Communications to the Editor

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SYNTHESIS OF L-TRYPTOPHAN FROM L-GLUTAMIC ACID[1)]

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L-Tryptophan was synthesized from L-glutamic acid via L-glutamic-γ-semialdehyde derivatives with almost no racemization.

KEYWORDS ——— L-tryptophan; L-glutamic acid; L-glutamic-γ-semialdehyde derivative; chiral synthesis; Fischer indole synthesis

In medical and nutritional studies much attention has been focused on L-tryptophan 1. Although many synthetic studies toward 1 have been recorded, optically pure 1 is actually being prepared by the optical resolution of DL-material with mold acylase.[2)] But this method requires a troublesome procedure to racemize the undesired optical antipode for recycling.

To overcome this difficulty we initiated studies to synthesize optically pure 1 starting from L-glutamic acid 2, one of the most inexpensive of many optically pure compounds that are commercially available in quantity. Early studies by Komachiya showed, however, that the conversion of 2 into 1 was unsuccessful due to the complete racemization during his reaction procedure.[3)]

Now we would like to report two successful methods for the synthesis of optically pure 1, which involve the preparation of optically pure L-glutamic-γ-semialdehyde derivatives from which 1 is obtainable by Fischer indole synthesis.

The first method is shown in Chart 1. Dehydration of the amide 3,[4)] prepared from 2, with p-TsCl in pyridine afforded the nitrile 4 of mp 78.5-81.5°C, $[\alpha]_D^{20}$ -27.6° (MeOH) in 61% yield. The nitrile 4 was catalytically hydrogenated in the presence of Raney-Ni deactivated with 3% Pb in aqueous acetic acid to give an oily product in 88% yield [TLC; Rf 0.45(silica gel, benzene:ethanol=4:1), IR; ν(max,neat) 3400,1740,1625, NMR; δ(DMSO-d_6) 5.93(1H,d,J=6Hz), 5.47(1H,m), 4.32(1H,d,J=9Hz), 3.60(3H, s), 2.10(3H,s), 1.52-2.42(4H,m)]. Since NMR analysis of this oil shows the absence of an aldehyde proton as well as the presence of a hydroxy proton (δ:5.93,1H,d) and a methin proton (δ:5.47,1H,m), the cyclic structure of 5a or 5b was suggested.

