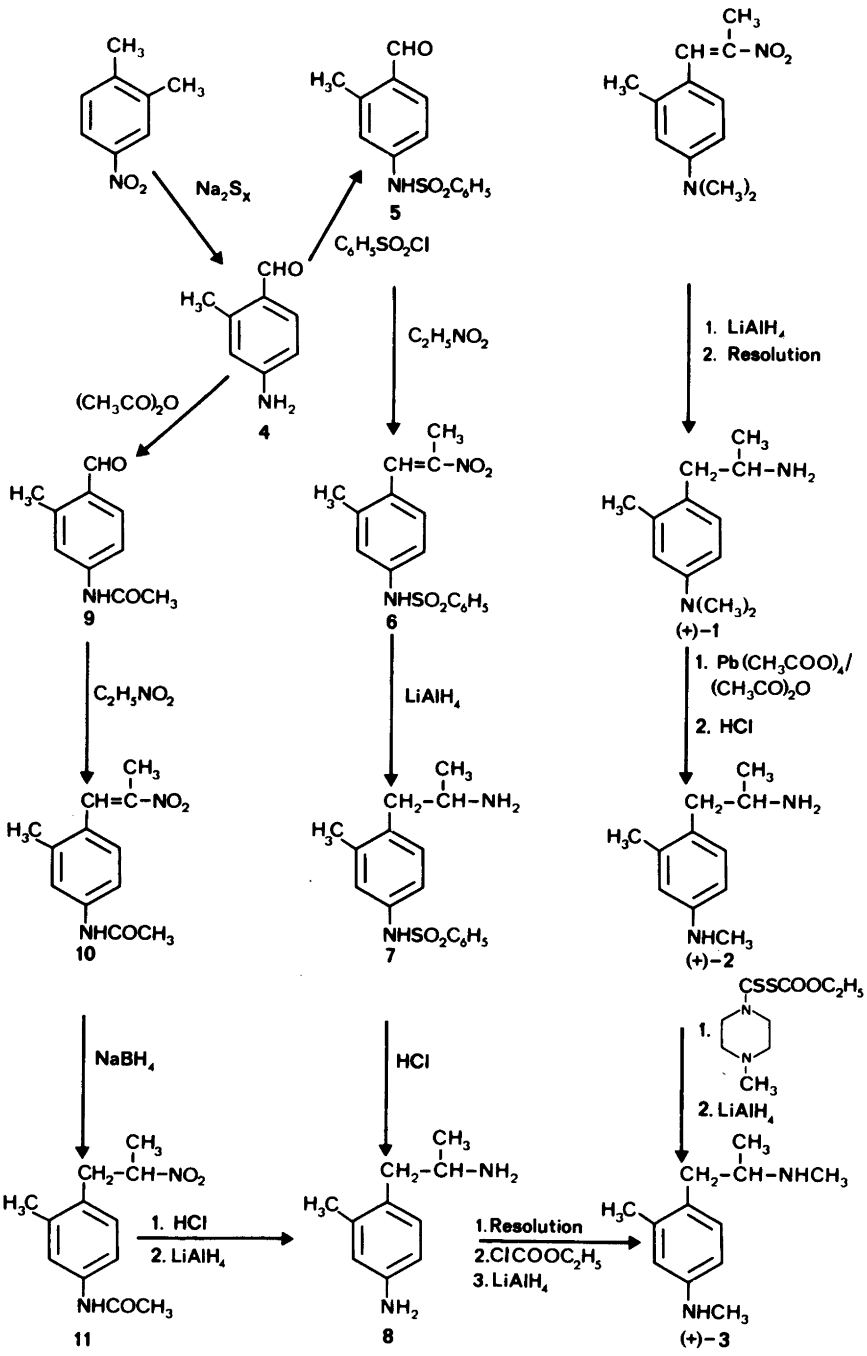
Na2Sx
C6H5SO2Cl
(CH3CO)2O
C2H5NO2
LiAlH4
NaBH4
HCl
1. HCl
2. LiAlH4
1. Resolution
2. ClCOOC2H5
3. LiAlH4
1. LiAlH4
2. Resolution
1. Pb(CH3COO)4/
(CH3CO)2O
2. HCl
2. LiAlH4
4
5
6
7
8
9
10
11
(+)-1
(+)-2
(+)-3

