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OXIDATION OF AMINO ACID ESTERS INTO N-HYDROXYAMINO ACID DERIVATIVES

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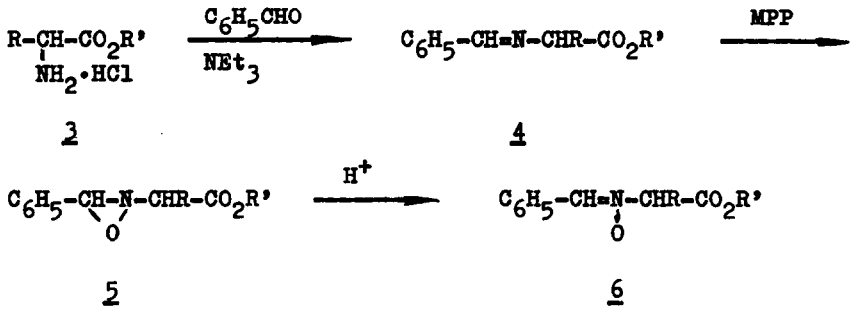
A variety of naturally occurring hydroxamic acids with structures related to peptides are known.[1,2] Elements for the synthesis of these N-hydroxypeptides / -CO·N/OH/- / may be either optically active N-hydroxyamino acids 1 or, still better, their esters 2. While racemic 1 and 2 have been obtained by a number of methods,[1,3] only three optically active 1 have so far been obtained by nucleophilic substitution of the corresponding α-bromo acids.[4-6] This reaction does not, however, give optically homogenous products [4] and can not therefore be used for the synthesis of 2. All of the methods hitherto employed do not offer a simple way of obtaining N-hydroxy analogues of common amino acids.

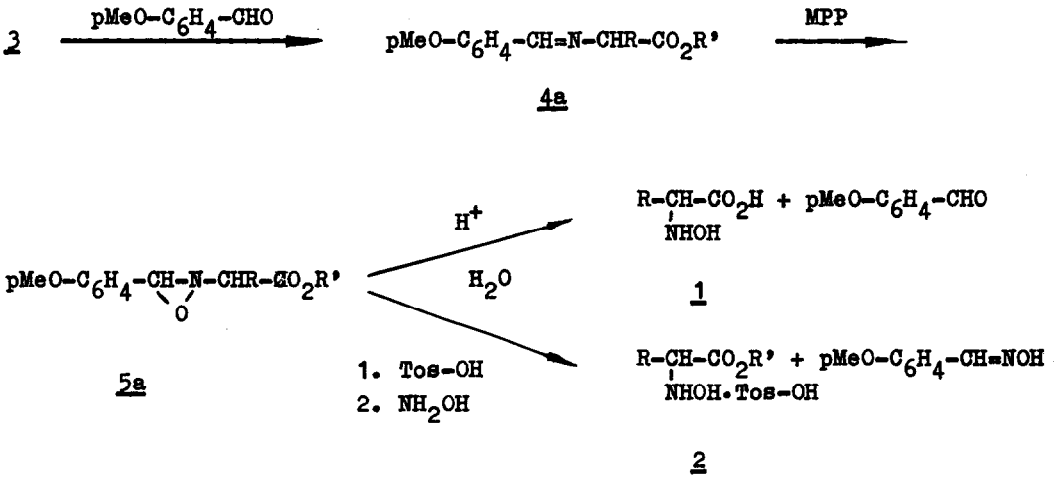
In this paper we wish to report a novel synthesis of 1 and 2 by indirect oxidation of esters of amino acids 3. Emmons [7] was the first who, by oxidation of Schiff bases with peracetic acid, obtained oxaziridines which under the action of acids, give the products of N-O or C-O /bond cleavage/.[7,8] Hydroxylamines /C-O cleavage/ are formed only from oxaziridines derived from aromatic aldehydes, and with the t-alkyl substituent on nitrogen. By acting with benzaldehyde on 3 liberated "in situ" from hydrochlorides, we obtained esters of benzylidene amino acids 4 which we oxidized with monoperphtalic acid /MPP/ in etheral solution at 0°C to the corresponding oxaziridines 6. Under the action

of acids, however, these oxaziridines underwent structural rearrangement to nitrones 6.



