CCA-197 547.435.07:541.632

Synthesis and Resolution of 1-Phenyl-1-*o*-chlorophenyl-3-dimethylamino-propanol-(1)*

A. Markovac-Prpić, D. Fleš, and M. Milohnoja

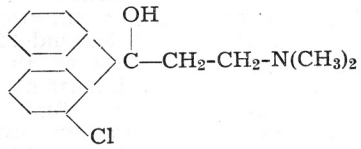
Research Department »Pliva« Pharmaceutical and Chemical Works, Zagreb, Croatia, Yugoslavia

Received October 10, 1960

Racemic 1-phenyl-1-*o*-chlorophenyl-3-dimethylamino-propanol-(1) was obtained from 1-*o*-chlorophenyl-3-dimethylamino-propanone-(1) hydrochloride *via* Grignard reaction. The corresponding (+) and (—)-amino alcohols were obtained by fractional crystallization of the diastereoisomeric tartrates.

It is known that in many synthetic and natural amino alcohols possesing asymmetric carbon atoms, the biological activity exhibited by the racemic mixture resides in one of the isomers. Beckett and collaborators[1] proved, for instance, that almost all analgetic activity of methadone resides in (—)-form, while in the case of antibiotic chloramphenicol only D-(−)-*threo* isomer shows the characteristic antibacterial activity.[2]

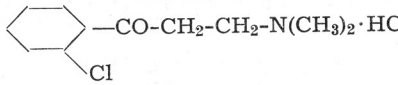
Recently a new amino alcohol, 1-phenyl-1-*o*-chlorophenyl-3-dimethylamino--propanol-(1) (I) was synthesised by Henecka and collaborators.[3] This compound was proved to be a very effective antitussic agent.[4] In order to study the relationship between antitussic activity and configuration of 1-phenyl-1-*o*--chlorophenyl-3-dimethylaminopropanol -(1) (I), it was necessary to prepare optically active I.[5]



I

Henecka *et al.*[4] prepared DL-amino alcohol I by condensing *o*-chlorobenzophenone with acetonitrile using sodium amide as a condensing agent. Reductive methylation of β-phenyl-β-*o*-chlorophenylhydracrylic acid nitrile in the presence of Raney cobalt catalyst under hydrogen pressure of 50—80 Atm., gave racemic 1-phenyl-1-*o*-chlorophenyl-3-dimethylamino-propanol-(1) (I).

The present paper reports a convenient new synthesis of 1-phenyl-1-*o*--chlorophenyl-3-dimethylamino-propanol-(1) and the resolution of the racemic mixture. The starting material was 1-*o*-chlorophenyl-3-dimethylamino-propanone-(1) hydrochloride (II), which was prepared from *o*-chloroacetophenone,[6]



II

* A. Markovac-Prpić, M. Milohnoja, Lj. Loborec and D. Fleš, Yugoslav. Patent Application P 631, May 13, 1960.

dimethylamine hydrochloride and paraformaldehyde by applying the Mannich reaction. Amino ketone hydrochloride II was treated with phenylmagnesium bromide and concverted in a 54% yield to the DL-amino alcohol I.

The resolution of DL-1-phenyl-1-o-chlorophenyl-3-dimethylamino-propanol-(1) (I) was effected by the fractional crystallization of the diastereoisomeric acid tartrate salts in acetone. The less soluble fraction of tartrates gave upon several crystallizations from a mixture of ethanol-ether (2:1) and treatment with potassium carbonate the levorotatory I with a specific rotation of $[\alpha]_D^{20}$ —29°. From the mother liquor, after crystallization from ethanol-ether (1:3), dextrorotatory amino alcohol I with a rotation of $[\alpha]_D^{20}$ +27° was obtained.

EXPERIMENTAL

All melting points are uncorrected.

1-o-Chlorophenyl-3-dimethylamino-propanol-(1) hydrochloride (II)

A mixture containing 15.5 g. of o-chloroacetophenone,[6], 8.2 g. of dimethylamine hydrochloride, 4.5 g. of paraformaldehyde, 20 ml. of ethanol and 0.3 ml. of concentrated hydrochloric acid was refluxed on a steam bath for six hours, while a clear solution was obtained. The solvent was evaporated in vacuo, and the solid residues was refluxed with 15 ml. of acetone .After cooling in the refrigerator the white precipitate was filtered off and washed with 10 ml. of cold acetone. A crop of 15 g. (61%) of ketone hydrochloride II was obtained, m. p. 173—175°. A sample was crystallized for analysis from ethanol and colorless prisms melting at 176° were obtained.

