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A Facile Synthesis of 6-Chloro-D-tryptophan

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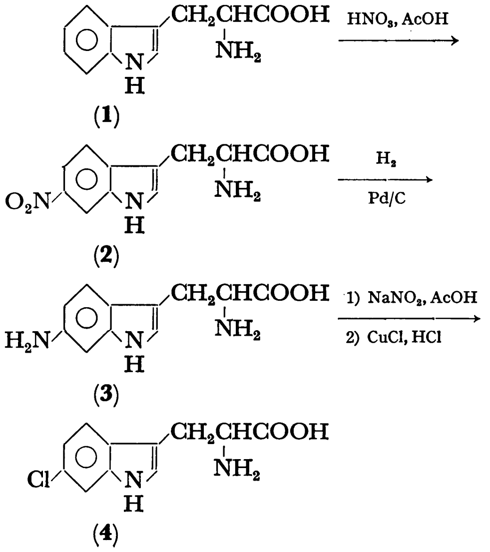
Synopsis. A nonnutritive sweetener, 6-chloro-D-tryptophan (**4**), was synthesized from D-tryptophan (**1**) by nitration, hydrogenation and diazotization, followed by a reaction with cuprous chloride. The optical rotation of **4** agreed with that of an authentic sample which had been prepared by the resolution of racemic **4** methanesulfonate.

6-Chloro-D-tryptophan (**4**) is known as a nonnutritive sweetener with a good sucroselike taste.[1] The use of racemic **4** as a sweetening agent is undesirable because the L-isomer has a somewhat bitter taste. In respect of the synthetic method, it has been reported only that racemic **4** had been prepared from 6-chloroindole *via* its gramine derivative.[2] Now we wish to report that the D-isomer of **4** was successfully synthesized through three steps starting from D-tryptophan (**1**), which can readily be obtained on an industrial scale.

The nitration of **1** was carried out by a slight modification of Fazi's method.[3] A suspension of **1** in acetic acid was treated with fuming nitric acid, without any isolation of the nitrate of **1**, to give the nitrate of 6-nitro-D-tryptophan (**2**) (yellow needles, 59.7%), which was then converted to the free amino acid (**2**) [yellow needles, $[\alpha]^{25}_{\mathrm{D}}$ +12.5° (c=0.2, 20% EtOH), 78.9%] by the addition of sodium carbonate.

The hydrogenation of **2** over palladium-carbon in aqueous hydrochloric acid furnished the amino derivative (**3**)[4] [colorless needles, $[\alpha]^{25}_{\mathrm{D}}$ −13.1° (c=1, 1M HCl), 91.2%].

At the final step of the synthesis, the Sandmeyer reaction for **3** was examined. It was reported that the reactions of nitrous acid with tryptophan and its derivatives led to the deamination of the N^{α}-amino group[5] and to the formation of N^1-nitrosamine derivatives.[6] In this study, the 6-amino group of **3** was selectively diazotized in acetic acid, though the reaction using hydrochloric acid gave complicated products. The resulting diazotized compound was treated with cuprous chloride to give 6-chloro-D-tryptophan (**4**) [colorless prisms, $[\alpha]^{25}_{\mathrm{D}}$ −11.3° (c=1, 1M HCl), 50.8%]. Both the spectral data and the optical rotation of **4** were in agreement with those of an authentic sample which had been obtained by the resolution of racemic **4** methanesulfonate by means of a preferential crystallization procedure in our laboratory.[7]



The new method promises to be both economical and convenient for the preparation of 6-chloro-D-tryptophan and would also serve for the synthesis of a variety of 6-substituted derivatives of optically active tryptophans.

Experimental

All the melting points are uncorrected. The IR spectra were obtained on a Shimadzu IR-27G spectrophotometer. The NMR spectra were recorded on a Hitachi R-20A instrument, using TMS as the internal standard. The observed rotations were measured with a Perkin-Elmer Model 141 polarimeter.

6-Nitro-D-tryptophan (2). To a suspension of D-tryptophan (40.8 g, 0.2 mol) and urea (0.5 g) in glacial acetic acid (500 ml) was added a solution of fuming nitric acid (d 1.50, 7.5 ml) in glacial acetic acid (30 ml). The resulting yellow clean solution was stirred at 0 °C until it changed to a suspension. Then, to the suspension was slowly added, drop by drop at 15 °C, additional fuming nitric acid (d 1.50, 17.5 ml) in glacial acetic acid (70 ml). After stirring for 18 hr at 20—25 °C, the resulting yellow precipitate was collected by filtration to yield **2**·HNO_3·1/2H_2O (28.33 g, 44.1%). The filtrate was then diluted with 300 ml of water ,and the solution was concentrated to 300 ml *in vacuo*. On standing in a refrigerator overnight a further crop of **2**·HNO_3·1/2H_2O (10.01 g, 15.6%) was deposited from the remainder. The recrystallization of the crude **2**·HNO_3·1/2H_2O from diluted nitric acid gave hygroscopic yellow needles; mp 192—194 °C (decomp). IR (KBr); 1750, 1500, and 1330 cm^{-1}.

