Arch. Pharm. (Weinheim) *311*, 796–798 (1978)

Hans Brussee, Ed A. Zonneveld, Adri C. A. Jansen, Kornelis W. Gerritsma

Syntheses of Some Derivatives of Dopamine

Department of Pharmacochemistry, Subfaculty of Pharmacy, University of Leyden, The Netherlands
(Eingegangen am 30. September 1977)

The syntheses of the optical isomers of 2-(3,4-Dimethoxyphenyl)propylamine (**4,5**) and of 2-(3,4-Dimethoxyphenyl)-*N*-methylpropylamine (**6,7**), are described. The starting material for the preparations was 3,4-dimethoxybenzyl cyanide (**1**). The resolution was carried out with tartaric acid.

Die Synthese einiger Dopaminderivate

Die Synthesen der optischen Isomere von 2-(3,4-Dimethoxyphenyl)-propylamin (**4, 5**) und 2-(3,4-Dimethoxyphenyl)-N-methyl-propyl-amin (**6, 7**) werden beschrieben. Ausgangsmaterial dieser Synthesen ist 3,4-Dimethoxy-benzylcyanid (**1**). Die Trennung der optischen Antipoden erfolgt durch fraktionierte Kristallisation der Tartrate.

In the course of our investigations on the influence exerted by the pH on the optical rotation of adrenaline and noradrenaline, it was decided to replace the β-OH group of these compounds with a β-CH_3 group, so as to exclude the possibility of H-bridge formation with the amino nitrogen. For this purpose the optical isomers of 2-(3,4-dimethoxyphenyl)-propylamine (**4, 5**) and of 2-(3,4-Dimethoxyphenyl)-N-methyl-propylamine (**6, 7**) were prepared. They are the parent compounds of β-methyldopamine and β-methylepinine, respectively.

The preparation of the racemic mixture 3 has been described in only a few publications[1,2,3]. In two cases[1,2] acetoveratrone is used as starting material, which is converted via a Reformatsky reaction and five subsequent steps, into the desired product. In both the papers the yield is not mentioned, nor is a resolution of the racemic mixture performed.

An alternative method is given in a patent on the preparation of N-aralkyl-aryl- and aralkyl-carboxamidines[3], in which the synthesis of the desired compound 3 is described as an intermediate product. As starting material, 3,4-dimethoxy-benzylcyanide (**1**) is used, dissolved in dimethylsulfoxide with the addition of sodium hydroxide as base. Direct methylation is performed with methyl iodide at a temperature below 30° C, during 2 hours, followed by reduction

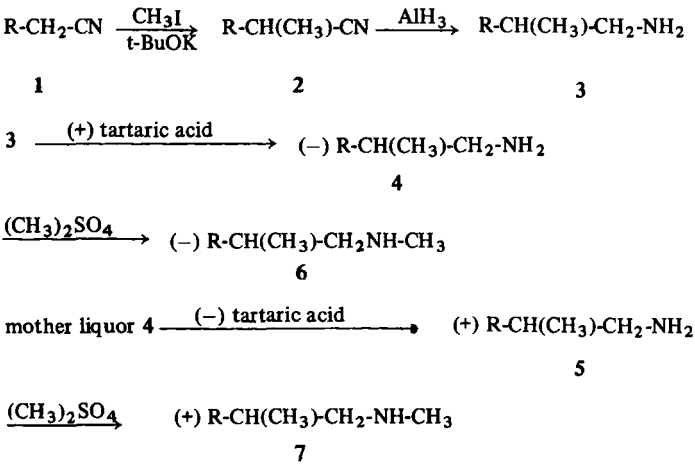
1 S. Sugasawa and N. Sugimoto, J. Pharm. Soc. Japan *61*, 62 (1941).
2 E. H. Woodruff, U.S. 2,293,876 and J. Am. Chem. Soc. *64*, 2859 (1942).
3 H. R. Rodriguez and G. DeStevens, U.S. 3,862,228.

of the product (dissolved in tetrahydrofuran) with borane. A resolution of the racemic mixture is not performed, whilst the yield nor the extent of dimethylation on the α-position is mentioned.

By starting with 3,4-dimethoxy-benzylcyanide (1) and potassium-t-butoxylate as base, it proved possible that the conditions for methylation (concerning the relative concentrations of reagents and their rate of addition, as well as temperature) can be chosen so that a reaction time of 1 hours is sufficient to obtain a product, which after one recrystallisation gives the pure α-monomethyl derivative 2 of the starting material, in a yield of 68 %. For the reduction to the corresponding amine, excellent results were obtained with aluminium hydride, according to *Brown*[4], obtained from lithium aluminium hydride with 100 % sulphuric acid. Resolution of the racemic mixture was performed with tartaric acid. With dextro-tartaric acid the laevo-rotary β-methyldopamine derivative 4 was obtained and with laevo-tartaric acid the dextro-rotary isomer 5 was isolated from the combined mother liquores. The tartrates were transformed in the usual way to the HCl-salts.