Scheme 1.

ethane resulted in the formation of polymeric products. To eliminate this tendency of self-condensation, the amino group of *4* was blocked by acetylation with acetic anhydride yielding compound *9*. Alternatively reaction of *4* with benzenesulfonyl chloride in the presence of pyridine gave the sulfonamide *5*. Condensation of *9* and *5* with nitroethane in ethanol, using ammonium acetate as a catalyst, yielded the corresponding nitrostyrenes *10* and *6*. Compound *6* was then reduced with lithium aluminium hydride to the intermediate sulfonamide *7*. In the next step the hydrolysis of *7* with hydrochloric acid yielded compound *8* (Method B). The preparation of *(+)-8* was achieved from *6* without isolating the intermediate sulfonamide *7*. The racemic amine *8* was readily resolved by means of L(+)-tartaric acid.

The acid hydrolysis of the acetanilide *10* resulted in tar formation. Attempts to convert *10* into the 4-acetamido analogue of *8* by means of selective reduction with lithium aluminium hydride were unsuccessful, the acetamide group of *10* being reduced at the same time. Thus, the synthesis of *8* from *10* was achieved in a two-step procedure. In the first step the double bond of *10* was selectively reduced with sodium borhydride. The obtained acetanilide *11* was then deacetylated with hydrochloric acid to give the intermediate compound 1-(4-amino-2-methylphenyl)-2-nitropropane, which on reduction with lithium aluminium hydride, yielded *8* (Method C).

Ethoxycarbonylation of the optical isomer *8(+)* with ethyl chloroformate followed by reduction of the intermediate di-carbamate with lithium aluminium hydride yielded *(+)-3* (Method D). The compound was identical with that prepared according to Method A.

EXPERIMENTAL

Melting points were determined in an electrically heated metal block, using calibrated Anschütz thermometers. Optical rotation were measured with a Perkin-Elmer Model 41 polarimeter and ^{1}H NMR spectra were recorded with a Varian A-60 A or a Bruker WP 200 NMR spectrometer. The analyses were performed by the Department of Analytical Chemistry at the University of Lund, Sweden. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4 % of the theoretical values. The absence of precursors in the prepared compounds was established by GLC using a Perkin-Elmer 3920 gas chromatograph equipped with flame ionization detector.

(+)-4-Dimethylamino-2,α-dimethylphenethylamine (+)-hydrogen tartrate [(+)-1]. A solution of 98.4 g (0.45 mol) of 4-dimethylamino-2,β-dimethyl-β-nitrostyrene in 250 ml of dry tetrahydrofuran was added dropwise while stirring and cooling in ice-water to 50.0 g (1.3 mol) of lithium aluminium hydride in 950 ml of dry ether. The mixture was stirred overnight at room temperature. Then 300 ml of saturated sodium sulfate solution was added dropwise with vigorous stirring and cooling. The mixture was filtered and the solid washed with ether. The filtrate and washings were dried over anhydrous sodium sulfate. The solvent was removed by evaporation and the residual crude base was dissolved in 500 ml of 95 % methanol. The solution was added to 75.0 g (0.5 mol) of L(+)-tartaric acid dissolved in 500 ml of 95 % methanol. The solution was allowed to stand for 18 h at room temperature. The solid was filtered, washed with ether and air-dried, giving 89.5 g of fluffy crystals. Four recrystallizations in a like manner (3 × 1000 ml 95 % methanol + 500 ml 95 % methanol) gave 22.5 g (29 %) of the pure compound, m.p. 191 – 192 °C. $[\alpha]_D^{20} = +27.2°$ ($c = 0.1$, H_2O). $[\alpha]_D^{20}$ of the base = $+33.7°$ ($c = 2$, EtOH). Anal. $C_{16}H_{26}N_2O_6$: C,H,N,O. NMR: (base, $CDCl_3$): 7.0 (dd, 1, phenyl), 6.5 (dd, 2, (overlap, phenyl), 3.1 (m, 1, methine), 2.9 (s, 6, *N,N*-dimethyl), 2.5 (dq, 2, methylene) 2.3 (s, 3, 2-methyl), 1.3 (s, 2, amino), 1.1 (d, 3, α-methyl).