Found: C, 41.01; H, 4.40; N, 17.19%. Calcd for $C_{11}H_{11}N_3O_4\cdot HNO_3\cdot 1/2H_2O$: C, 41.13; H, 4.08; N, 17.44%.

The crude **2**·HNO_3·1/2H_2O (25.0 g) in hot water (200 ml) was converted to the free amino acid (**2**·H_2O, 16.4 g, 78.9%) by the addition of sodium carbonate (4.2 g). Yellow needles (from ethanol), mp 250—252 °C (decomp). $[\alpha]^{25}_{\mathrm{D}}$ +12.5 ° (c=0.2, 20% EtOH). IR (KBr); 3200, 1620, 1495, and 1330 cm^{-1}. NMR (D_2O–NaOH); δ 1.5—3.2 (2H, m), 3.3—3.6 (1H, m), 7.10 (1H, d, J=8.7 Hz), 7.23 (1H, s), 7.28 (1H, dd, J=2.2, 8.7 Hz) and 7.54 ppm (1H, d, J=2.2 Hz).

Found: C, 49.50; H, 4.50; N, 16.18%. Calcd for $C_{11}H_{11}N_3O_4\cdot H_2O$: C, 49.44; H, 4.90; N, 15.72%.

Hydrochloride: Yellow needles (from dil. HCl); mp 243 °C (decomp). IR (KBr); 3520, 3280, 3000, 1730, 1490, and 1340 cm^{-1}.

6-Amino-D-tryptophan (3). A mixture of **2**·H_2O (12.46

g, 0.047 mol) in 2.2% hydrochloric acid (320 ml) and methanol (200 ml) containing 10% palladium-carbon (1.0 g) was shaken at 25 °C under an atmospheric pressure of hydrogen until the absorption of hydrogen ceased. After 3.4 l (3.2 molar equivalents) of hydrogen had been absorbed (3.5 hr), the catalyst was removed and the filtrate was concentrated to dryness *in vacuo*. The residue was dissolved in water (30 ml), and the pH of the solution was adjusted to 6.0 with a saturated aqueous sodium bicarbonate to separate **3**·H_2O as colorless needles (10.06 g, 91.2%); mp 252 °C (decomp). (from ethanol). $[\alpha]_D^{25}$ -13.1 ° ($c=1$, 1 M HCl), IR (KBr); 3580, 3290, 3150, 1590, 1400, 1345, and 802 cm^{-1}. NMR (DMSO-d_6); δ 2.7—3.3 (2H, m), 3.3—3.7 (1H, m), 6.34 (1H, dd, $J=8.3$, 1.5 Hz), 6.50 (1H, d, $J=1.5$ Hz), 6.86 (1H, s), 7.19 (1H, d, $J=8.3$ Hz) and 10.3 ppm (1H, broad).

Found: C, 55.82; H, 6.33; N, 17.59%. Calcd for $C_{11}H_{13}N_3O_2 \cdot H_2O$: C, 55.68; H, 6.37; N, 17.71%.

6-Chloro-D-tryptophan (4). To a solution of **3**·H_2O (4.75 g, 0.02 mol) in acetic acid (80%, 120 ml) was added an aqueous solution (20 ml) of sodium nitrite (1.38 g, 0.02 mol) drop by drop at 0 °C with stirring. The resulting solution was stirred for 20 min longer and then added to a solution of cuprous chloride [prepared from cupric sulfate pentahydrate (7.46 g, 0.03 mol)] in 15% hydrochloric acid (110 ml) at 0 °C over a 10-min period. After stirring at room temperature for 15 hr and then at 80 °C for an hour, the reaction mixture was concentrated to dryness *in vacuo*. The residue, in 400 ml of water, was treated with hydrogen sulfide, and then the cupric sulfide was removed by filtration. The filtrate was concentrated to separate colorless prisms of crude **4**·HCl. A solution of **4**·HCl in water (30 ml) was treated with active charcoal and neutralized (pH 6.0) with 10% sodium hydroxide. The precipitate was collected and recrystallized from aqueous alcohol to afford **4** as colorless prisms (2.42 g, 50.8%); mp 264—265 °C (decomp). $[\alpha]_D^{25}$ -11.3 ° ($c=1$, 1 M HCl). IR (KBr); 3400, 3080, 1665, 1585, 810, and 530 cm^{-1}. NMR (D_2O-NaOH); δ 2.8—3.4 (2H, m), 3.5—3.7 (1H, m), 7.06 (1H, dd, $J=8.3$, 2.0 Hz), 7.40 (1H, d, $J=2.0$ Hz) and 7.61 ppm (1H, d, $J=8.3$ Hz).

Found: C, 55.49; H, 4.54; N, 11.90; Cl, 14.74%. Calcd for $C_{11}H_{11}N_2O_2Cl$: C, 55.35; H, 4.65; N, 11.74; Cl, 14.86%.

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