E.g., from DL-alanine methyl ester we obtained on this way the N-oxide of benzylidene DL-alanine methyl ester: /m.p. 160°/ NMR: /$CDCl_3$, δ / 8,15 /2H,m, ArH/ and 7,30 /4H,m,ArH + -CH=/, 4,7 /1H,q, $C_\alpha H$/, 3,7 /3H,s,CO_2CH_3/, and 1,7 /3H,d,$C_\beta H_3$/; IR /KBr/: 1750, 1585, 1220, 775.

For this reason we modified that method by using anisyl aldehyde, which gave very acid sensitive oxaziridines.



The corresponding oxaziridines 5a, obtained in the same way as 5, gave N-hydroxyamino acids 1, during heating with hydrochloric acid.

Acid hydrolysis could of course not be used to obtain esters 2. To achieve this, we developed a new method for oxaziridine cleavage under very mild conditions. By acting on 5 with hydroxylamine p-toluenesulfonate in dioxane or stepwise with p-toluenesulfonic acid and then with hydroxylamine in alcoholic solution, we obtained 2 from the reaction mixture in the form of readily crystallizing p-toluenesulfonates. In the method developed by us, the intermediate products 4a and 5a have not been isolated. The results are summarized in the Table. All products were characterized by determining their NHOH content by titration, and through elementary analysis. Examples of NMR and IR spectral details are also given.

Table. $R-\underset{\underset{NHOH}{|}}{CH}-CO_2R'$ /L configuration/

R	R'	Total yield /from 3 to 1/, %	M.p. °C	$[\alpha]_D^{20}$
$CH/CH_3/_2$	H	30	154-155[a/]	+22,4 /c12, 1N HCl/
$CH_2C_6H_5$	H	42	161-163[a/]	+25,4 /c2, 1N HCl/
$CH/CH_3/_2$	CH_3	29	162-163[a,b/]	+33,4 /c3, MeOH/
$CH_2CH/CH_3/_2$[d/]	CH_3	47	128-130[a,c/]	+13,3 /c3, $CHCl_3$/
$CH_2CH/CH_3/_2$	$CH_2C_6H_5$	25	141-144[c/]	+ 2,5 /c3,5, $CHCl_3$/
$CH_2C_6H_5$[e/]	CH_3	30	63	+16,5 /c1, C_6H_6/
$CH_2CH_2CO_2CH_3$	CH_3	42[b/]	123-125	+ 8,0 /c3, $CHCl_3$/

a/ with dec., b/ hydrochloride, c/ p-toluenosulfonate,

d/ NMR /$CDCl_3$, δ /: 8,2 /3H, br, NH_2OH^+/, 7,6 /2H, m, Ar<u>H</u>/ and 7,0 /2H,m,Ar<u>H</u>/, 3,8 /1H,m,$C_\alpha H$/, 3,5 /3H,s/CO_2CH_3/, 2,25 /3H,s,Ar<u>CH_3</u>/, 1,55 /3H,complex,$CHCH_2$/, 0,65 /6H,d,$CH/C\underline{H}_3/_2$; IR /KBr/: 3170 /br/, 2950 /br/, 2770 /br/, 1755

e/ NMR /$CDCl_3$, δ /, 7,15 /5H,s,Ar<u>H</u>/, 6,0 /2H,br,NHOH/, 3,75 /1H,m,$C_\alpha H$/, 3,65 /3H,s,CO_2CH_3/, 2,85 /2H,m,Ar<u>CH_2</u>/; IR /KBr/: 3255, 3210 /br/, 2925 /br/, 1750, 760, 705.

This new method of indirect oxidation of amino acids to N-hydroxy-amino acids and their derivatives, does not require conducting the reaction on the centre of asymmetry and gives optically pure products.

As illustrated by a further example,[9] it also permits the preparation of multifunctional optically active hydroxylamines.

References and Notes

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9. Additionaly we obtained by this method L/-/-α-phenylethylhydroxylamine with 81% yield /M.p. 93°/, $[\alpha]_D^{20}$ = -43,5° /c1, EtOH/, NMR /$CDCl_3$, δ/: 7,25 /5H,s,ArH/, 5,8 /2H,s,NHOH/, 4,0 /1H,q,ArOH/, 1,12 /3H,d,CH_3/; IR /KBr/: 3265, 3150 /br/, 2875 /br/, 765, 705; satisfactory C,H,N, NHOH analysis.