Anal. 11.51 mg. subst.: 22.60 mg. CO_2, 6.01 mg. H_2O
2.91 mg. subst.: 0.147 ml. N_2 (27°, 759 mm.)
$C_{11}H_{15}Cl_2NO$ (248.10) calc'd.: C 53.25; H 6.10; N 5.65%
found: C 53.58; H 5.84; N 5.74%

DL-*1-Phenyl-1-o-chlorophenyl-3-dimethylamino-propanol-(1)* (I)

Amino ketone hydrochloride II (9.9 g.) was dried for two hours at 100°, pulverized and with stirring and external cooling (ice and water) added to a Grignard reagent prepared from 4.9 g. of magnesium and 31.4 g. of bromobenzene in 50 ml. of ether. The reaction mixture was stirred and refluxed for six hours and after cooling to room temperature it was poured on a mixture of 200 g. of ice and 22 g. of ammonium chloride. After standing for one hour at room temperature, the ether layer was separated and the water layer extracted with four 20-ml. portions of ether. The total etheral extract was washed with water, dried over potassium carbonate and the solvent evaporated in vacuo. The crude crystalline residue was refluxed for 30 minutes with 20 ml. of petroleum ether (b. p. 40—60°), and the light yellow suspension cooled in a refrigerator. The crystalline material was removed by filtration and washed with cold petroleum ether. A crop of 5.4 g. (47.3%) of DL-base. I was obtained; m. p. 123°. A sample for analysis was crystallized from a mixture of ethylacetate-petroleum ether (b. p. 40—60°) (1:1), and melted at 125°. From the petroleum ether extract some of the unreacted ketone II could be obtained.

Anal. 13.11 mg. subst.: 33.74 mg. CO_2, 8.40 mg. H_2O
3.06 mg. subst.: 0.142 ml. N_2 (32°, 753 mm.)
$C_{17}H_{20}ClNO$ (289.79) calc'd.: C 70.45; H 6.96; N 4.84%
found: C 70.23; H 7.17; N 5.14%

DL-1-Phenyl-1-o-chlorophenyl-3-dimethylamino-propanol-(1) hydrochloride was crystallized from a mixture of ethanol-ether (1:1) and had a melting point of 193°.

Anal. 11.32 mg. subst.: 25.85 mg. CO_2, 6.26 mg. H_2O
2.37 mg. subst.: 0.098 ml. N_2 (25°, 759 mm.)
$C_{17}H_{21}ClNO_2$ (326.25) calc'd.: C 62.59; H 6.69; N 4.29%
found: C 62.32; H 6.18; N 4.63%

Resolution of DL-*1-phenyl-1-o-chlorophenyl-3-dimethylamino-propanol-(1)* (I)

A mixture of 29 g. of DL-base I and 15 g. of (+)-tartaric acid was dissolved under reflux in 150 ml. of acetone and let stand at room temperature for twenty four hours. The crystalline salt, predominantly tartrate of the (—)-form, was removed by suction filtration, and crystallized seven times from a mixture of ethanol-ether (2:1) to give 10 g. of the (—)-tartrate with a rotation of $[\alpha]_D^{20}$ —9.2° (c 2.5% in 50% ethanol), m. p. 135°.

Anal. 10.52 mg. subst.: 22.13 mg. CO_2, 5.79 mg. H_2O
$C_{21}H_{26}ClNO_7$ (439.88) calc'd.: C 57.34; H 5.96%
found: C 57.41; H 6.15%

The acetone mother liquor, containing predominantly (+)-tatrate, was evaporated in vacuo and crystallized from a mixture of ethanol-ether (1:3) to a rotation of $[\alpha]_D^{20}$ + 17.5° (c 4.75% in 50% ethanol); m. p. 110°.