The optical purity was checked in the following manner. An appropriate amount of the tartrate (10 – 50 mg) was dissolved in 2 ml of dry pyridine and a molar excess (300 %) of (−)-campanic acid chloride added. The mixture was incubated at 50 °C for 10 min and the solution was subjected directly to GLC analysis. A 2 m × 3 mm glass column was used, with 3 % OV-17 as liquid phase and 100 – 120 mesh Gas Chrom Q as support. Samples were injected at a column temperature of 230 °C with a nitrogen flow rate of *ca.* 30 ml/min. Under these conditions retention times of *ca.* 30 min were observed, with 1 – 2 min separation between isomer peaks. Isomer purities of >95 % (peak heights) were found by this technique.

(+)-4-Methylamino-2,α-dimethylphenethylamine (+)-hydrogen tartrate [(+2)]. To 68.4 g (0.2 mol) of *(+)1* was added with stirring 400 ml of 10 % NaOH. The resulting mixture was extracted with ether. The extract was dried over sodium sulfate, filtered and the ether was evaporated. To the residue, 37.6 g oil, 120 ml of acetic anhydride was added dropwise while stirring. The resulting mixture was refluxed for 10 min and then cooled down to room temperature. To the stirred solution was added dropwise while cooling in tap water a solution of 115.0 g (0.22 mol) of 85 % lead tetraacetate

in 500 ml of chloroform. After standing overnight at room temperature the precipitated lead acetate was filtered off and washed with chloroform. The filtrate and washings were combined and extracted with 3 × 100 ml of water. The chloroform was evaporated and to the residue, 55.0 g of brown oil, was added 100 ml of concentrated hydrochloric acid and 100 ml of water. The mixture was refluxed overnight and then evaporated to half its volume and made basic with NaOH. Extractions with ether and drying of the extract with sodium sulfate gave, after evaporation of the solvent, 32.3 g of a brown oil. The product was distilled at reduced pressure giving 18.3 g of a fraction boiling at 141–145 °C/2 mm. The obtained base was dissolved in 400 ml of ethanol. The solution was added to 16.5 g (0.11 mol) of L(+)-tartaric acid dissolved in 400 ml of ethanol. The mixture was left overnight at room temperature. The precipitated solid was collected and washed with ethanol and ether. Yield 31.0 g. M.p. 169–170 °C. The salt was recrystallized from 1000 ml of 98 % ethanol, giving 27.8 g (42 %) of *(+)2*. M.p. 170–171 °C $[\alpha]_D^{20} = +30.3°$ ($c=1$, H_2O). Anal. $C_{15}H_{24}N_2O_6$: C,H,N,O.

(+)-4-Methylamino-2,α,N-trimethylphenethylamine dihydrochloride [(+)3]. *Method A.* To 7.5 g (0.023 mol) of *(+)2* was added 40 ml of 10 % NaOH. The mixture was extracted with 2 × 100 ml of ether. The extract was dried over sodium sulfate and was added dropwise while stirring and cooling in ice to a solution of 5.8 g (0.023 mol) of fresh prepared *S*-ethoxycarbonyl 4-methyl-1-piperazinecarbodithioate. The mixture was stirred for 18 h at room temperature. The precipitated 4-methyl-1-piperazinedithiocarboxylic acid (4.0 g, 97 %) was filtered off and washed with ether. The filtrate and washings were combined and evaporated. The residue, 6.1 g of colourless oil, was dissolved in 100 ml of dry ether. The solution was added dropwise while stirring to 7.6 g (0.2 mol) of lithium aluminium hydride in 200 ml of dry ether. The mixture was refluxed for 5 h. After the addition of 25 ml of saturated sodium sulphate the mixture was filtered. The filtrate was dried with anhydrous sodium sulfate and treated with dry hydrogen chloride in ether. The precipitate was recrystallized from ethanol–isopropyl ether. Yield 4.7 g (77 %). M.p. 218–219 °C $[\alpha]_D^{20} = +9.6°$ ($c=1$, H_2O).

