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A NEW METHOD FOR OXIDATIVE DECARBOXYLATION OF N-ACYL-α-AMINO-ACIDS AND PEPTIDES

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The oxidative decarboxylation of α-amino-acids has received continuous attention by organic chemists. Implication of this reaction with oxidations in living organisms and with alkaloid biogenesis is well known. Until recently, however, N-halodecarboxylation of α-amino-acids induced by hypohalogenites[2] and by N-bromosuccinimide[3], has been the only method which has found synthetic applications[2b,4]. Two substantially new procedures concern the recently reported syntheses of β-lactams by oxidative decarboxylation of N-substituted azetidine carboxylic acids[5]. Comparatively few data are available concerning N-acylaminoacids and peptides; aqueous peroxydisulphate[6] or lead tetraacetate[2b,7] have been used to degradate N-acetylamino-acids, while N-bromosuccinimide was found to be effective only on the corresponding silver salts[8]. A fully characterized peptide which underwent oxidative decarboxylation has been reported only recently[9] and the mechanism of such reaction is under investigation.

We now describe a new general procedure for the oxidative decarboxylation of the title compounds. The reaction involves brief treatment of p-nitrophenyl-esters (ONp) of N-acyl-α-amino-acids and peptides with m-chloroperbenzoic acid (MCPBA) at room temperature in mild alkaline aqueous medium. The method is exemplified by the reaction on benzyloxycarbonyl-L-proline p-nitrophenylester. To a solution of Z-Pro-ONp (1.0 mmol) in 24 ml of dioxane, 12 ml of 0.1 M $NaHCO_3$ and 12 ml of 0.1 M Na_2CO_3, MCPBA (2.0 mmol) was added. The solution was allowed to stand 3.0 h at room temperature, treated with saturated aqueous Na_2CO_3 and extracted with chloroform. The organic phase was washed with water, dried and evaporated to give essentially pure 8b(90%)[10].

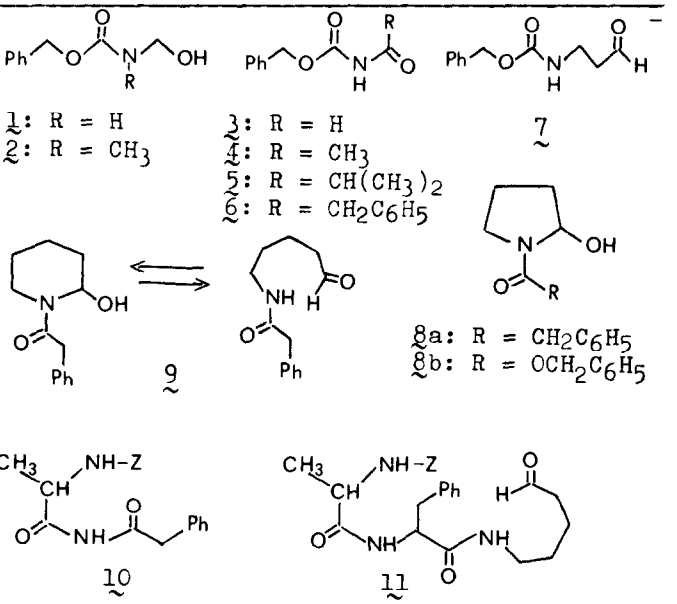
The results summarized in the Table show that α-amino-acid and α-imino-acid derivatives give two different types of compounds. Starting from

derivatives of sarcosine, azetidine-2-carboxylic acid, proline and pipecolic acid, compounds 2, 7, 8, 9 and 11 are obtained, in which the carboxyl group has been replaced by an hydroxyl group. In the case of cyclic imino-acids the compounds so formed are amido-aldehydes, carbinolamides or a mixture of both, according to the expected ring chain tautomerism[11].

