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THE FIRST CHEMICAL CONVERSION OF L-PROLINE TO L-GLUTAMIC ACID

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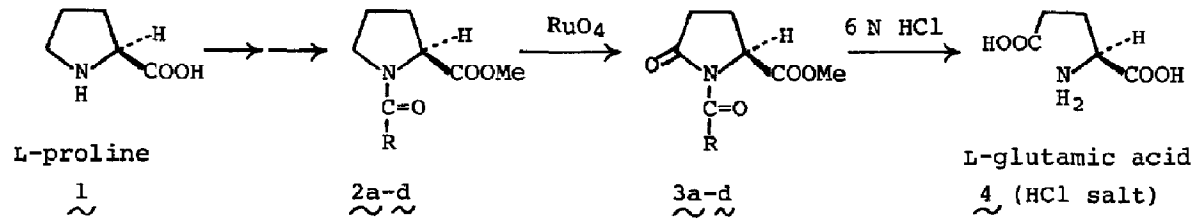
Abstract: The ruthenium tetroxide oxidation of N-acyl-L-proline esters gave the corresponding L-pyroglutamic acid derivatives in good yields with no appreciable racemization, which led to the first chemical conversion of L-proline to L-glutamic acid.

There are many examples[1] of chemical interconversion of natural amino acids. But L-glutamic acid has not been chemically derived from any other amino acids except for its homologues, which seems to be structurally related to L-proline through the dehydrated form, L-pyroglutamic acid.

We now wish to report the first conversion of L-proline to L-glutamic acid involving an effective oxidation of the pyrrolidine ring in the former using ruthenium tetroxide, which has been found recently to be a capable oxidant for preparation of lactam compounds from N-acylated cyclic amines.[2] Therefore, the key step of the present conversion(1→2→3→4), illustrated in Chart, is the



a: R= CH_3 ; b: R= C_2H_5 ; c: R=  ; d: R= $OCH_2C_6H_5$

Chart

ruthenium tetroxide oxidation of N-acyl-L-proline esters(2a-d), readily prepared from commercial L-proline. The oxidation was carried out at room temperature in carbon tetrachloride or chloroform using catalytic amount of ruthenium dioxide and excess 10% aqueous sodium metaperiodate in a two-phase system. The reaction was easily controlled due to the low concentration of ruthenium tetroxide generated in situ under above conditions. The desired lactams(3a-d) were isolated from each organic phases of reactions as the only product in the three cases of

Table Oxidation of N-Acyl-L-proline Esters(2a-d) with RuO_4[a)]

Starting compound	Solvent	Time (hr)	Yield (%)	Product	Appearance	$[\alpha]_D$ (c 1, EtOH)
2a	$CHCl_3$	78	91	3a	colorless oil bp 138°(2mmHg)	$[\alpha]_D^{15}$ -50.4°
2b	$CHCl_3$	69	80	3b	colorless oil bp 116°(2mmHg)	$[\alpha]_D^{29}$ -53.2°
	CCl_4	72	78			
2c	CCl_4	22	92	3c	colorless plates mp 70–71°	$[\alpha]_D^{14}$ -45.4°
2d	CCl_4	57	54	3d	colorless oil	$[\alpha]_D^{21}$ -41.3°

a) Substrate: 12 mmoles ; Solvent: 40 ml ; $RuO_2 \cdot xH_2O$: 240 mg (Alfa Products) ; 10% Aqueous $NaIO_4$: 120 ml ; Temperature: room temperature ; Stirring: a mechanical stirrer using a glass blade, ca. 350 rpm.

2a-c and together with the side product in the case of 2d. Remaining a matter of racemization, the structure of lactams was characterized by their analytical and spectral data. The result were summarized in Table. N-Cyclohexylcarbonyl derivative(2c) was oxidized with the best result both in reaction time and yield

Now, these lactams(3a-d), which may be called pyroglutamic acid derivative, were hydrolyzed in 6 N hydrochloric acid in the usual manner to give quantitatively L-glutamic acid as the hydrochloride(4) with high optical purities, respectively. This result proves that the chirality at the C-2 position of the proline moiety is not disturbed during the oxidation. Thus, the chemical conversion of L-proline to L-glutamic acid has been established.

In the light of the present result, it appears that the ruthenium tetroxide oxidation can be extended to chemical modification of natural cyclic amino acids and peptides.

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