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CHEMICAL SIMULATION OF TROPIC ACID BIOSYNTHESIS. STEREOSELECTIVE CHEMICAL CONVERSION OF OPTICALLY ACTIVE PHENYLALANINE TO (R)- AND (S)-TROPIC ACID

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(R)- and (S)-tropic acid were prepared by trifluoroacetolysis of O-nitrobenzenesulfonate((S)-III) of optically active 3-phenyllactic acid ester((S)-II) in good yield and with high retention of optical purity according to the biosynthetic pathway starting from L-phenylalanine(L-I). Based on the above findings, natural (-)-littorine(VIII) and (-)-hyoscyamine(X) were synthesized from D-phenylalanine.

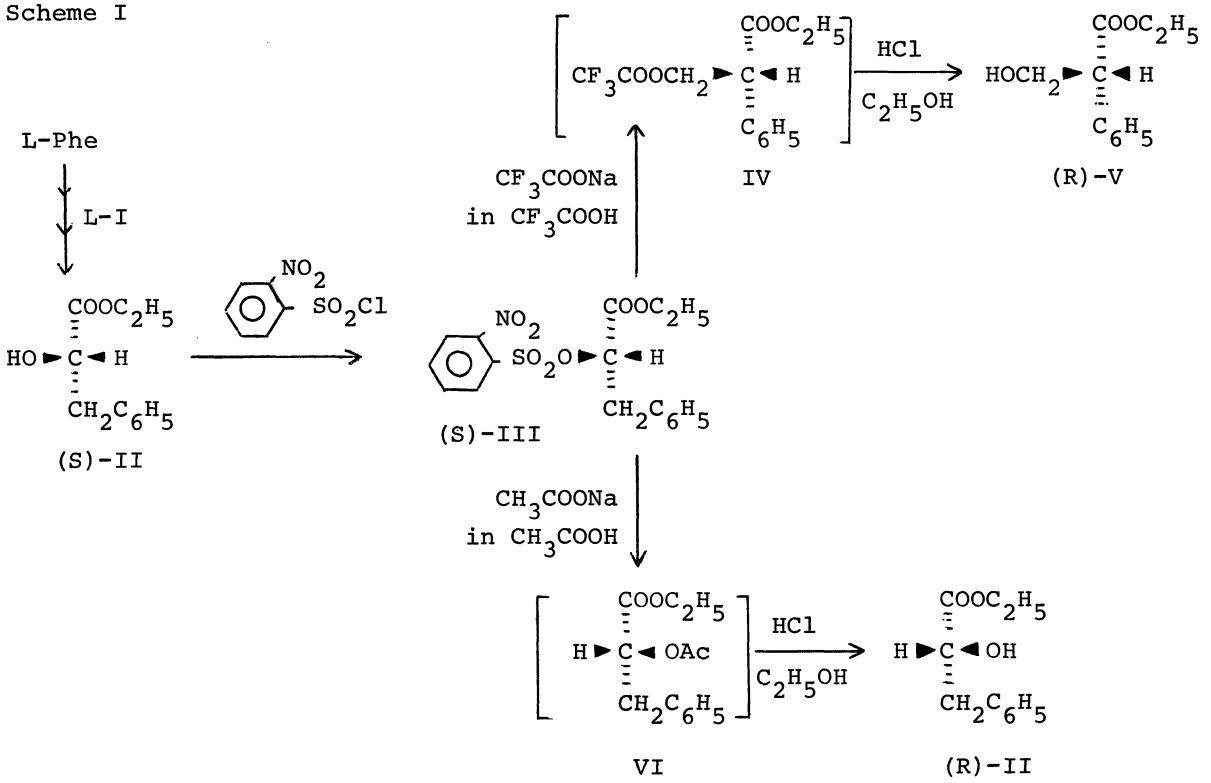
Phenylalanine has been reported[1] to be a precursor of tropic acid, the acid moiety of hyoscyamine and hyoscine, in plants.