Derivatives of glycine, alanine, valine and phenylalanine give, on the other hand, imides or N-acylcarbamates 3, 4, 5, 6 and 10, showing that decarboxylation

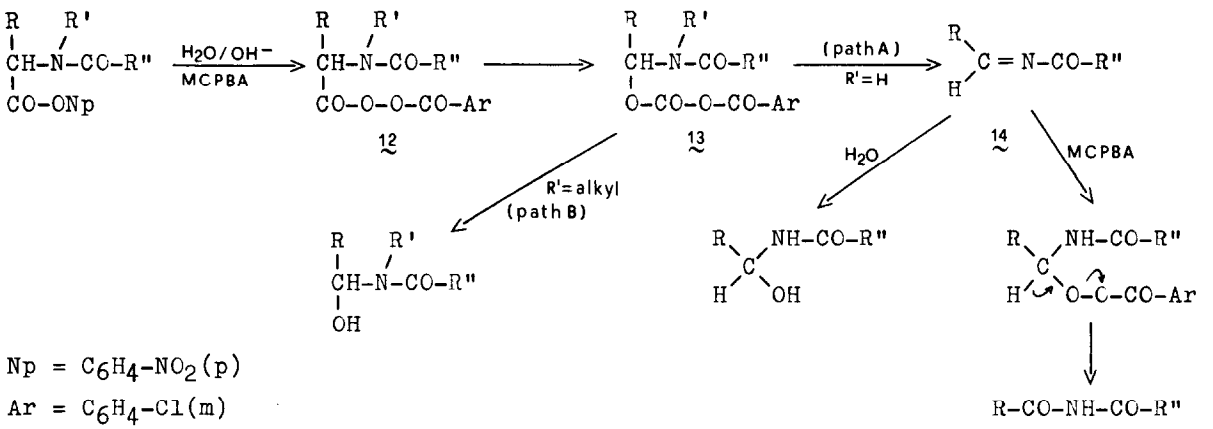
T A B L E [a]

Substrate	Product[b] (Yield%)		M.p. °C
Z-Gly-ONp	1[c]	(60)	81-2
	3	(30)	62-4
Z-Ala-ONp	4	(80)	102-4
Z-Val-ONp	5	(75)	82-4
Z-Phe-ONp	6	(65)	140-2
Z-Sar-ONp	2	(90)	oil
Z-Aze-ONp	7	(30)	53-5
Z-Pro-ONp	8b	(90)	45-6[d]
Ph-CH_2CO-Pro-ONp	8a	(85)	55-6
Ph-CH_2CO-Pip-ONp	9	(70)	102-4
Z-Ala-Phe-ONp	10	(65)	78-80
Z-Ala-Phe-Pip-ONp	11	(60)	140-1



[a] All new compounds gave correct elemental analyses and spectral data consistent with the assigned structures. PLC on silica gel was used to isolate the products when necessary. The abbreviated formulae follow the IUPAC-IUB recommendations; Pip = piperidine-2-carboxylic acid; Aze = azetidine-2-carboxylic acid. [b] Typical PMR signals (90 MHz, δ ppm, $CDCl_3$); 1: 4.65(d,2H,CH_2N), 6.18(t,1H, NH), 4.28(br,1H,OH); 3: 8.97(d,1H,J=9.6Hz,HCO), 8.68(br d,1H, NH), 5.21(s,2H, CH_2); 4: 2.38(s,3H,CH_3), 8.20(br s,1H,NH); 5: 1.13(d,6H,methyls), 3.20(m,1H,CH), 7.68(br s,1H,NH); 6: 5.18(s,2H,CH_2O), 4.03(s,2H,CH_2CO), 7.8(s,1H,NH); 2: 3.0(s, 3H,CH_3), 3.5(br,1H,OH), 4.8(s,2H,CH_2N); 7: 9.78(t,1H,J=1.0Hz,HCO), 2.60(t,2H, CH_2CO), 3.45(dt,2H,CH_2N), 5.38(br s, 1H,NH); 8b: 5.5(br s, NCHOH), 3.9(br s,OH); 8a: 5.68, 5.40(br s,NCHOH), 3.62, 3,81(s,2H,PhCH_2), 4.40(br s,OH); 9: 9.73(t, 0.4H,J=1.5Hz,HCO), 6.1-5.5(complex,NCHOH), 3.71, 3.52(s,2H,PhCH_2), 2.35(m,0.8H, CH_2CHO), 3.9(br,OH), 5.6(br,NH); 10: 9.45(s,1H,imidic NH), 5.75(d,1H,NHCOO), 5.10(s,2H,CH_2O), 4.58(m,1H,AlaCαH), 3.90(s,2H,CH_2CO), 1.27(d,3H,AlaCβH_3); 11: (100MHz) 9.68(t,0.5H,J=1.5Hz,HCO), 5.51(d,1H,NHCOO), 4.65(dt,1H,PheCαH), 4.23(m, 1H,AlaCαH). PMR spectra of 8 and 9 clearly show cis/trans isomerism about the amide bond. [c] Identical with an authentic specimen prepared according to S. Takeuchi et al., Makromol.Chem., 157, 63(1972). [d] Reaction of 8b with hydroxylamine ($NH_2OH\cdot HCl$, AcONa, EtOH, H_2O; 2.0 h reflux) gave the oxime ZNH$(CH_2)_3$-CH=NOH m.p. 94-95°C, yield 85%.

