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NON ENZYMIC TRANSFORMATION OF PHENYLALANINE TO TROPIC ACID

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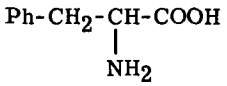
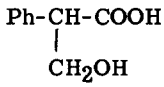
It has been previously shown that phenylalanine (I) is a precursor of tropic acid (II), the acid moiety of the ester alkaloids hyoscyamine and hyoscine by means of radioactive I fed to Datura stramonium plants (1).

We wish now to communicate the chemical transformation of I to II, especially optically active II in case of L-I.



I



II

The nitrous acid deamination of DL- or L-phenylalanine ethyl ester was found to give a racemic or optically active tropic acid skeleton accompanied with several other products by one-step reaction. The following is a typical procedure: To the solution of phenylalanine ethyl ester or its hydrochloride in acetic acid was added an equimolar amount of sodium nitrite for 5 hours at 18 - 20°, a mixture of reaction products was obtained by working up as usual. G.l.c. analysis of these products revealed seven peaks showing different retention times, that is; A, 7.3 minutes, B, 10.9 min., C, 12.0 min., D, 13,5 min., E, 19.8 min., F, 22.9 min., and G, 26.0 min. by using a 2.25 m. 5% PEGA column on Diasolid at 159°(column temperature) and 180° (sample heater temperature). To separate each reaction product, a mixture of these reaction products was chromatographed in benzene on silica gel to give pure E, F and G fractions respectively. Physical properties and elementary analyses of E, F and G are shown

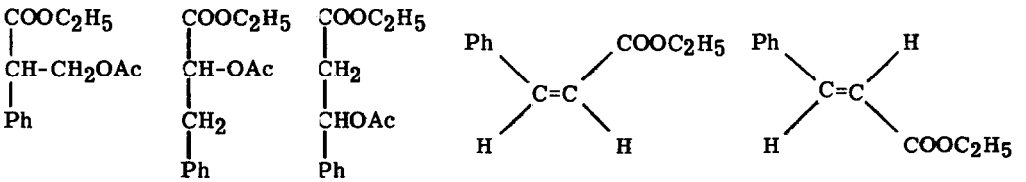
in Table I.

TABLE I

	b.p. °C	Specific Rotation	Calcd. % C	Calcd. % H	Found % C	Found % H
E	b.p.$_{2.5}$ 110-115°	$[\alpha]_D^{25}$ +1.72°(c=2.89, EtOH)	66.08	6.83	65.85	6.96
	(b.p.$_{7}$ 133-135°)				(66.38)	(6.80)
F	b.p.$_{6}$ 130-132°	$[\alpha]_D^{25}$ +18.6°(c=2.05, EtOH)	66.08	6.83	66.23	6.94
	(b.p.$_{4}$ 125-130°)				(66.31)	(7.20)
G	b.p.$_{4}$ 138-140°	$[\alpha]_D^{25}$ -3.63°(c=1.93, EtOH)	66.08	6.83	66.21	7.04
	(b.p.$_{35}$ 127°)				(66.13)	(6.92)

The figures in parentheses show the data on the racemic compounds.
*Each calculation is based on the molecular formula $C_{13}H_{16}O_4$.

Based on the above results (Table I, F) and nmr and IR spectra, the racemic compound F was supposed to be ethyl 3-acetoxy-2-phenylpropionate (III), and further, the structure of this compound was established by hydrolysis with 10% hydrobromic acid to the known racemic II (m.p. 113-115°). To determine the absolute configuration of (+)-III obtained from L-phenylalanine ethyl ester hydrochloride (m.p. 153°, $[\alpha]_D^{27}$ +35.1° (c=2.18 EtOH)), the transformation of S(-)-II(m.p. 126-128°, $[\alpha]_D^{16}$ -80.9°(c=1.4, H_2O)) of known configuration (2), which was obtained from hyoscine, to III was attempted. The esterification of (-)-II with ethanol and thionyl chloride followed by acetic anhydride in

