Amino Acid Studies. Part III *. Synthesis and Properties of some Isomerides of Albizziine

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In a previous paper of this series [1], syntheses were described of L- and DL-albizziine (2-amino-3-ureidopropionic acid), as well as of L-2-ureido-3-aminopropionic acid (L-*iso*albizziine). It is the purpose of the present communication to report on the preparation and physical data of the isomeric compounds: D-albizziine, D-*iso*albizziine and DL-*iso*albizziine.

D-Asparagine was transformed into N-(*p*-toluenesulphonyl)-D-asparagine (I, Ts = *p*-$CH_3C_6H_4SO_2$) by a modification of the procedure employed in the L-series by Zaoral and Rudinger [2]. Hofmann-degradation of the latter compound, conducted according to Rudinger *et al.*[3], afforded D-2-(*p*-toluenesulphonamido)-3-aminopropionic acid (II) which was further converted into D-2-(*p*-toluenesulphonamido)-3-ureidopropionic acid (III) and thence to D-albizziine (IV) as described for the enantiomeric series by the same authors [3].

Detosylation of (II) afforded optically pure D-2,3-diaminopropionic acid, (V), which was converted into D-*iso*albizziine, (VIII), through the steps (VI) and (VII), according to the procedure utilized in this laboratory for the preparation of L-*iso*albizziine [1]. A similar sequence of reactions, starting from DL-2,3-diaminopropionic acid, yielded racemic *iso*albizziine. Synthetic D-albizziine, (IV), and D-*iso*albizziine, (VIII), as well as all intermediate products, possessed specific rotations similar in magnitude but opposite in sign to those of the L-series. Likewise, the infra-red spectra determined in the solid state coincided for the individual enantiomers throughout the two series, whereas the corresponding racemic modifications showed considerable deviations in their IR-patterns.

Results of some microbiological studies of the synthetic amino acids will be presented elsewhere.

Experimental. N-(p-Toluenesulphonyl)-D-asparagine (I). Several trial runs indicated that the tosylation of asparagine proceeded more satisfactorily than formerly described [2], when the following conditions were employed. In the course of 3 h, a total of 9.5 g of *p*-toluenesulphonyl chloride was added portionwise to a vigorously stirred and ice-cooled suspension of D-asparagine * (5.0 g) and magnesium oxide (5.0 g) in water (100 ml). The suspension was stirred overnight at room temperature, cooled in ice, and then acidified with conc. hydrochloric acid. The precipitate was filtered off and thoroughly extracted with ether. Practically pure N-(*p*-toluenesulphonyl)-D-asparagine (I) remained in a yield of 91 % (8.6 g). The product was recrystallized from methanol (175 ml) to give 6.5 g of pure material, m.p. 182° **, $[\alpha]_D^{22}$ −10.7° (*c* 2, H_2O, containing 1 equiv. of NaOH, pH 6.6) ***.

(Found: C 46.20; H 5.03; N 9.63. Calc. for $C_{11}H_{14}N_2O_5S$: C 46.14; H 4.93; N 9.79.) Reported for the enanti-omeric L-compound: m. p. 175°[4], 191°[2]; $[\alpha]_D^{20}$ +6.8° (K-salt in H_2O)[4]; $[\alpha]_D^{20}$ +9.7° ± 0.5° (*c* 5.4, H_2O + 1 equiv.KOH).

D-2-(p-Toluenesulphonamido)-3-aminopropionic acid (II). The Hofmann-degradation of N-tosyl-D-asparagine was performed essentially as described for the L-enantiomer [3], yet in somewhat smaller yields (*ca.* 50 %) than reported [3] (60 %). A pure specimen of D-2-(*p*-toluenesulphonamido)-3-aminopropionic acid hemihydrate (*cf.* Ref.[3]) was obtained on repeated recrystallizations from water, m. p. 200°, $[\alpha]_D^{22}$ −19.6° (*c* 2.5, 5 N HCl). (Found: C 44.85; H 5.60; N 10.38. Calc. for $C_{10}H_{14}N_2O_4S$, 0.5 H_2O: C 44.93; H 5.66;

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** All melting points are uncorrected and determined in capillary tubes in an Anschütz-Hershberg apparatus, with a rate of heating of about 1° per minute near the melting points. For most compounds in the present series these are decomposition temperatures, highly dependent on the rate of heating, as has been pointed out also by other authors [2,3].