For the preparation of the corresponding epinine derivatives 6 and 7, the optical isomers of the β-methyldopamine derivatives 4 and 5 were methylated at the nitrogen atom with dimethylsulphate[5]. The total syntheses is given in Scheme I.

Scheme I. (R=-$C_6H_3(OCH_3)_2$)



Experimental

Melting points: apparatus Tottoli (uncorr.). *Optical rotations:* ETL-NPL Automatic Polarimeter 143A. *NMR-spectra:* Jeol PS-100 spectrometer. *Mass spectra:* GEC-AET MS902 spectrometer.

4 H. C. Brown and N. Nin Yoon, J. Am. Chem. Soc. *90*, 2927 (1968).
5 E. F. Kiefer, J. Med. Chem. *15*, 214 (1972).

3,4-Dimethoxy-α-methyl-benzylcyanid (2)

A solution of 25 g (0.22 mole) of t-BuOK in 250 ml t-BuOH is added at once to a solution of 30 g (0.17 mole) of 1 and 40 g (0.28 mole) of CH_3 I in 250 ml t-BuOH.

The temp. is maintained at 35–38° C for 60 min. The reaction is stopped by adding the mixture to 500 g crushed ice and when the first crystals are formed, water is added to a total volume of 3 l. Upon standing, 18 g 2 crystallises. An extraction of the water layer produces about 10 g crude product, which on recrystallisation from ethanol, yields 4.2 g 2. Total amount 22.2 g 2 (68 %). Purity about 95 %, as measured with NMR. m. p. 69–71° C.
NMR ($CDCl_3$) δ (ppm) = 1.61 (d, J = 7Hz, CH_3); 3.85 (s, OCH_3); 3.87 (s, OCH_3); ∿3.86 (q, J = 7Hz, CH); 6.85 (s, arom).

2-(3,4-Dimethoxyphenyl)-propylamine (3)

Prepared from 2, according to the preparation of β-phenylethylamine as described in literature[4]. Yield of 3: 84–90 %; bp 120° C/0.4 mm (lit.[2] 160° C/14 mm). NMR ($CDCl_3$) δ (ppm) = 1.25 (d, J = 7Hz, CH_3); 2.81 (m, CH_2 and CH); 3.85 (s, OCH_3); 3.87 (s, OCH_3); 6.80 (m, arom).
Mass: M^+ = 195.1257 ($C_{11}H_{17}NO_2$).

(–)2-(3,4-Dimethoxyphenyl)-N-methyl-propylamine (4)

A warm solution of 41 g 3 in 200 ml EtOH is added to a warm solution of 40 g (+) tartaric acid in 300 ml EtOH. On cooling, crude 4-tartrate crystallises. Four times recrystallisation from EtOH produces 30 g 4-tartrate with mp. 166–167° C, $[\alpha]_D^{23}$ = –7° (c = 0.5; MeOH).
4-tartrate was converted to the HCl-salt in the usual manner. 4-HCl mp. 191–193° C.

Overall yield (3 to 4-HCl) 60–70 %. $[\alpha]_D^{23}$ = –24° (c = 0.5; MeOH).

(+) 2-(3,4-Dimethoxyphenyl)-propylamine (5)

The mother liquor of the previous reaction was evaporated i. vac. The crude residue was freed form (+)tartaric acid, the amine dissolved in EtOH and treated with a solution of (–) tartaric acid in EtOH. Three times recrystallisation from EtOH produced pure 5-tartrate m.p. 169–170° C; $[\alpha]_D^{23}$ = +6° (c = 0.5; MeOH)
5-tartrate was converted to 5-HCl. m.p. 192–193° C; $[\alpha]_D^{23}$ = +25° (c = 0.5; MeOH).
Overall yield (3 to 5-HCl) 60–70 %.

(–) And (+) 2-(3,4-Dimethoxyphenyl)-N-methyl-propylamine (6) resp. (7)

Prepared from 4 resp. 5 with dimethylsulphate according to [5]. NMR (free base, $CDCl_3$) δ (ppm) = 1.24 (d, J = 7 Hz, C-CH_3); 1.44 (s, NH); 2.34 (s, N-CH_3); 2.72 (m, CH_2 and CH); 3.80 (s, OCH_3); 3.83 (s, OCH_3); 6.78 (m, arom).
Mass: M^+ = 209.1413 ($C_{12}H_{19}NO_2$)
6-HCl: m.p. 193–194° C; $[\alpha]_D^{23}$ = –36° (c = 0.5; MeOH) yield: 70 %.
7-HCl: m.p. 193–194° C; $[\alpha]_D^{23}$ = +35° (c = 0.5; MeOH) yield: 70 %.

Anschrift: Dr. A. C. A. Jansen, Wassenaarseweg 76, Leiden, Niederlande. [Ph 917]