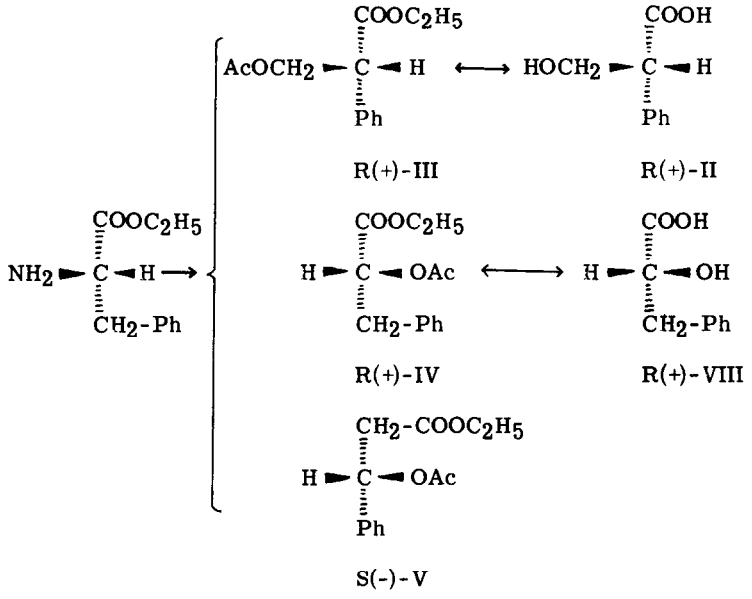


III IV V VI VII

pyridine gave (-)-III $[\alpha]_D^{25}$ -54.4°(c=2.28, EtOH) which was identified with (+)-III by means of coventional g.l.c. techniques, nmr and IR spectra and elementary analysis.

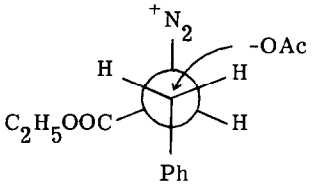
Thus, the absolute configuration of (+)-III has been proved to be R-series (R-III) and its optical purity was considered to be 34% based on the reported $[\alpha]_D$ value of L-phenylalanine ester and (-)-II. Therefore, it was found that the reaction from L-phenylalanine ester to R(+)-III was accompanied by some racemization.

Besides III, the IR and nmr spectra of racemic E fraction and its elementary analysis suggested the structure to be IV which is further confirmed by converting racemic IV to DL-2-hydroxy-3-phenylpropionic acid and by identification with an authentic sample. The structure of optically active (+)-IV (Table I, E) was also confirmed by the comparison with racemic compound and the absolute configuration of (+)-IV was assigned as the R series by leading it to R(+)-VIII of known configuration(3). The structure of racemic G fraction was demonstrated to be V by admixture with an authentic sample prepared from ethyl benzoylacetate. The absolute configuration of (-)-V(Table I, G) has been established to be S seris (4), and whose optical purity is supposed to be 70.3% based on the reported value (5).

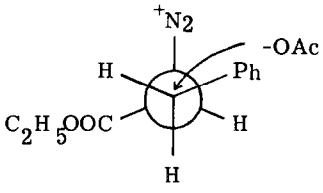


The peaks A and C have proved that A is identified as ethyl cis-cinnamate (VI) and C ethyl trans-cinnamate (VII) by means of g. l. c. techniques. In comparison with the authentic sample, the peaks B and D were recognized only when the hydrochloride of phenylalanine ester was used, hence, these peaks seem to be derived from halogen derivatives but the structures are now uncertain. The average ratio of products obtained is: III, 24%, IV 26%, V, 35%, VI, 7-8% and VII, 7-8%.

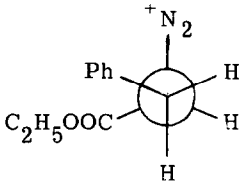
A comprehensive attempt has tentatively been made to account for the stereochemistry of this reaction which should obtain in a variety of products. The conformational effect will be important, three conformations IXa, b and c are suggested. The concerted migration of phenyl group from C-3 to C-2 from the backside of the nitrogen atom with loss of nitrogen from the diazonium ion and solvolytic reaction at C-3 with acetic acid in IXa conformation of L-phenylalanine, is supposed to provide R(+)-III.



IXa



IXb



IXc

A similar hydride shift from C-3 to C-2 concerted with acetoxylate anion attack from the backside of the shifted hydrogen in IXb is to give S(-)-V, and the conformation IXc is expected to be less populated. The formation of R(+)-IV is due to the ordinary direct displacement of the solvent molecule with the inversion of configuration.

The formation of ethyl cis and trans cinnamates is considered to arise from a carbonium ion intermediately different from the above mechanism, since the cis/trans ratio of two olefins is nearly equal. Moreover, this carbonium ion mechanism might partly participate in the formation of III, IV and V along with the concerted diazonium ion mechanism, since some racemization took place in forming III, IV and V. However the detailed reaction mechanisms are not clear at present.

It should be noted that S(-)-II is probably derived from L-I in Datura Stramonium plants, whereas the chemical transformation of L-I to II provided the rather surprising result that R(+)-II was produced from L-I. This different result may be explained by a different pathway for this chemical reaction from that of Datura Stramonium plants.

We are extending the deamination reaction with nitrous acid to a variety of amino acids and their derivatives.

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