*** This rotation is quite dependent on pH-values. Thus, for the L-isomeride we found the following $[\alpha]_D^{25}$- values at *c* = 1.7; + 9.3° to + 9.8° at pH 5.3 to 9.3, + 5.5° at pH 10.3, and −3.2° at pH 11.2.

N 10.48.) A specimen of the corresponding L-isomeride, prepared in this laboratory by exactly the same procedure, had m. p. 200° and $[\alpha]_D^{22}$ +19.9° (*c* 2.5, 5 N HCl). Reported for the L-compound [3]: m. p. 225–226° (capillary, corr.) and 214–216° (decomp. Kofler-block) *, $[\alpha]_D^{22}$ +16.5° ± 0.8° (*c* 2.4, 5 N HCl) (anhydrous specimen).

D-*2-(p-Toluenesulphonamido)-3-ureidopropionic acid* (III). This compound was prepared as described for the L-isomer [3], yet in slightly lower yield. An analytical specimen (from water) had m. p. 169–170°, and $[\alpha]_D^{22}$ −15.8° (*c* 1, 96 % EtOH). (Found: C 43.70; H 5.12; N 13.80. Calc. for $C_{11}H_{15}N_3O_5S$: C 43.84; H 5.02; N 13.95.) Reported value for the enantiomer: m. p. 174–179° (decomp. Kofler-block), (no rotation reported).

D-*Albizziine* (IV). Again, the procedure employed in the L-series for detosylation [3] was followed, except that 6 h in stead of 36 h was found sufficient for complete reaction. A specimen for analysis was obtained by three recrystallizations of the crude product from aqueous ethanol, m. p. 202–205°, the same as that of natural L-albizziine when determined in the same bath. $[\alpha]_D^{24}$ +65.5° (*c* 1.7, H_2O), (Found: C 32.55; H 6.17; N 28.72. Calc. for $C_4H_9N_3O_3$: C 32.65; H 6.17; N 28.56.)

D-*2,3-Diaminopropionic acid* (V). In order to remove the tosyl-grouping from 2-N-tosyl-D-diaminopropionic acid (II), the latter (3.75 g) was heated at 70° for 6 h in a 35 % solution of anhydrous hydrogen bromide in glacial acetic acid (70 ml) containing phenol (4 g), conditions similar to those employed by Poduška *et al.*[5] in the detosylation of glycyl-peptides of diaminopropionic acid. Addition of anhydrous ether to the reaction mixture caused the hydrobromide of (V) (3.5 g) to separate as colourless crystals. The salt was purified by dissolving in water and addition of alcohol, to give a pure product (1.70 g), m. p. *ca.* 240°, $[\alpha]_D^{21}$ −17.3° (*c* 2, 1 N HCl). Reported rotation for D-2,3-diaminopropionic acid hydrochloride: $[\alpha]_D^{25}$ −25.2° (*c* 2, 1 N HCl) [6]. With due corrections for the different anions, this value suggested that partial racemization had occurred during the detosylation reaction, conceivably analogous to the recently demonstrated hydrogen bromide-induced racemization of L-diaminopropionic acid in aqueous solution [1]. That this was not the case, however, was proved by transforming an optically pure sample of L-diaminopropionic acid hydrochloride, $[\alpha]_D^{24}$ +25.0° (*c* 4.7, 1 N HCl or 1 N HBr), by means of an ion exchange column, into the corresponding hydrobromide with the rotation $[\alpha]_D^{21}$ +17.4° (*c* 2, 1 N HCl or 1 N HBr), comparable to that of the antipode described above. Reconversion of the hydrobromide into the hydrochloride afforded material with unchanged rotation (+25.3°).