In previous papers[2], the chemical conversion of L-phenylalanine and its ester to (R)- and (S)-tropic acid by nitrous acid deamination was reported. However, the chemical and optical yields of tropic acid were not satisfactory and various by-products were also obtained.

We have now accomplished a new synthetic route of optically active (R)-tropic acid in good yield by trifluoroacetolysis of O-nitrobenzenesulfonate((S)-III) of (S)-3-phenyllactic acid ester((S)-II) according to the biosynthetic route[3] as shown in Scheme I.

The sulfonate((S)-III)[4b] [oil, $[\alpha]_D^{25}$+17.9°(C=2.98, C_2H_5OH)] was easily prepared in good yield from (S)-3-phenyllactic acid ester((S)-II), which was obtained from L-phenylalanine(L-I) by nitrous acid deamination[5] followed by esterification. (S)-III was submitted to solvolysis in trifluoroacetic acid or

Scheme I



acetic acid.

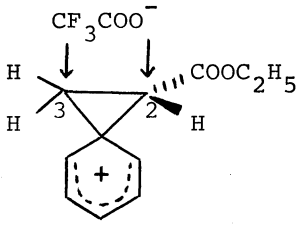
Trifluoroacetolysis of (S)-III (5 mmoles) in trifluoroacetic acid (30 ml) in the presence of sodium trifluoroacetate (25 mmoles) was carried out at 69°C for 36 hr. After removal of the trifluoroacetic acid, the residue was extracted with ethyl acetate, and the ethyl acetate was evaporated to give a mixture of trifluoroacetates. This mixture was treated with 15% HCl-C_2H_5OH (W/V%) under reflux for 3 hr to remove trifluoroacetyl group. Evaporation to dryness and purification of the residue by chromatography on silica gel with ether-n-hexane (1:1) as eluting solvent gave two compounds. The one obtained in 87% yield was the optically pure phenyl migration product, (R)-V[4] [b.p. 125°C (5 mmHg), $[\alpha]_D^{25}$+50.1° (C=3.25, C_2H_5OH)[6a)]], and the other obtained in 4% yield was the substitution product, (S)-II[4] [oil, $[\alpha]_D^{25}$-13.7°[6b)] (C=0.802, benzene)], corresponding to be 59% optically pure. Thus, the trifluoroacetolysis of (S)-III was found to give unnatural tropic acid, (R)-V, as a main product by complete inversion of

configuration accompanied by a small amount of (S)-II with considerable retention of configuration.

Acetolysis of (S)-III (3 mmoles) was also carried out at 100°C for 20 hr in acetic acid (15 ml) with sodium acetate (15 mmoles), and the alcoholysis of the crude products with HCl in C_2H_5OH gave almost optically pure (R)-II[4b] [b.p. 120°C (10 mmHg), $[\alpha]_D^{25}$+21.6°(C=4.208, benzene)[6b]] in 82% yield accompanied with (R)-V [oil, $[\alpha]_D^{25}$+49.4°(C=0.174, C_2H_5OH)[6a]] in 2% yield under similar work-up and purification as above. Thus, the acetolysis of (S)-III was found to give mainly the corresponding substitution product, (R)-II, with almost complete inversion of configuration, and a small amount of the phenyl migration product.

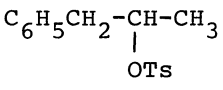
The result of the solvolysis of (S)-III in trifluoroacetic acid which has powerful ionizing ability and weak nucleophilicity, is conspicuously different from that in acetic acid. The special feature of the trifluoroacetolysis of (S)-III is the predominance of the phenyl migration to give primary alkyl trifluoroacetate(IV) from secondary sulfonate(III).

The formation of the phenyl migration product (R)-V with the inversion of configuration, and the substitution product (S)-II with the retention of configuration in this solvolysis shows that this reaction proceeds by way of phenonium ion VII. The attack of trifluoroacetate anion at C-3 of VII gives (R)-V and the similar attack at C-2 gives (S)-II.



