Preparation of Optically Active Heterocyclic Compounds. A Facile Synthesis of S-(-)-1,2,3,5,6,9-Hexahydro-7,8-benzopyrrocoline

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In two previous notes the synthesis of several octahydropyrrocoline (1) and hexahydrobenzopyrrocoline (2) derivatives have been reported. Some of these compounds possessed a somewhat hypnotic-sedative action (2).

The importance of new benzopyrrocoline syntheses has been emphasized due to the interesting pharmacologic behaviour that seems connected with these heterocyclic structures (2-4a,b), considering that the pyrrocoline nucleus is present in many alkaloids (Solanum, Veratrum, *etc.*) (1).

In our continuing study of benzopyrrocoline derivatives, we thought it would be interesting to devise a simple method to synthesize S-(-)-1,2,3,5,6,9-hexahydro-7,8-benzopyrrocoline, because of the importance of the absolute configuration of drugs when they react with a receptor and also due to the lack in the literature of methods to obtain optical isomers of hexahydrobenzopyrrocoline. This note describes this synthesis.

S(-)-2-Phenylpyrrolidine (5) (I) was reacted with bromoethanol to give the S(-)-*N*-(2-hydroxyethyl) derivative (II) which was converted into the halogeno derivative (III); the latter was then cyclized to give the S(-)-benzopyrrocoline (IV) by means of the Friedel-Crafts reaction.

I R = H IV

II R = CH_2-CH_2OH

III R = $CH_2-CH_2-Br \cdot HBr$

It is to be noted that Saito, *et al.*, during the degradation of the natural alkaloid, norsecurinine, in order to prove its absolute configuration, obtained an optical antipode of compound IV (6a,b). This antipode was chemically correlated with securinine (6a,b), whose absolute configuration had been previously established by X-ray investigation (7), ORD curves and by degradation to (+)-*N*-benzoylpipecolic acid (8).

From the stereochemical point of view, the present work confirms the chirality of 2-phenylpyrrolidine previously determined (5) from the absolute configuration of 2-phenylglutaric acid and allows the completion of the chemical reactions that correlate the latter to securinine. This correlation concurs with the one chemically obtained between 2-phenylglutaric acid and cephalosporine-C (whose configuration has been determined by an X-ray study (9a,b) from tetralin-1-carboxylic acid (10a,b), 1,2,3,4-tetrahydro-1-naphthylamine (11) and 2-aminoadipic acid (12).

From the synthetic point of view, the method described in this note does not lead to racemization, therefore it can be used with certainty for the systematic preparation of optically active heterocyclic systems with a bridgehead nitrogen atom, starting from type I compounds variously substituted on the benzene ring. The latter are easily obtained from condensation between acrylonitrile and substituted benzaldehydes (13) followed by reductive cyclization (5,14).

EXPERIMENTAL

Microanalyses were carried out by Dr. R. De Leonardis, Istituto di Chimica Farmaceutica, Bari, with a Hewlett-Packard Model 185 C,H,N analyzer. The melting points, determined with a Buchi-Tottoli capillary melting point apparatus, are uncorrected. Optical rotations were determined on a Roussel-Jouan electronic micropolarimeter; concentrations are expressed in g./100 ml. Ir, nmr and mass spectra were determined with a Perkin-Elmer Model 257, a Varian HA-100 and a Perkin-Elmer Model 270 spectrometers, respectively. Nmr chemical shifts are expressed in τ (s = singlet, d = doublet, t = triplet, m = multiplet).

S(-)-1-(β-Hydroxyethyl)-2-phenylpyrrolidine (II).

S(-)-2-Phenylpyrrolidine (I) (5.35 g.) with $[\alpha]_D$ = -15.88° (c 1.671 in methanol) (optical purity 48.9%) (5) was allowed to reflux for 5 hours with 13.62 g. of 2-bromoethanol and 11.55 g. of anhydrous sodium carbonate in 75 ml. of ethanol-water (4.5:1). Ethanol evaporation and extractions with ether, gave 6.01 g. (yield 86.47%) of an oil showing one single peak on glc analysis. The crude alcohol was purified by distillation (b.p. 0.04 = 96-98°) to give 5.10 g. (yield 73%) of a colorless oil; $[\alpha]_D$ = -68.34° (optical purity 48.9%, c 1.1667 methanol); ir (neat) ν max: 3420-3340 (large band), 2860 and 2780, 1600, 1300-1270, 1050 cm^{-1}; nmr

(deuteriochloroform) τ: 2.6-2.9 (5H, m, aromatic), 6.3-6.8 (4H, m, 2, β, O-H), 7.05-8.45 (8H, m); MS, m/e: 191 (M^+), 174, 160 (base peak), 131, 117, 104, 91.

