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A Novel Synthesis of L-Pipecolic Acid

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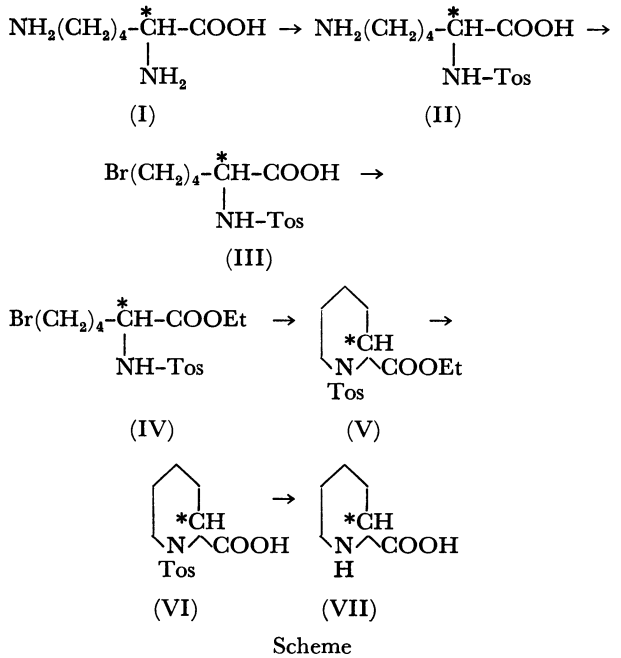
Synopsis. A novel synthesis of L-pipecolic acid from L-lysine is described. Bromination of ε-NH_2 group on N^{α}-tosyl-L-lysine, followed by cyclization with NaH in DMF gave *N*-tosyl-L-pipecolic acid in 45% yield.

Pipecolic acid, a non-proteinogenic amino acid, was first prepared in DL form by Ladenburg in 1891,[1] then it was resolved into optically active components by Mende.[2] Later, Morrison[3] isolated the amino acid having levo rotation from *trifolium repens* (white clover). Since then, the widespread occurrence of L-pipecolic acid in plant kingdom has attracted an interest in the metabolism of the amino acid, and several possible biosynthetic routes have also been suggested.[4] Although the full role of pipecolic acid in metabolism still remains obscure, several experiments reported so far give support that lysine may be a precursor in the biosynthesis of pipecolic acid.[5-8]

Up to date, L-pipecolic acid has been usually synthesized by reduction of 2-picolinic acid,[9] followed by resolution of the racemate. Attempts to obtain the L-form by the conversion of naturally occuring six-membered ring compounds were carried out *via* the oxidation of L-conhydrine[10] or *via* the reduction of L-baikiain.[11] The preparation of D-pipecolic acid from L-lysine by the use of Walden inversion has also been reported,[12] however, a synthetic route of L-pipecolic acid from L-lysine has not been established as yet.

In a series of our studies[13] on the conversion of L-amino acid to the optically active one, we have found a new synthesis of L-pipecolic acid from L-lysine, as shown in the scheme.



Scheme

Ring closure was performed *via* dehydrobromination by the abstraction of the NH proton at the α-position of L-lysine. Since this new route does not involve any substitution reaction on the asymmetric carbon of the starting material, full optical activity may be retained throughout the reaction.

Diazotization of N^{α}-tosyl-L-lysine (II) was investigated under several conditions: reaction temperature (0—80 °C) and the concentration of bromine ion (5—20 equivalents). Bromination of II took place with difficulty as compared with that of N^{α}-tosyl-diaminopropionic acid.[13a] It seems that the rate of substitution of the amino group with bromine at the ω-position would be decreased in proportion to the length of the alkyl chain. III was obtained as an oil, however, the esterification gave crystalline product (IV): the over-all yield of IV from II was about 45% after recrystallization.

Cyclization of IV with sodium hydride in DMF quantitatively proceeded as expected. It is noted that the ester moiety was unaffected during the cyclization reaction (IV→V) under the same condition reported previously on the synthesis of *N*-tosyl-L-azetidine-2-carboxylic acid;[13b] in that case the ester was completely saponified to the corresponding acid.

The detosylation was carried out successfully either by the treatment of V with 47% hydrobromic acid in acetic acid or by the reduction of VI with metallic sodium (4—5 equivalents) in liquid ammonia.

L-Pipecolic acid thus obtained was proved to be identical with an authentic specimen by the physical and the spectral data.

Experimental

The melting points are uncorrected. IR spectra were recorded on Shimadzu IR-27G. NMR spectra were taken at 60 MHz with tetramethylsilane as the internal standard using Hitachi R-20A.

$^{\varepsilon}$Bromo-N$^{\alpha}$-tosylamide-L-caproic acid (III). N^{α}-Tosyl-L-lysine* (60.0 g) and potasium bromide (60.0 g) were dissolved in 16% hydrobromic acid (500 ml). To the solution was added dropwise a solution of sodium nitrite (42.0 g) in water (100 ml) at 50—55 °C with vigorous stirring for 1 hr. Then, the reaction mixture was stirred for additional 1 hr at the same temperature, and the resulting oil was extracted with ether (200 ml × 3). The ether solution was washed with saturated sodium chloride solution and dried over magnesium sulfate. The dried solution was concentrated *in vacuo* to obtain an oily residue (III, 77.4 g), which was used to the following reaction without further purification.