Anal. 10.20 mg. subst.: 21.33 mg. CO_2, 5.47 mg. H_2O
$C_{21}H_{26}ClNO_7$ (439.88) calc'd.: C 57.34; H 5.96%
found: C 57.07; H 6.00%

(—)-1-Phenyl-1-o-chlorophenyl-3-dimethylamino-propanol-(1) was obtained from the (—)-tartarate in the following manner: 5 g. of the salt was dissolved in 5 ml. of water, made alkaline with solid potassium carbonate and extracted with ether. After drying over potassium carbonate ether was evaporated in vacuo and 2.5 g. of (—)-base was obtained. The product was crystallized for analysis from ethyl acetate and melted at 118°; $[\alpha]_D^{20}$ —29° (c 2.25% in chloroform).

Anal. 11.50 mg. subst.: 29.78 mg. CO_2, 6.82 mg. H_2O
$C_{17}H_{20}ClNO$ (289.79) calc'd.: C 70.45; H 6.96%
found: C 70.66; H 6.64%

Hydrochloride of the (—)-base I was prepared in the usual manner and was crystallized from ethanol to a melting point of 189°; $[\alpha]_D^{20}$ —14.0° (c 1.05% in 96% ethanol).

Anal. 7.05 mg. subst.: 16.10 mg. CO_2, 3.88. H_2O
$C_{17}H_{21}Cl_2NO$ (326.25) calc'd.: C 62.59; H 6.49%
found: C 62.32; H 6.15%

(+)-1-Phenyl-1-o-chlorophenyl-3-dimethylamino-propanol-(1) was prepared from (+)-tatrate in the same way as described for (—)-form. M. p. 122°; $[\alpha]_D^{20}$ + 27° (c 4.5% in chloroform).

Anal. 10.55 mg. subst.: 27.17 mg. CO_2, 6.28 mg. H_2O
$C_{17}H_{20}ClNO$ (289.79) calc'd.: C 70.45; H 6.96%
found: C 70.28; H 6.66%

Hydrochloride of the (+)-base I had a melting point at 192° (from ethanol), $[\alpha]_D^{20}$ + 11.2° (c 0.75% in 96% ethanol).

Anal. 11.57 mg. subst.: 26.42 mg. CO_2, 6.41 mg. H_2O
$C_{17}H_{21}Cl_2NO$ (326.25) calc'd.: C 62.59; H 6.49%
found: C 62.30; H 6.20%

Acknowledgment. The authors are indebted to Mrs. Lj. Loborec for her technical assistance and to Mr. N. Manger and his associates for performing the microanalyses.

REFERENCES

1. A. H. Beckett and A. C. Casy, *J. Chem. Soc.* **1955**, 900;
   A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, **6** (1954) 986;
   A. H. Beckett and N. J. Harper, *J. Chem. Soc.* **1957**, 858
2. M. C. Rebstock, H. M. Crooks Jr., J. Controlius, and Q. R. Bartz, *J. Am. Chem. Soc.* **71** (1949) 2458.
3. H. Henecka, R. Lorenz, and R. Gosswald, *DPB* 1 051 281, September, 1959.
4. R. Lorenz, R. Gooswald and H. Henecka, *Brit.* 815, 217, Jun. 1959.
5. A. Markovac-Prpić, M. Milohnoja, Lj. Loborec, and D. Fleš, *Yugoslav. Patent Application* P-631, May, 1960.
6. H. G. Walker and C. R. Hauser, *J. Am. Chem. Soc.* **68** (1944) 1386.

IZVOD

Sinteza i odjeljivanje antipoda 1-fenil-1-*o*-klorofenil-3-dimetil-amino-propanola-(1)

A. Markovac-Prpić, D. Fleš i M. Milohnoja

Racemični 1-fenil-1-o-klorofenil-3-dimetilaminopropanol-(1) dobiven je Grignardovom reakcijom iz 1-o-klorofenil-3-dimetilamino-propanon-(1) hidroklorida i brombenzena. Frakcioniranom kristalizacijom diastereoizomernih tartarata priređeni su pripadni (+) i (—)-1-fenil-1-o-klorfenil-3-dimetilamino-propanol-(1).

ISTRAŽIVAČKI INSTITUT
»PLIVA« TVORNICA FARMACEUTSKIH I KEMIJSKIH PROIZVODA
ZAGREB

Primljeno 10. listopada 1960.