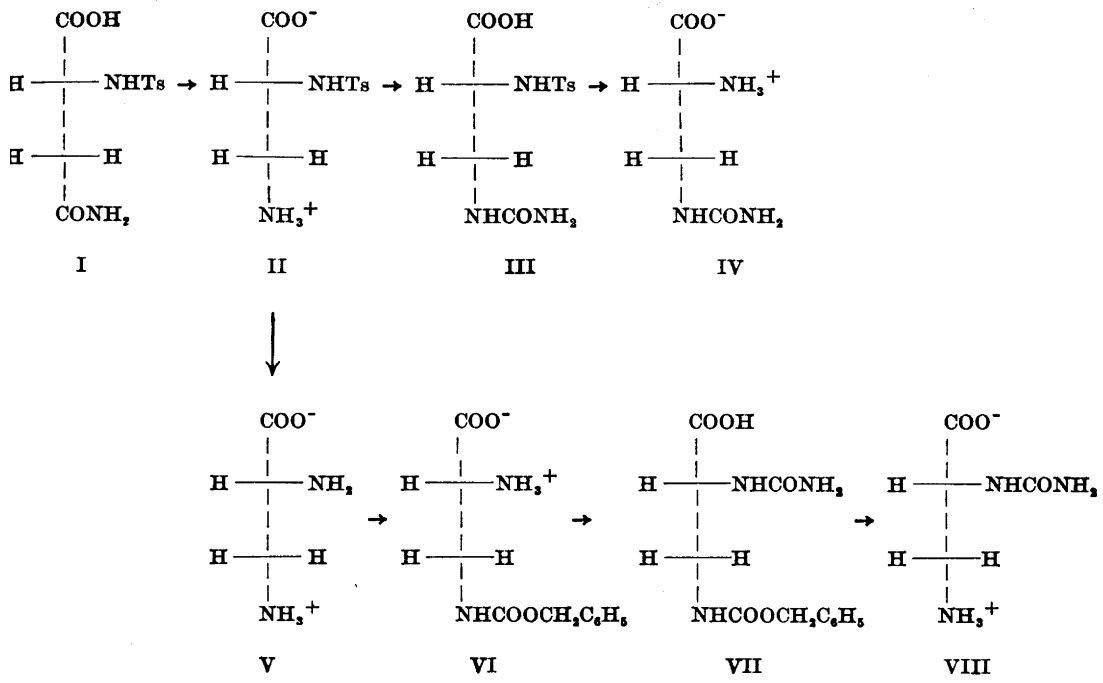
D-*2-Amino-3-benzyloxycarbamidopropionic acid* (VI). D-2,3-Diaminopropionic acid hydrobromide was subjected to carbobenzoxylation in 84 % yield (crude product) as described for the L-acid [1], with the sole modification that four times as much water was used in order to bring the less soluble hydrobromide into solution. A specimen for analysis was produced by two recrystallizations from hot water, m. p. 225°, $[\alpha]_D^{24}$ +15.9° (*c* 1, 1 N HCl). (Found: C 55.65; H 6.00; N 11.82. Calc. for $C_{11}H_{12}N_2O_4$: C 55.45; H 5.92; N 11.76). Reported for the L-enantiomer [1]: m. p. 227–229°, $[\alpha]_D^{21}$ −18.7° (*c* 1, 1 N HCl).

D-*2-Ureido-3-benzyloxycarbamidopropionic acid* (VII). This compound was synthesized according to the directions previously given for the L-isomer [1]. An analytical specimen separated from water in colourless needles, m. p. 190–191°, $[\alpha]_D^{22}$ −4.7° (*c* 1, dimethylformamide). (Found: C 51.10; H 5.34; N 14.79. Calc. for $C_{12}H_{15}N_3O_5$: C 51.24; H 5.38; N 14.94). The formerly described L-isomeride [1], m. p. 188–190°, had the rotation $[\alpha]_D^{22}$ +5.2° (*c* 1, dimethylformamide).