Anal. Calcd. for $C_{12}H_7NO$: C, 75.3; H, 8.9; N, 7.3. Found: C, 74.8; H, 8.8; N, 7.1.

S(-)-1-(β-Bromoethyl)-2-phenylpyrrolidine (III).

A stirred, refluxing solution of alcohol S(-) II (4.5 g.) in 48% hydrobromic acid (36 ml.) and concentrated sulphuric acid (1.8 ml.), was treated, after 13 hours, with potassium bromide (9 g.) and concentrated sulphuric acid (4.9 ml.). The mixture was heated at reflux, with stirring, for an additional 10 hours, cooled to 0°, made alkaline with 28% ammonium hydroxide and extracted with chloroform. The dried and evaporated chloroform extracts yielded a dark brown liquid (5.9 g., yield 98%) that showed only one peak in glc analysis: $[\alpha]_D$ = -63.65° (optical purity 48.9%, c 1.175 methanol).

The bromo derivative was purified *via* its hydrobromide salt; the material was treated with 100 ml. of 48% hydrobromic acid and then extracted with chloroform. Evaporation of the chloroform extracts yielded the hydrobromide as a brown powder (5.77 g., yield 73%). The crude product was further purified on animal charcoal and crystallized from absolute ethanol and hexane to give 4.65 g. (yield 59%); m.p. = 158-159°; $[\alpha]_D$ = -15.66° (optical purity 48.9%, c 1.009 methanol); ir (potassium bromide disc) ν max: 2920 and 2810, 2620-2480 (series of bands), 1490, 1450, 1410 cm^{-1}; nmr (deuteriochloroform) τ: 2.0-2.4 (2H, m, aromatic), 2.4-2.7 (3H, m, aromatic), 5.1-5.5 (1H, m, 2-H), 5.7-6.7 (6H, m), 7.2-8.0 (4H, m, 3.4-H); MS, m/e: 255 and 253 (M^+), 174, 160 (base peak), 131, 117, 104, 91.

Anal. Calcd. for $C_{12}H_{16}BrN \cdot HBr$: C, 43.0; H, 5.1; N, 4.2. Found: C, 43.2; H, 5.1; N, 3.9.

S(-)-1,2,3,5,6,9-Hexahydro-7,8-benzopyrrocoline (IV).

The bromide hydrobromide (III.HBr) (1.8 g.) was dissolved in anhydrous decaline (57 ml.) and recently sublimed aluminium chloride (2.157 g.) was added. The suspension was vigorously stirred at 145-150° for 3 hours and then allowed to reflux at the boiling point for several minutes.

The reaction mixture was cooled and a mixture of water (40 ml.) and concentrated hydrochloric acid (25 ml.) was added, then washed with hexane. It was made alkaline with sodium hydroxide tablets and extracted with ether. Removal of the dried ethereal extracts, under reduced pressure, afforded a crude oil in quantitative yield, which, once distilled, had b.p. 0.8 = 160°. Since some fractions of the distillate, on glc analysis, appeared to be slightly impure for the starting base, the product was further purified *via* the picrate salt from an alcoholic solution. After several crystallizations from absolute ethanol, 0.42 g. was obtained, m.p. 171-173° dec., [Lit. (6) m.p. 170-172° dec.]; $[\alpha]_D$ = -10.95° (optical purity 48.9%, c 0.1825 methanol).

Anal. Calcd. for $C_{12}H_{15}N \cdot C_6H_3N_3O_7$: C, 53.7; H, 4.5; N, 13.9. Found: C, 54.1; H, 4.3; N, 13.6.

The base was obtained again by filtration through an alumina column (15). After evaporation of the basic and colorless fractions (0.16 g.), the product was distilled. It showed only one peak on glc analysis: $[\alpha]_D$ = -47.33° (optical purity 48.9%, c 0.7733 methanol); ir (carbon tetrachloride) ν max: 2860 and 2780, 1490, 1450, 1430 cm^{-1} [Lit. (6) identical spectrum]; nmr (deuteriochloroform) τ: 2.8-3.2 (4H, m, aromatic); 6.5-8.6 (11H, m, alicyclic); MS, m/e: 173 (M^+), 172, 160, 145, 117, 103, 91, 77.

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