VII

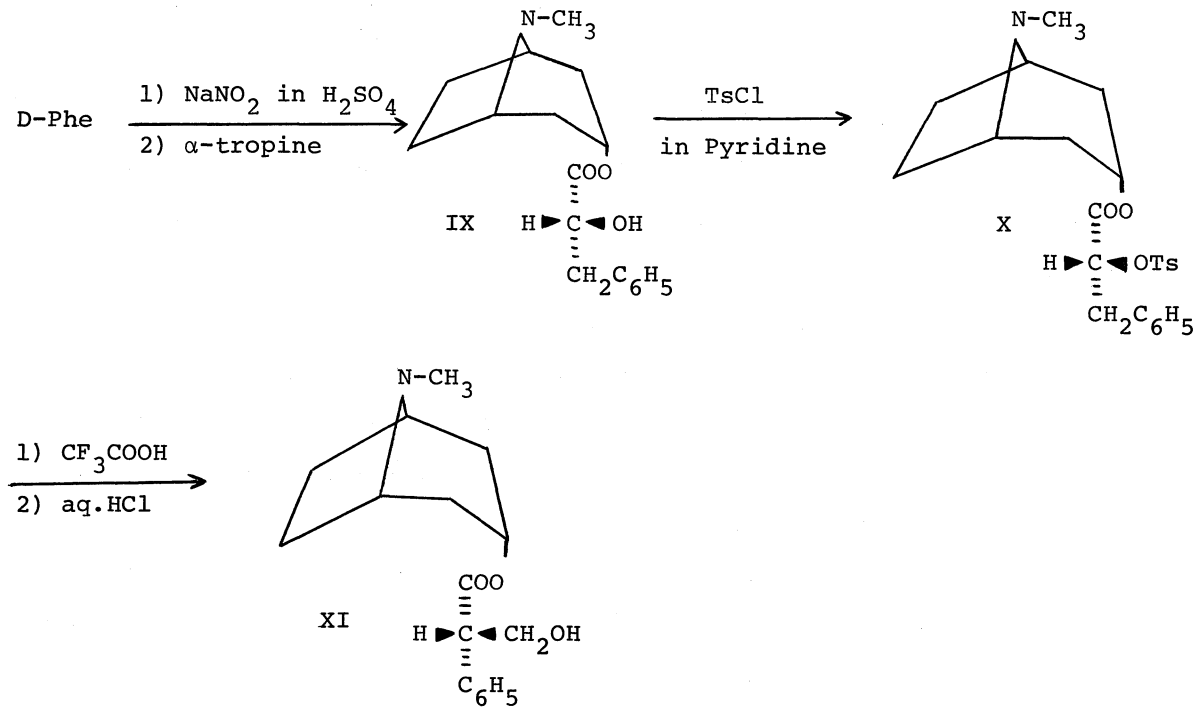
No phenyl migration was observed in the trifluoroacetolysis of 1-phenyl-2-propyl tosylate(VIII)[7,8]. It is thought that a carbonium cation on the secondary carbon atom attached to a carboxylic ester might be more unstable than that on the usual primary carbon atom due to the electron-withdrawing effect[9] of the ester group, resulting in the formation of the primary rather than the secondary alcohol derivative.



VIII

In acetolysis of (S)-III in the presence of sodium acetate in acetic acid which has strong nucleophilicity, formation of VII to give the phenyl migration product is scarcely found, and (R)-II is mainly produced by S_N2 type reaction with high stereoselectivity.

Scheme II



Based on the above findings, in order to synthesize natural (S)-tropic acid from optically active phenylalanine, 1) D-phenylalanine should be used as a starting material, or 2) (R)-II obtained from acetolysis of (S)-III should be again employed under the reaction sequence of II → V.

It is reported[3] that 3-phenyllactic acid is a precursor for tropic acid biosynthesis in plants, and phenylalanine is a precursor of 3-phenyllactic acid moiety of littorine(IX). The biosynthesis of tropic acid from phenylalanine is supposed to proceed via phenylalanine, 3-phenyllactic acid and tropic acid in this order. Moreover, (R)-littorine(IX) was recently isolated together with (S)-hyoscyamine(XI) from Anthocercis Littorea[10].

