CCA - 71

547.425:547.466.2:541.63

The Correlation of Configuration of Optically Active Nor-*pseudo*-ephedrine and Alanine

D. Fleš and A. Markovac-Prpić

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

Received July 16, 1957

D-Nor-*pseudo*-ephedrine was prepared from *N*-phthaloyl-D-alanyl chloride through the intermediate D-α-phthalimido-propiophenone which was reduced with aluminum isopropoxide to the appropriate carbinol. L-Nor-*pseudo*-ephedrine was prepared in the same way from L-alanine. The configurational correlation between D-nor-*pseudo*-ephedrine and D-alanine and L-nor-*pseudo*-ephedrine and L-alanine was established. The configurational relation of $C_{(2)}$ atom of chloramphenicol and D-(—)-nor-*pseudo*-ephedrine was thus established since chloramphenicol was previously synthetized from D-serine.

By working up the sirupy residue obtained in the manufacturing of ephedrine from Chinese herb called »Ma Huang«, Smith[1] and Nagai and Kanao[2] isolated in 1928 (+)-nor-*pseudo*-ephedrine. The synthesis of racemic nor-*pseudo*-ephedrine was published a year earlier by Kanao[3] who also converted nor-*pseudo*-ephedrine to ephedrine. Kanao[4] and Nagai and Kanao[5] achieved the resolution of nor-*pseudo*-ephedrine through the fractional crystallization of diastereomeric tartrates. Sah[6] reported in 1938 a synthesis of DL-nor-ephedrine and DL-nor-*pseudo*-ephedrine using *N*-carbobenzyloxy-DL-alanine as starting material. The correlation of configuration of nor-*pseudo*-ephedrine and *pseudo*-ephedrine was achieved by Smith[1], who converted (+)-nor-*pseudo*-ephedrine to (+)-*pseudo*-methylephedrine iodomethylate and correlated this compound with the one obtained through the methylation of *pseudo*-ephedrine.

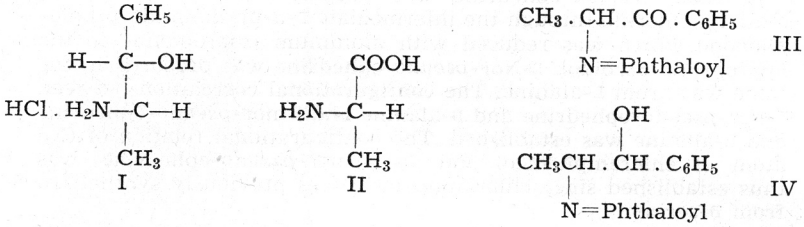
In a series of papers Freudenberg *et al.*[7,8] correlated the configuration of ephedrine with D-mandelic acid and with L-alanine. The correlation of configuration of *pseudo*-ephedrine and L-alanine was achieved by means of a synthesis of (-)-α-phenyl-β-methylaminopropanone iodomethylate from dimethylamino-L-alanyl-dimethylamide. The same iodomethylate was also prepared from *pseudo*-ephedrine. L-Alanine used in this synthesis was correlated with the optically active α-chloropropionic acid of the known configuration.

(-)-Nor-*pseudo*-ephedrine has not been found in the nature, but chloramphenicol which can be considered as a member of ephedrine series, was correlated by Rebstock *et al.*[9] to (-)-nor-*pseudo*-ephedrine. The correlation was based on the optical rotation data of chloramphenicol and its derivatives. The correctness of this assumption was confirmed by Fodor *et al.*[10] who establi-

shed the configurational relation of DL-1-phenyl-2-amino-1,3-propanediol to DL-nor-*pseudo*-ephedrine by means of chemical interconversion.

So far as we know a direct synthesis of L- and D-nor-*pseudo*-ephedrine from a compound of the known configuration has not been published hitherto. In this paper a description of synthesis of L- and D-nor-*pseudo*-ephedrine hydrochloride (I) from L- and D-alanine (II) is given. Reactions used in this synthesis are essentially the same as those used in the preparation of chloramphenicol from D-serine[11].

N-Phthaloyl-alanyl chloride was subjected to the usual Friedel-Crafts reaction, and optically active α-phthalimido-propiophenone (III) was thus obtained in a yield of 92%. The ketone III was then reduced with aluminum isopropoxide in isopropyl alcohol, and a yield of 60% of the corresponding *threo*-epimer IV was obtained. The *threo*-carbinol IV was easily separated from its diastereomer, being less soluble in ethanol.