Ethyl $^{\varepsilon}$Bromo-N$^{\alpha}$-tosylamido-L-caproate (IV). A solution

* This was prepared from L-lysine by Barrass and Elmore; mp 272—273 °C (dec.), $[\alpha]_D^{20}$ +13.9 °C (*c* 1, AcOH). [lit.[14] mp 263—264 °C (dec.)]

of III (77.4 g) in absolute ethanol (300 ml) was treated with hydrogen chloride under bubbling at 60—70 °C for 1 hr. After standing overnight at room temperature, the reaction mixture was concentrated, and the resulting oil was dissolved in ether (600 ml). The ether solution was washed with aqueous solution of 5% sodium carbonate and of saturated sodium chloride, successively. The solution was dried over magnesium sulfate and was evaporated *in vacuo*. The residual oil was crystallized from ether-petroleum ether to afford IV, which was positive to Beilstein test, 35.3 g (45% from II), mp 65—66 °C, $[\alpha]_D^{20}$ −2.3° (*c* 1, EtOH). IR (Nujol) ν_{NH}: 3280, $\nu_{C=O}$ 1740, ν_{SO_2} 1375, 1160 cm^{-1}; NMR (CCl_4, δ): 7.75—7.15 (4H, arom), 5.58—5.44 (1H, NH), 4.1—3.64 (3H, CH–CH_2), 3.39—3.18 (2H, CH_2–Br), 2.41 (3H, CH_3– ).

Found: C, 46.34; H, 5.69; N, 3.49%. Calcd for $C_{15}H_{22}NO_4SBr$: C, 45.91; H, 5.65; N, 3.57%.

Ethyl N-*tosyl*-L-*pipecolinate (V).* To a solution of IV (13.7 g) in DMF (250 ml) was added sodium hydride (1.84 g, 50% oil dispersion) at 10—15 °C, and the reaction mixture was stirred at the same temperature for 45 min. The reaction mixture was neutralized with a few drops of AcOH, and the insoluble materials were filtered. The filtrate was evaporated *in vacuo* below 40 °C, then the residue was extracted with ether and water. The ether solution was washed well with water and dried over magnesium sulfate. The dried solution was evaporated *in vacuo* to afford an oily residue (V, 11.5 g), which was negative to Beilstein test. IR (Film): $\nu_{C=O}$ 1740, ν_{SO_2} 1350, 1155 cm^{-1}.

N-*Tosyl*-L-*pipecolic Acid Dicyclohexylamine Salt (VI·DCHA).* To a solution of V (11.5 g) in methanol (100 ml) was added dropwise 2M sodium hydroxide solution (70 ml) at 15—17 °C under stirring. After 4 hr, the reaction mixture was neutralized and methanol was evaporated *in vacuo*. The residue was dissolved in sodium carbonate solution (100 ml) and the solution was washed with ether. Aqueous phase was acidified with 6M hydrochloric acid, and the resulted oil was extracted with ether. The ether solution was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The dried solution was evaporated *in vacuo* to afford VI, 9.8 g. To a solution of the oily compound VI in ethyl acetate (70 ml), dicyclohexylamine (6.3 g) was added to obtain VI·DCHA salt, 13.3 g (82%), mp 166—168 °C, $[\alpha]_D^{20}$ −20.3° (*c* 1, MeOH), IR (Nujol): $\nu_{NH_2^+}$ 2300—2700, $\nu_{C=O}$ 1625, 1560, ν_{SO_2} 1375, 1155 cm^{-1}; NMR (DMSO-d_6, δ): 7.8—7.2 (4H, arom), 6.4—5.6 (2H, NH_2^+) 4.1—4.4 (1H, α-CH), 3.6—0.6 (30H, complex, other protons). Found: C, 64.26; H, 8.68; N, 5.97; S, 6.90%. Calcd for $C_{25}H_{40}N_2O_4S$: C, 64.63; H, 8.68; N, 6.03; S, 6.88%.

L-*Pipecolic Acid (VII).* A suspension of VI·DCHA (11.13 g) in 0.5 M sulfuric acid was vigorously shaken with ethyl acetate and the extract was concentrated *in vacuo*. The residue was detosylated with metallic sodium (2.2 g) in liquid ammonia (200 ml). After evaporation of excess ammonia, the residue was dissolved in 0.5M sulfuric acid solution, and the solution was washed with ether. The aqueous phase was treated with ion-exchange resin, Dowex 50 (H^+ form). The resin was eluted with 5% ammonium hydroxide solution, and the eluate was evaporated *in vacuo* to afford VII. Crude VII was recrystallized from methanol-ether, 2.33 g (76%), mp 259—260 °C, $[\alpha]_D^{20}$ −30.6° (*c* 1, water) [lit,[3] mp 271 °C (dec.), $[\alpha]_D^{18}$ −25.4° (*c* 5, water)]. IR (Nujol): $\nu_{NH_2^+}$ 2380—2500, $\nu_{C=O}$ 1615 cm^{-1}. Found: C, 55.30; H, 8.50; N, 11.02%. Calcd for $C_6H_{11}NO_2$: C, 55.77; H, 8.38; N, 10.84%.

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