S-Ethoxycarbonyl 4-methyl-1-piperazinecarbodithioate. To a stirred suspension of 20.0 g (0.1 mol) of sodium 4-methyl-1-piperazinecarbodithioate in 200 ml of ether was added gradually while stirring and cooling in ice a solution of 9.5 ml (0.1 mol) of ethyl chloroformate in 25 ml of ether. The mixture was stirred overnight at room temperature and filtered. The filtrate was evaporated and the residue was crystallized from ether–lightpetroleum yielding 13.5 g (54 %) of yellow crystals melting at 44–45 °C. Anal. $C_9H_{16}N_2O_2S_2$: C,H,N,S. The compound was unstable and liquified at room temperature within a few weeks. When stored in a refrigerator no signs of decomposition were found for a period of one year.

The following compounds were obtained in a similar way. *S*-Isopropoxycarbonyl 4-methyl-1-piperazinecarbodithioate, yield 30 %, m.p. 60–61 °C. Anal. $C_{10}H_{18}N_2O_2S_2$: C,H,N,S. *S*-Benzyloxycarbonyl 4-methyl-1-piperazinecarbodithioate, yield 11 %, m.p. 90–91 °C. Anal. $C_{14}H_{18}N_2O_2S_2$: C,H,N,S.

In a model reaction a solution of 7.9 g (0.05 mol) of *N*-ethoxycarbonylpiperazine in 50 ml of ether was added by portions to a stirred solution of freshly prepared *S*-ethoxycarbonyl 4-methyl-1-piperazinecarbodithioate in 100 ml of ether. The mixture was stirred overnight at room temperature. The precipitate was filtered off and washed with ether giving 8.8 g (99.5 %) of *N*-methyl-*N'*-dithiocarboxylic acid, m.p. 185 °C (subl.). The melting point was undepressed on admixture with an authentic sample of *N*-methyl-*N'*-dithiocarboxylic acid. Anal. $C_6H_{12}N_2S_2$: C,H,N,S. The filtrate and washings were combined and the ether was evaporated yielding 11.4 g (99 %) of *N,N'*-diethoxycarbonylpiperazine melting at 43–45 °C (lit.[9] m.p. 44–45 °C). An analytical sample, recrystallized from ligroin, melted at 46–46.5 °C. Anal. $C_{10}H_{18}N_2O_4$: C,H,N,O.

4-Amino-2-methylbenzaldehyde (4). 108.8 g (0.72 mol) of 1,2-dimethyl-4-nitrobenzene was dissolved in 600 ml of ethanol and added slowly while heating at reflux temperature to a stirred solution of 54 g of sodium hydroxide, 160 g of sodium sulphide nonahydrate and 30 g of sulfur in 1.0 l of water. The solution was boiled under reflux for 3 h and the ethanol was evaporated at reduced pressure. The mixture was extracted with chloroform. The extract was dried with sodium sulphate and the chloroform was evaporated. The residual yellow oil was crystallized from toluene–ligroin yielding 51.7 g (53 %) of *4*. M.p. 83–84 °C (Lit.[8] m.p. 83–84 °C).

4'-Formyl-3'-methylbenzenesulfonanilide (5). To a stirred solution of 51.9 g (0.38 mol) of *4* in 200 ml of tetrahydrofuran and 80 ml of pyridine was added by portions 75 ml (0.59 mol) of benzenesulfonyl chloride. After stirring for 1 h at room temperature 1.5 l of ice-water was added. The precipitate was filtered off and washed with water giving 99.8 g (95 %) of *5*. M.p. 156–158 °C. An analytical sample, melting at 161–62 °C was obtained by recrystallization of this material from aqueous EtOH. Anal. $C_{14}H_{13}NO_3S$: C,H,N,O,S.

3'-Methyl-4'-(2-nitropropen-1-yl)benzenesulfonanilide (6). A mixture of 142 g (0.51 mol) of *5*, 65 ml (0.9 mol) of nitroethane, and 10 g of ammonium

acetate in 1.2 L of ethanol was heated under reflux for 3 h. To the hot solution was added 1 l of water and the mixture was cooled in ice. The precipitate was filtered off and washed with water yielding 120.8 g (71 %) of the crude compound melting at 135–137 °C. An analytical pure sample (76.2 g) was obtained by recrystallization of 87.0 g of this material from 1 l of 75 % EtOH. M.p. 138–139 °C. Anal. $C_{16}H_{16}N_2O_4S$: C,H,N,O,S.