It is interesting to note that Šorm and collaborators[12] found that p-nitrophenyl - 2 - benzamido- od 2 - carbobenzyloxamido - propiophenones gave the *threo*-isomer by reduction with aluminum isopropoxide, only if the free hydroxyl group was attached to the β-carbon atom. If the hydroxyl group was esterified, etherified, or replaced by chlorine or hydrogen, *erythro* isomer was predominant. However, in the course of our work we found that *threo*-isomers were predominant when β-methoxy[11,13], β-ethoxy[14], or β-unsubstituted-α-phthalimido-propiophenones were reduced with aluminum isopropoxide.

Müller[15] has recently described the preparation of DL-nor-ephedrine from DL-α-phthalimido-propiophenone. He claimed that reduction of DL-α-phthalimido-propiophenone with aluminum isopropoxide gave the *erythro*-isomer in a yield of 78%. The phthaloyl group of the *erythro*-carbinol was removed with hydrobromic acid, and DL-nor-ephedrine was obtained in a yield of 75%. In our hands reduction of L- and D-α-phthalimido-propiophenone with aluminum isopropoxide gave predominantely *threo*-isomer. The stereospecifity of the preparation of *threo*-IV from III by using the aluminum isopropoxide, allows an application of the rule of steric control of asymmetric induction proposed by Cram and Elhafez.[16]

The phthaloyl group of the compound IV was removed by hydrazinolysis and the optically active nor-*pseudo*-ephedrines were isolated and purified as hydrochlorides (I). Since an authentic sample of optically active nor-*pseudo*-ephedrine was not available, we compared the mixture of equal amounts of L- and D-nor-*pseudo*-ephedrine hydrochloride with an authentic sample of DL-nor-*pseudo*-ephedrine hydrochloride, and we found that they were identical in all properties.

Since the reactions used in this paper are sterically straightforward and do not involve the asymmetric carbon atoms, we consider that by means of this synthesis an additional proof of the configuration of L- and D-nor-*pseudo*-ephedrine is given. The synthesis of D-(-)nor-*pseudo*-ephedrine from D-alanine, described in this paper proves that the C(2) atoms of chloramphenicol and D-nor- *pseudo*-ephedrine are of the same configuration since chloramphenicol was previously prepared from D-serine.[11]

EXPERIMENTAL*

D-α-*Phthalimido-propiophenone* (III)

A mixture of 30 ml. of benzene and 7.03 g. (0.053 mole) of anhydrous aluminum chloride was placed in a 500-ml. three-necked flask, equipped with a mechanical stirrer, a dropping funnel and a reflux condenser. The reaction mixture was heated to 70° and with rapid stirring a solution of 5 g. (0.021 mole) of *N*-phthaloyl-D-alanyl-chloride in 20 ml. of benzene was added at such a rate as to maintain constant refluxing. The reaction mixture was refluxed for additional three hours, cooled and hydrolyzed with 30 g. of ice and 4 ml. of concentrated hydrochloric acid. The water layer was separated and extracted with three 20-ml. portions of benzene. The benzene layer was washed with 20 ml. of water, followed by two 20-ml. portions of a saturated sodium bicarbonate solution and dried over magnesium sulfate. The benzene was removed under reduced pressure and the brown oily residue (8.5 g.) was crystallized from 96% ethanol to give 5.4 g. (92%) of ketone III. M. p. 79—80°, $[\alpha]_D^{20}$ + 145.5° (c, 1.19 in ethanol). An analytical sample was crystallized twice from 75% ethanol. Colorless prisms melting at 81—82°, $[\alpha]_D^{20}$ + 165.5° (c, 1.44 in ethanol.

Anal. 11.87 mg. subst.: 31.70 mg. CO_2, 4.68 mg. H_2O
3.42 mg. subst.: 0.157 ml. N_2 (23°, 755 mm.)
$C_{17}H_{13}NO_3$ (279.28) calc'd.: C 73.11; H 4.69; N 5.02%
found: C 72.87; H 4.41; N 5.25%

2.4-Dinitrophenylhydrazone was prepared in quantitative yield in an alcoholic solution. The analytical sample was crystallized from ethanol to a melting point of 210—212°.