SCHEME



is accompanied by oxidation of the α-carbon atom to carbonyl group.

In the case of Z-Gly-ONp the reaction mixture contains appreciable amounts of the hydroxymethyl derivative 1 in addition to the acylcarbamate 3 (see Table). The product composition is approximatively inverted when 1.0 mole of MCPBA per mole of Z-Gly-ONp is used, but in this case the mixture is contamined by the starting material. It is of interest to note that the hydroxymethyl derivative 1 is unaffected when treated with MCPBA in the standard conditions. This finding parallels the independent observation that no significant amounts of imides or N-acyl-lactams are found in the oxidative decarboxylation of imino-acid derivatives.

A preliminary interpretation of the experimental results is illustrated in the Scheme. At the early stages of the reaction, diacyl peroxides 12 and their "carboxy inversion" products 13 are proposed as key intermediates[12], common to both α-amino and α-imino-acid derivatives. For the first class of compounds formation of N-acylimines 14 from mixed carbonates 13 (path A) and subsequent reaction of this species with MCPBA to give imides or N-acylcarbamates represents the prevailing pathway. Only in the case of the unsubstituted N-acyl-imine derived from Z-Gly-ONp the reaction with water, leading to carbinolamide 1, is found to compete significantly (see Table).

α-Imino-acid derivatives cannot form N-acylimines and N-acylimmonium ions are probably too high-energy intermediates[15] to be considered in the adopted conditions. Hydrolysis of mixed carbonates (path B) to give carbinolamides seems then the favoured route.

It is of interest to note that carbinolamides of type 8, which can be

obtained in high yield with the present method, should be useful intermediates for the synthesis of cyclic N-acylenamines, a class of compounds difficult to obtain[16]. This and other applications of the present method are currently under investigation.

References and Notes

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10. The present method derives from the initial observation that the cyclic carbinolamide 8b was neatly formed when active esters of Z-Pro were treated with H_2O_2 in mild alkaline medium in order to investigate peroxy acid formation. The yield of 8b reached a maximum value of 40-45% when 1.5-2.0 mole of H_2O_2 per mole of active ester was used. Higher molar ratios produced further enhancement of the hydrolysis of the active ester.
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12. Under the conditions adopted, the hydrolysis of the p-nitrophenyl esters is scarcely competitive and nucleophilic attack of the peroxycarboxylate anion leading to α-amido-acyl-m-chloro-benzoyl peroxide can reasonably represent the prevailing pathway. Propensity of diacyl peroxides of type 12 to undergo ionic decomposition in polar solvents to give aroyl-alkyl carbonate 13 (carboxy inversion) is well known (see ref.13) and alkaline hydrolysis of mixed diacyl peroxides to give alcohols from the next higher acids is an interesting utilization of such property (ref.14).
In accordance with the proposed mechanism are the following observations concerning Z-Pro-ONp : the yield of 8b changes from 90% to ~40% when MCPBA is replaced by hydrogen peroxide (see note 10); no reaction occurs when MCPBA is replaced by t-butyl hydroperoxide.Furthermore Z-N(CH_3)CH_2CO-O-O-COC_6H_4Cl(m) [prepared by following the procedure of F.D.Green and J.Kazan, J.Org.Chem., 28, 2168(1963)] is found to decompose to 2 when treated with the buffered alkaline medium under the conditions adopted in the present method.
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