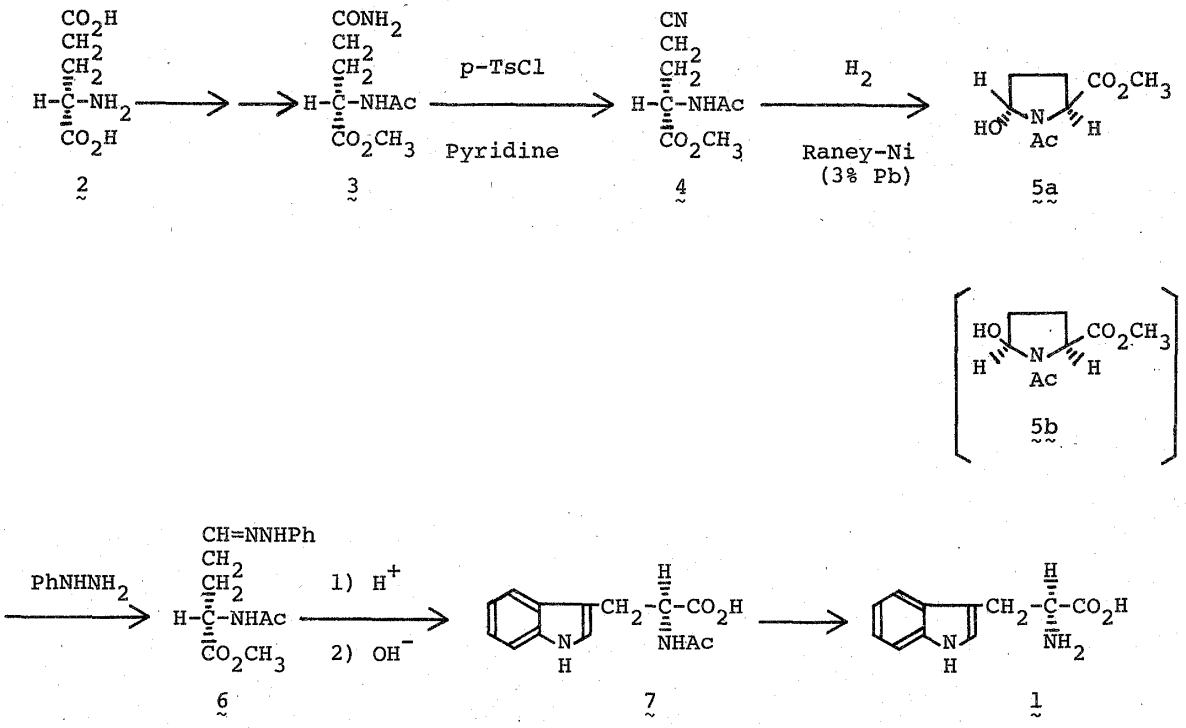

Chart 1

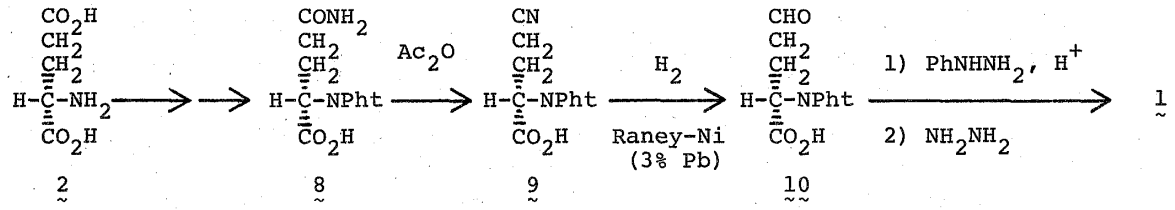

Chart 2

The analytical sample was obtained by silica gel chromatography as colorless plates of mp 99.0-102.0°C, $[\alpha]_D^{20}$ -128.5°(H_2O). X-ray crystallographic analysis of the crystal confirmed the cyclic structure of 5a as trans of the hydroxy group for the carbomethoxy group.[5] The compound 5a was treated with phenylhydrazine to give 6 of mp 105.5-108.0°C, $[\alpha]_D^{20}$ +39.2°($CHCl_3$). Phenylhydrazone 6 was heated to reflux in 0.1 N HCl for 1 h followed by hydrolysis with 1 N NaOH giving optically pure N-acetyl-L-tryptophan 7 of mp 174.0-179.0°C, $[\alpha]_D^{20}$ +24.5°(95%EtOH) in 37% overall yield. The spectral data and optical rotation were completely identical with those of authentic sample.

Improvement of the synthetic scheme for industrial preparation was also carried out by shortening the reaction steps (Chart 2). The amide 8 was easier to prepare than 3,[6] and this material made it possible to minimize the reaction steps. The amide 8 was converted to 1 similar to the above sequence.

Dehydration of 8 with Ac_2O gave the nitrile 9 of mp 115.0-126.0°C, $[\alpha]_D^{20}$ -61.5° (MeOH) in 67% yield.[7] Catalytic hydrogenation of 9 yielded 10 of mp 129.0-132.0°C, $[\alpha]_D^{20}$ -32.0°(MeOH). Then Fischer indole synthesis followed by treatment with hydrazine afforded optically pure 1 of $[\alpha]_D^{20}$ -30.7°(H_2O) in 26% overall yield. The optical rotation of the synthetic 1 is identical with that of the authentic sample.

We avoided the racemization by using mild conditions that didn't enolize the α-carbon of amino acid derivatives. Successful demonstration described above holds promise for the industrial preparation of 1 starting from 2. Further efforts are being continued in our laboratory.

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REFERENCES AND NOTES

1) Satisfactory analytical data (IR, ^1H NMR, and elementary analysis) have been obtained for all compounds for which the melting points and $[\alpha]_D$ values have been given.
2) I. Chibata, T. Ishikawa and S. Yamada, Bull. Agr. Chem. Soc. Japan, 21, 304 (1957).
3) Y. Komachiya, Nippon Nogei Kagaku Kaishi, 35, 845 (1961).
4) The amide 3 was prepared by the esterification of N-acetyl-L-glutamine which was obtained from 2 according to the literature; I. J. Maschler and N. Lichtenstein, Biochem. Biophys. Acta, 57, 252 (1962).
5) Details will soon be reported elsewhere.
6) a) F. E. King and D. A. A. Kidd, J. Chem. Soc., 3315 (1949); b) H. A. Dewald and A. M. Moore, J. Am. Chem. Soc., 80, 3947 (1958).
7) The complete racemization resulted from using p-TsCl in pyridine at this stage; so we used an acidic dehydrating reagent, such as Ac_2O.

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