Anal. 11.64 mg. subst.: 25.71 mg. CO_2, 3.60 mg. H_2O
1.63 mg. subst.: 0.216 ml. N_2 (24°, 756 mm.)
$C_{33}H_{17}N_5O_6$ (459.41) calc'd.: C 60.13; H 3.73; N 15.24%
found: C 60.27; H 3.46; N 15.12%

L-α-Phthalimido-propiophenone was prepared in the same way from *N*-phthaloyl-L-alanyl chloride. M. p. 81—82°, $[\alpha]_D^{20}$ — 160.5° (c, 2.01 in ethanol).

D-threo-*1-Phenyl-1-hydroxy-2-phthalimidopropane* (IV)

In a 100-ml. round-bottomed flask were placed 3.5 g. (0.0125 mole) of ketone III, 7.0 g. (0.0345 mole) of distilled aluminum isopropoxide and 70 ml. of dry isopropyl alcohol. A Hahn partial condenser was attached, and the reaction mixture heated at such a rate as to maintain the slow distillation of acetone. When the theoretical amount of acetone was obtained (five hours), the isopropyl alcohol was removed *in vacuo* and the residue hydrolyzed with a solution of 45 g. of tartaric acid in 120 ml. of water in the presence of 20 ml. of benzene. The water layer was removed and extracted with three 30 ml. portions of benzene. The combined benzene solutions were dried, the benzene removed *in vacuo*, and the residue (3.3 g.) crystal-

* Melting points are uncorrected, unless otherwise stated.

lised from 7 ml. of ethanol to give 2·1 g. (60%) of the carbinol IV; m. p. 150—54°, $[\alpha]_D^{27}$ —107° (c, 3.145 in benzene). An analytical sample was crystallized twice from ethanol; m. p. 159—160°, $[\alpha]_D^{20}$ —111.3° (c, 0.93 in benzene).

Anal. 15.83. mg. subst.: 42.10 mg. CO_2, 7.33 mg. H_2O
3.83 mg. subst.: 0.176 ml. N_2 (25°, 764 mm.)
$C_{17}H_{15}NO_3$ (281.30) calc'd.: C 72.58; H 5.37; N 5.37%
found: C 72.57; H 5.18; N 5.30%

L-*threo*-1-Phenyl-1-hydroxy-2-phthalimidopropane was prepared in the same way from L-α-phthalimido-propiophenone. M. p. 156—157°, $[\alpha]_D^{20}$ + 108° (c, 1.22 in benzene).

A mixture of equal amounta of L- and D-*threo*-1-phenyl-1-hydroxy-2-phthalimidopropane had a melting point of 130—132°.

D-threo-*1-Phenyl-1-hydroxy-2-aminopropane hydrochloride* (I)

The carbinol IV (1.44 g., 0.0051 mole) was refluxed for two hours with 14 ml. of ethanol and 14 ml. of *M*-hydrazine hydrate in ethanol. The solvent was removed under reduced pressure, and the residue treated for ten minutes at 50° with 25 ml. of 10% hydrochloric acid, then kept for an hour at room temperature, and phthalyl hydrazide was removed by filtration under suction. The filtrate was evaporated under reduced pressure (bath below 50°) and the crystalline residue (1.44 g.) was dissolved in 5 ml. of 96% ethanol and crystallized by the addition of 16 ml. of ether. Yield 760 mg., $[\alpha]_D^{28}$ —42° (c, 2.125 in water). By working up the mother liquor, an additional quantity of I was obtained. The total yield of I was 0.820 g. (85%). An analytical sample was recrystallized from a mixture of ethanol and ether (1:2) to a melting point of 178—179° (corr.) and $[\alpha]_D^{20}$ —42.9° (c, 1.825 in water).*

Anal. 15.94 mg. subst.: 33.71 mg. CO_2, 10.59 mg. H_2O
$C_9H_{14}ClNO$ (187.67) calc'd.: C 57.60; H 7.52%
found: C 57.71; H 7.43%

For L-*threo*-1-phenyl-1-hydroxy-2-aminopropane m. p. 175—176°, $[\alpha]$ + 42.1° (c, 2.35 in water).

Anal. 14.10 mg. subst.: 29.81 mg. CO_2, 9.60 mg. H_2O
18.60 mg. subst.: 4.90 ml. 0.02 N $AgNO_3$
$C_9H_{14}ClNO$ (187.67) calc'd: C 57.60; H 7.52; Cl 18.89%
found: C 57.69; H 7.61; Cl 18.70%

A mixture of equal amounts of L- and D-nor-*pseudo*-ephedrine hydrochloride had a melting point of 168—169** and was undepressed upon admixture with an authentic sample of DL-nor-*pseudo*-ephedrine hydrochloride, but was strongly depressed when melted with a sample of DL-nor-ephedrine hydrochloride; mixed melting point was 131°.*** The paper chromatography was carried out on the Whatman No. 1 paper, at 24°, with descending technique, using solvent system: butanol-acetic acid-water (4:1:5). The mixture of L- and D-I gave the same spot with ninhydrin for R_f 0.78 as the authentic specimen of DL-nor-*pseudo* ephedrine hydrochloride.