D-*Isoalbizziin* (VIII). Hydrogenolysis of (VII), performed as described in the L-series [1], yielded D-*iso*albizziin, m. p. 204°, $[\alpha]_D^{22}$ +44.6° (*c* 1, 0.1 N HCl). (Found: C 32.30; H 6.09; N 28.48. Calc. for $C_4H_9N_3O_3$: C 32.65; H 6.17; N 28.56.) Reported values for the L-isomeride[1]: m. p. 204–210°, $[\alpha]_D^{25}$ −43° (*c* 1, 1 N HCl.)

DL-*2,3-Diaminopropionic acid.* This racemic amino acid was conveniently synthesized by the method of Hellmann and Haas [7] with a few modifications. Thus, *diethyl benzamidomethyl-acetamidomalonate*, synthesized from

* For a specimen of this hemihydrate, kindly furnished by Dr. Rudinger, we found the m. p. 200°, when determined in the same bath as our D-isomer. The two compounds furthermore had identical IR-spectra.



N,N-dimethylaminomethylbenzamide[7] and ethyl acetamidomalonate[8], (m. p. 149—150°, from toluene). (Found: C 57.85; H 6.13; N 7.84. Calc. for $C_{17}H_{22}N_2O_6$: C 58.27; H 6.33; N 8.00), was used in stead of the dimethyl ester formerly employed[7]. Furthermore, boiling xylene was found preferable to toluene as a solvent for the condensation reaction. Racemic diaminopropionic acid hydrobromide was obtained from the ester upon hydrolysis with hydrogen bromide (83 % yield), m. p. 240° (decomp.).

DL - *2 - Amino - 3 - benzyloxycarbamidopropionic acid.* Upon carbobenzoxylation under the same conditions as employed in the optically active series, DL-2,3-diaminopropionic acid afforded DL-2-amino-3-benzyloxycarbamidopropionic acid in 70 % yield. An analytical sample (from water) had the m. p. 241° (Found: C 55.20; H 5.87; N 11.86).

DL - *2 Ureido - 3 - benzyloxycarbamidopropionic acid.* Again, conversion of the above acid into the ureidoacid was performed as described in the L-series [1] to give a 70 % yield of crude reaction product, which was recrystallized twice from water before analysis, m. p. 186°. (Found: C 51.20; H 5.35; N 14.70).

DL-*Isoalbizziin.* Decarbobenzoxylation of the foregoing acid in the customary way [1] afforded racemic *iso*albizziin which was recrystallized twice from water before analysis, m. p. 201°; the racemate was considerably less soluble in water than the optically active forms. (Found: C 32.25; H 6.05; N 28.32).

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1. Kjær, A. and Olesen Larsen, P. *Acta Chem. Scand.* **13** (1959) 1565.
2. Zaoral, M. and Rudinger, J. *Collection Czechoslov. Chem. Communs.* **24** (1959) 1993.
3. Rudinger, J., Poduška, K. and Zaoral, M. *Collection Czechoslov. Chem. Communs.* **25** (1960) 2022.
4. Berlingozzi, S. *Gazz. chim. ital.* **57** (1927) 814.
5. Poduška, K., Rudinger, J. and Šorm, F. *Collection Czechoslov. Chem. Communs.* **20** (1955) 1174.
6. Birnbaum, S. M., Koegel, R. J., Fu, S-C. J. and Greenstein, J. P. *J. Biol. Chem.* **198** (1952) 335.
7. Hellmann, H. and Haas, G. *Chem. Ber.* **90** (1957) 1357.
8. Shaw, K. N. F. and Nolan, C. *J. Org. Chem.* **22** (1957) 1668.

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