4'-(2-Aminopropyl)-3'-methylbenzenesulfonanilide (7). A solution of 22.0 g (0.066 mol) of *6* in 130 ml of tetrahydrofuran was added dropwise while stirring to a mixture of 7.9 g (0.21 mol) of lithium aluminium hydride in 200 ml of dry ether. The reaction mixture was refluxed for 1.5 h. After dropwise addition of 25 ml of a saturated sodium sulfate solution while stirring and cooling, the mixture was filtered. The filter cake was extracted with 4 × 200 ml of boiling ethanol. The combined extracts were acidified with hydrogen chloride in ether. Concentration of the solution to 200 ml and the addition of 100 ml of isopropyl ether gave a small amount of precipitation which was filtered off. The filtrate was evaporated and the residue recrystallized from ethanol–ether giving 10.7 g (48 %) of the hydrochloride. M.p. 217–219 °C. The hydrochloride was dissolved in water and converted into the free base by the addition of NaOH to a pH-value of ~7. The compound was extracted with methylene chloride and recrystallized from ethanol–light petroleum. M.p. 121.5–122.5 °C.

Anal. $C_{16}H_{20}N_2O_2S$: C,H,N,O,S.

4-Amino-2,α-dimethylphenethylamine dihydrochloride (8). Method B. A mixture of 0.5 g (0.0016 mol) of 7 and 3.5 ml of 25 % hydrochloric acid was refluxed for 5 h. The solution was extracted with ether and the aqueous layer was made alkaline with NaOH. Extraction with ether and acidifying of the sodium sulfate dried extract yielded the crude hydrochloride. The salt was filtered off and recrystallized twice from ethanol–isopropyl ether giving 0.20 g (53 %) of *8*. M.p. 296–298 °C (D). Anal. $C_{10}H_{16}N_2 \cdot 2\,HCl$: C,H,Cl,N.

4-Formyl-3-methylacetanilide (9). To 1.0 g (0.0074 mol) of compound *4* was added 10 ml of acetic anhydride. After stirring at room temperature for 2 h the reaction mixture was poured into ice-water. The obtained precipitate was filtered off and washed with water. Yield 1.3 g (99 %). M.p. 109–112 °C. An analytical sample was obtained by recrystallization of this material from aqueous ethanol. M.p. 112.5–113.5 °C. Anal. $C_{10}H_{11}NO_2$: C,H,N,O.

3-Methyl-4-(2-nitropropen-1-yl)acetanilide (10). A mixture of 34.4 g (0.19 mol) of *9*, 22.5 g (0.3 mol) of nitroethane and 20 g of ammonium acetate in 200 ml of ethanol was heated under reflux while stirring for 5 h. To the hot solution was added 300 ml of water. After cooling the obtained precipitate was filtered off and recrystallized from aqueous ethanol yielding 17 g (38 %) of *10*. M.p. 130–31 °C. Anal. $C_{12}H_{14}N_2O_3$: C,H,N,O.

3-Methyl-4-(2-nitropropyl)acetanilide (11). To a stirred solution of 20.0 g (0.085 mol) of *10* in 600 ml of ethanol was added by portions 5.7 g (0.15 mol) of sodium borohydride. Stirring was continued for 4.5 h when a portion of 1.0 g of sodium borohydride was added. After 0.5 h the mixture was diluted with 100 ml of water and made acidic with acetic acid to pH 4. The ethanol was evaporated and aqueous ammonia was added to pH 10. The mixture was extracted with 3 × 500 ml of chloroform. The extract was washed with water, dried with sodium sulfate and the solvent was evaporated. The residue was recrystallized from ethanol–light petroleum yielding 17.0 g (85 %) of crude *11*, melting at 79–81 °C. An analytical sample was obtained from a repeated crystallization. M.p. 88.5–90 °C. Anal. $C_{12}H_{16}N_2O_3$: C,H,N,O.