Acknowledgments. The authors wish to thank Dr. J. Sicher from the Czechoslovakian Academy of Science and Dr. L. Urbanek from V.Ú.F.B., Prague for the generous supply of DL-nor-*pseudo*-ephedrine, and Professor G. Fodor from the University of Szeged for a sample of DL-nor-ephedrine. Thanks are also due to Miss. E. Jaeger for microanalyses and Miss. S. Iskrić for paper chromatograms.

* Reported for L-nor-*pseudo*-ephedrine hydrochloride, m. p. 178—179° [1], 180—181°, $[\alpha]_D^{20}$ + 42.5 (c, 7 in water)[5]

** Reported for DL-nor-*pseudo*-ephedrine hydrochloride, m. p. 168—169° [5]

*** Reported for DL-nor-ephedrine hydrochloride, m. p. 194° [5].

REFERENCES

1. S. Smith, *J. Chem. Soc.* **1928**, 52.
2. W. N. Nagai and S. Kanao, *J. Pharm. Soc. Japan* **48** (1928) 101; cit. from *Chem. Zentr.* **1928** I, 2553.
3. S. Kanao, *J. Pharm. Soc. Japan* **1927**, No. 540, 17; cit. from *Chem. Zentr.* **1927** I, 2538.
4. S. Kanao, *J. Pharm. Soc. Japan* **48** (1928) 122; cit. from *Chem. Zentr.* **1929 I**, 240.
5. W. N. Nagai and S. Kanao, *Ann.* **470** (1929) 157.
6. P. P. T. Sah, *Ber.* **71** (1938) 2300.
7. K. Freudenberg, E. Schöffel and E. Braun, *J. Am. Chem. Soc.* **54** (1932) 234.
8. K. Freudenberg and F. Nicholai, *Ann.* **510** (1934) 223.
9. M. C. Rebstock, H. M. Crooks, Jr., J. Controulis and Q. R. Bartz, *J. Am. Chem. Soc.* **71** (1949) 2458.
10. G. Fodor, J. Kiss and I. Sallay, *J. Chem. Soc.* **1951**, 1858.
11. D. Fleš and B. Balenović, *J. Am. Chem. Soc.* **78** (1956) 3072.
12. J. Sicher, M. Svoboda, M. Hrda, J. Rudinger and F. Šorm, *Chem. Listy* **47** (1955) 565.
13. D. Fleš and B. Balenović, *Arhiv kem.* **27** (1955) 149.
14. D. Fleš, B. Balenović, R. Marušić, and N. Manger, *Arhiv kem.* **27** (1955) 1.
15. H. K. Müller, *Ann.* **598** (1956) 70.
16. D. J. Cram and F. A. A. Elhafez, *J. Am. Chem. Soc.* **74** (1952) 5828.

IZVOD

Odnos konfiguracije optički aktivnih nor-*pseudo*-efedrina i alanina

D. Fleš i A. Markovac-Prpić

U prije objavljenoj publikaciji opisana je sinteza kloramfenikola iz D-serina[11]. Primjenom istih metoda opisana je u ovom radu priprava L-nor-*pseudo*-efedrina iz L-alanina i D-nor-*pseudo*-efedrina iz D-alanina. N-Ftaloil-L- (ili D-) alanil klorid dao je Friedel-Craftsovom reakcijom pripadni optički aktivni propiofenon III, koji je redukcijom po Meerwein-Ponndorfu preveden u karbinol IV. Hidrazinolizom karbinola IV priređeni su L- i D-nor-*pseudo*-efedrin hidrokloridi. (I). Utvrđeno je, da je smjesa L- i D-nor-*pseudo*-efedrin hidroklorida identična s originalnim uzorkom DL-nor-*pseudo*-efedrina.

ISTRAŽIVAČKI INSTITUT
»PLIVA« TVORNICA FARMACEUTSKIH
I KEMIJSKIH PROIZVODA
ZAGREB

Primljeno 16. srpnja 1957.