As an application of our findings, chemical simulation of biosynthesis of natural littorine and hyoscyamine from D-phenylalanine was undertaken as shown in Scheme II. Deamination of D-phenylalanine with sodium nitrite in 5% H_2SO_4 yielded (R)-(+)-3-phenyllactic acid, [m.p. 125-128°C, $[\alpha]_D^{25}$+32.9° (acetone)]. The reaction of (R)-(+)-3-phenyllactic acid with α-tropine according to the reported method[11] afforded natural (R)-(-)-littorine(IX) [m.p. 96-98°C, $[\alpha]_D^{20}$ -12.2° (C_2H_5OH)[4,10]] which was tosylated with tosyl chloride in pyridine to give

(X), [oil, $[\alpha]_D^{25}$+32.1°(C=2.486, C_2H_5OH)[4b)]] in 68% yield. The tosylate (X) was solvolyzed at 69°C for 210 hr in CF_3COOH buffered with CF_3COONa. Selective hydrolysis of the product with aqueous HCl at room temperature for 6 hr yielded crude reaction product, which was purified by chromatography on Al_2O_3 with chloroform as eluting solvent to give natural (S)-(-)-hyoscyamine(XI)[4)] [$[\alpha]_D^{20}$ -14.6°(C=1.592, C_2H_5OH)] (lit. -21.0°(C=1, C_2H_5OH))[12)] with 70% optical purity in 46% yield based on (X). This partial racemization might occur in work-up process because (-)-hyoscyamine is reported to racemize easily[13)]. Beside hyoscyamine, formation of apoatropine was recognized by nmr spectrum in 14% yield.

Further investigations are now in progress.

REFERENCES

1 M. L. Louden, and E. Leete, J. Am. Chem. Soc., 84, 4507(1962).

2 S. Yamada, T. Kitagawa, and K. Achiwa, Tetrahedron Lett. 3007(1967); K. Koga, Chin C. Wu, and S. Yamada, Tetrahedron Lett. 2283, 2287(1971); Idem, Chem. Pharm. Bull. (Tokyo), 20, 1272, 1282(1972).

3 W. C. Evans, J. G. Woolley and J. A. Woolley, The 4th International Symposium of Biochemistry and Physiology of Alkaloids 1969, p.227, Edited by K. Mothers, Akademic Verlag, Berlin 1972.

4 Satisfactory a) analytical and b) spectroscopic data were obtained for this substance.

5 S. G. Cohen and S. Y. Weinstein, J. Am. Chem. Soc., 86, 5326(1964).

6 a) $[\alpha]_D^{25}$+50.3°(C_2H_5OH) for optically pure (R)-V(Ref. 2) b) $[\alpha]_D^{23}$+ 23.2° (benzene) for optically pure (R)-II(Ref. 5).

7 a) J. E. Norlander and W. G. Deadman, J. Am. Chem. Soc., 90, 1590(1968); b) J. E. Norlander and W. J. Kelly, ibid, 91, 996(1969).

8 Trifluoroacetolysis of tosylate of (S)-II gives predominantly the similar phenyl migration product.

9 A. Streitwieser, Jr. "Solvolytic Displacement Reactions" McGraw Hill Book Company, Inc. 1962, p.119. The rate retarding effect of neighbouring carboxylic acid and ester in solvolysis is well discussed.

10 J. R. Cannon, K. R. Joshi, G. V. Meehan and J. R. Williams, Aust. J. Chem.,

22, 221(1969): (R)-(-)-littorine, m.p. 96-97°, $[\alpha]_D^{26}$-12.7°(C=4.42, C_2H_5OH).

11 H. A. D. Jowett and F. L. Pyman, J. Chem. Soc., 95, 1020(1919).

12 H. Beckurts, Apoth. Ztg. 27, 683(1912).

13 H. L. Holmes, "The Alkaloids. Chemistry and Biochemistry", Vol 1, ed. by R. H. F. Manske and H. L. Holmes, Academic Press, New York (1950), p.271.

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