4-Amino-2,α-dimethylphenethylamine dihydrochloride (8). Method C. A solution of 11.6 g (0.050 mol) of compound *11* was dissolved in a mixture of 200 ml of ethanol and 40 ml of concentrated hydrochloric acid. The stirred solution was refluxed for 2 h and was then evaporated. Saturated sodium hydrogen carbonate solution was added to the residue and the mixture was extracted with chloroform. The extract was dried with sodium sulphate and the solvent was evaporated. The evaporation of the solvent gave 9.9 g of crude 1-(4-amino-2-methylphenyl)-2-nitropropane as an oil. A solution of 4.99 g (0.025 mol) of the oil above in 25 ml of dry ether was added while stirring to 3.3 g (0.087 mol) of lithium aluminium hydride in 300 ml of dry ether. The mixture was refluxed for 3.5 h and 25 ml of saturated sodium sulfate solution was added. The filtrate was dried over sodium sulfate and the ether was evaporated. The residual oil was dissolved in 225 ml of ethanol and 5.0 g (0.04 mol) of oxalic acid dihydrate was added. The precipitate was collected and recrystallized from 300 ml of aqueous ethanol giving 3.0 g (40 %) of the oxalate. M.p. 184–185 °C. Anal. $C_{10}H_{16}N_2 \cdot 1.5\,C_2H_2O_4$: C,H,N,O.

The melting point of the dihydrochloride, 297–298 °C (D), was undepressed on admixture with the product prepared by Method B.

A little amount of the crude intermediate compound, 1-(4-amino-2-methylphenyl)-2-nitropropane, was dissolved in ether and a slight excess of toluene-4-sulfonic acid was added. The precipitated sulfonic acid salt melted at 177–178 °C. Anal. $C_{10}H_{14}N_2O_2 \cdot C_7H_8O_3S$: C,H,S,O.

(+)-4-Amino-2,α-dimethylphenethylamine (+)-hydrogen ditartrate [(+)8]. 76.2 g (0.23 mol) of compound *6* was reduced with 31.0 g of lithium aluminium hydride according to the directions given for 7. The combined ethanol extracts were

evaporated and the residue (69.3 g) was dissolved in 200 ml of concentrated hydrochloride acid and 200 ml of water. The solution was refluxed overnight, concentrated to half its volume and then diluted with water to 800 ml and extracted with ether. The water layer was alkalized with sodium hydroxide and extracted with 3 × 300 ml of ether. The extracts were dried with sodium sulfate and the ether was evaporated. The residue, 26.0 g oil, was dissolved in 100 ml of ethanol and the solution was added to 48.0 g (0.32 mol) of L(+)-tartaric acid in 300 ml of ethanol. The mixture was cooled in ice-water and the obtained precipitate was filtered off giving 60.8 g of crude tartrate. M.p. 146–150 °C. The salt required three recrystallizations from 80% methanol (1500 ml + 2 × 1000 ml) before constant physical properties were attained. Yield 22.7 g (43 %). M.p. 152–155 °C. $[\alpha]_D^{20} = +26.3°$ ($c = 1$, H_2O). Anal. Found: C 45.81; H 6.34; N 5.58; O 41.78. Calc. for $C_{10}H_{16}N_2 \cdot 2C_4H_6O_6$: C 46.55; H 6.08; N 6.03; O 41.34.

(+)-4-Methylamino-2,α,N-trimethylphenethylamine dihydrochloride [(+)3]. *Method D.* To a solution of 18.6 g (0.04 mol) of *(+)8* in 50 ml of water was added 25 ml of 45 % NaOH. The mixture was extracted with 2 × 150 ml of ether. The extract was evaporated and to the residual oil was added 200 ml of toluene and a solution of 12.0 g (0.3 mol) of NaOH in 150 ml of water. The mixture was stirred and cooled in ice-water while 30 ml (0.3 mol) of ethyl chloroformate was added by portions. The mixture was stirred for 2 h at room temperature and 200 ml of ether was added. The solvent layer was separated and dried with anhydrous sodium sulfate. The solvent was evaporated giving 11.8 g of the solid intermediate carbamate. The compound (11.8 g) was dissolved in 100 ml of tetrahydrofuran and added to 15.0 g (0.4 mol) of lithium aluminium hydride in 200 ml of ether according to the direction in Method A. The crude hydrochloric salt was recrystallized twice from ethanol–isopropyl ether giving 7.7 g (73 %) of *(+)3*. M.p. 218–219 °C. $[\alpha]_D^{20} = +9.3°$ ($c = 1$, H_2O). The melting point was undepressed on admixture with the compound prepared by Method A. The NMR spectrum of the compound was found to be identical with that obtained from the product prepared by Method A. Anal. $C_{12}H_{20}N_2 \cdot 2HCl$: C,H,Cl,N.

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