Tetrahedron Letters No. 27, pp. 2471-2472, 1971. Pergamon Press. Printed in Great Britain.

N-ACYL-(o-NITROPHENYL-SUBSTITUTED)-AMINOACIDS IN PEPTIDE SYNTHESIS

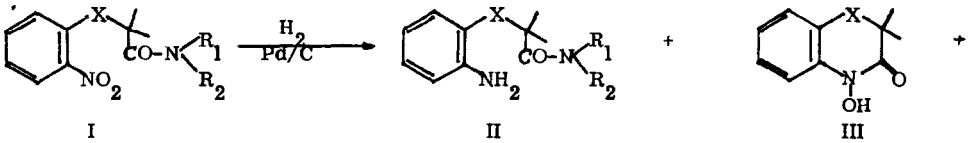
Flavian Cuiban

Chemistry Department, Polytechnic Timişoara, Bv. 30 December nr.2, Roumania.

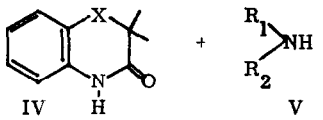
(Received in UK 18 May 1971; accepted in UK for publication 2 June 1971)

The suggestion to use o-nitrophenoxyacetic and chloroacetic acids as aminoprotecting groups in the peptide synthesis[1,2] has not been extended because in the elimination phase heating is required which may promote secondary reactions. More recently it has been shown[3], that upon catalytic reduction o-nitrophenoxyacyl penicillins split into 6-aminopenicillanic acid and the corresponding benzoxazines.

Starting from these data, first the cyclization tendency of o-nitrosubstituted amides (I) were tested by their hydrogenation in standard condition, with Pd/C, at room temperature and pressure. Quantitative data included in table 1 show that after reduction substituted anilines (II) resulted, or cyclic hydroxamic acids (III) and lactams (IV) if the amino function (V) is eliminated.



I II III



IV V

where: X= nil or CH_2, O, S, NH.

R_1=Ph, PhCH_2, Et, Cyclohexyl.

R_2=H or Et.

Subsequently, starting from the only two acids A and D from table 1 which showed the highest cyclization tendency, acylated aminoacids were prepared and the elimination conditions of the protecting groups were established. A slower elimination of the phenylacetyl residue from the terminal amino group of lysine was observed. The elimination of 2-methyl-2-o-nitrophenoxypropionyl residue occurred more easily during reduction and only lactam (IV) was obtained as cyclized product. The free aminoacids separated after elimination of protecting groups conserved entirely their initial optical activity.

The peptide bond synthesis with 2-methyl-2-o-nitrophenoxy-propionyl-aminoacids proceeding through acid chlorides leads to completely racemised compounds because of azlactone formation. With mixed anhydrides and N,N'-dicyclohexylcarbodiimide optical purity is preserved. Among the advantages

Table 1. Percentage composition[a/] of products resulted after reducing the o-nitrophenylsubstituted acid amides.

o-Nitro-acid \ Amine	Benzylamine			Cyclohexylamine			Aniline			Diethylamine		
	II	III	IV	II	III	IV	II	III	IV	II	III	IV
A. Phenylacetic	-	40	60	-	40	60	-	33	66	98	-	tr.[d/]
B. Cinnamic	-	-	100	-	-	100	-	-	100	100	-	-
C. Phenoxyacetic	-	tr.	95	-	tr.	95	-	tr.	95	98	-	tr.
D. 2-Methyl-2-phenoxy-propionic	-	68	32	-	65	35	-	45	55	-	tr.	98
E. N-Phenylglycine[c/]	-	-	98									
F. Phenyl-thioglycollic[c/]	-	tr.	60[b/]									

a/ Determined through isolation of the reaction products, or TLC on silicagel, or hydrogen consumption in reduction, or titration of resulted amine (V). b/ Reduction was not complete even after repeated catalyst additions. c/ The reduced tendency towards cyclization and synthetic difficulties decided us to discontinue investigations.

offered by the N-aminoacid protection with the 2-methyl-2-o-nitrophenoxypropionyl residue, we may quote: obtention of a high purity protecting agent, its stability in time and that of the protected products, a better crystallinity, high efficiency in protecting without danger of racemization as with the phthalyl, formyl or trifluoroacetyl groups.

The stability of protected aminoacids in acid medium determined us to use N^{ε}-(2-methyl-2-o-nitrophenoxypropionyl)-L-lysine in the preparation of N^{α}-methyl-L-lysine. Owing to the absence of deprotection in hot formic acid during the methylation step, contrary to other protecting groups[4], an almost quantitative yield was obtained.

Synthetic details and experimental conditions will appear in Revue Roumaine de Chimie.

References

1. R.W.Holley and A.D.Holley, J.Amer.Chem.Soc. 74, 3069 (1952).
2. S.Akabori, S.Sakakibara and Y.Shimonishi, Bull.Chem.Soc.Japan, 31, 784 (1958); 34, 739 (1961).
3. D.A.Johnson, C.A.Panetta and R.R.Smith, J.Org.Chem. 31, 2560 (1966).
4. P.Quitt, J.Hellerbach and K.Vogler, Helv.Chim.Acta, 46, 327 (1963).