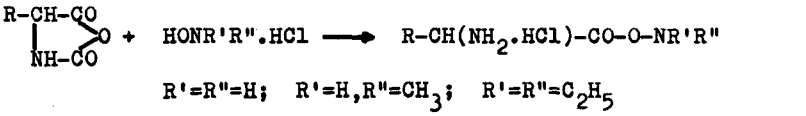
Tetrahedron Letters No.2, pp. 95-99, 1965. Pergamon Press Ltd.
Printed in Great Britain.

ACTIVE α-AMINOACYL O-DERIVATIVES OF N-SUBSTITUTED HYDROXYLAMINE. O TO N MIGRATION AND A METHOD FOR PEPTIDE SYNTHESIS

Shmuel Bittner[+], Yehuda Knobler and Max Frankel
Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem, Israel

(Received 21 November 1964)

PREVIOUSLY (1, 2) we have shown that N-carboxy-α-amino acid anhydrides react with hydrochlorides of amines to yield amino acid amides, aminohydroxamic acids and amidooxy-peptides. This reaction was then applied to hydrochlorides of hydroxylamine and of N-alkyl and N,N-dialkyl hydroxylamine, with the aim of obtaining their O(α-aminoacyl) derivatives and of studying their properties.

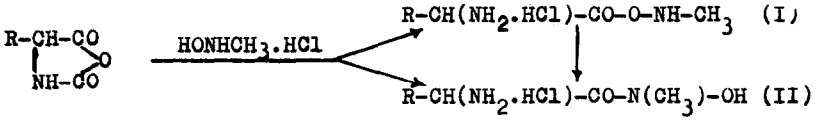


We assumed that the salts of O(α-aminoacyl)hydroxylamine or of O(α-aminoacyl)N-alkylhydroxylamine would be stable enough to allow isolation, and that this kind of carbonyl activated compounds would be useful in peptide synthesis.

[+] Part of the Ph.D. thesis of S.B. to be submitted to the Senate of the Hebrew University.

Unstable O-acylhydroxylamines rearranging to hydroxamic acids were investigated by Jencks (3), who isolated O-benzoylhydroxylamine on treatment of hydroxylamine with p-nitrophenyl benzoate at neutral pH. The same compound was also obtained as hydrochloride by Carpino, Giza, and Carpino (4), on cleavage of a carbo-t-butoxy group from t-butyl N-benzoyloxycarbamate. Recently, Bruice and Fedor (5) studied the kinetics of O- versus N-acylation of hydroxylamine by thiophenyl esters.

Whereas we could not obtain O(α-aminoacyl)hydroxylamine, in addition to α-aminohydroxamic acid, on treatment of N-carboxyanhydride with hydroxylamine hydrochloride in ethanol - water, treatment with N-methylhydroxylamine hydrochloride led to the expected O(α-aminoacyl)N-methylhydroxylamine hydrochlorides (I) (70-90%). These were isolated in crystalline form, and could be subsequently converted into the appropriate α-amino-N-methylhydroxamic acids (II) by moderate heating in solution or on keeping at room temperature for longer time intervals.



R=$C_6H_5CH_2$; L-I, m.p. 151-2°, $[\alpha]_D^{20}$ = +4°(c=12.5 in water); DL-I, m.p. 142-3°; L-II, m.p. 175-6°.

R=H; I, m.p. 87-8°; II, m.p. 165°.

The relative stability of the salt of O(α-aminoacyl)N-methylhydroxylamine, as compared to the unstable salt of O(α-aminoacyl)hydroxylamine, should be attributed to steric hindrance and to increased negative charge on the hydroxylamine oxygen exerted by the methyl group. Both effects

inhibit the transformation to the thermodynamically more stable aminohydroxamic acid; they seem also to increase the rate of O-acylation. The relative amounts of O- and N-acylation (ferric chloride test indicates a very rapid hydroxamic acid formation) vary with reaction temperature and depend also upon the nature of solvent. Lowering of temperature ($25^{\circ} \rightarrow 0^{\circ}$) increases the yield of the O-acyl derivative. Lowering the water content in the reaction solution increases considerably the yield of the O-acyl compound (I), to a maximum of 90% conversion in absolute ethanol (Mg). This increase is apparently due to decrease of association with the hydroxylamine oxygen before interaction and with the carbonylic oxygen after the acylation.

Glycylbenzylamide was prepared (50%) in order to examine the activation of O(α-aminoacyl)N-methylhydroxylamine. Coupling with benzyloxycarbonylglycine was performed on the α-amine of I by the DCC method, and subsequent reaction with glycine ester led to ethyl benzyloxycarbonylglycyl-glycyl-glycinate, according to the procedure of Goodman and Stueben (6). As yields were limited (30-40%) by O to N migration to give glycyl-N-methylhydroxylamine, advantageous use was made of the N,N-dialkylated hydroxylamine: reaction of phenylalanine- or glycine-N-carboxyanhydride with N,N-diethylhydroxylamine hydrochloride yielded the respective O-aminoacyl hydrochloride (III).

(III)

III, R=$C_6H_5CH_2$; DL-m.p. 75-76°; L-m.p. 113-15°

R=H; m.p. 90-91°.

O(α-Aminoacyl)N,N-diethylhydroxylamine (III) was coupled as above with benzyloxycarbonylglycine and, in the same fashion, the tripeptide was produced in good yield (80%). The dialkylated aminoacyl derivative precludes the aforementioned side reaction; O to N migration would lead in this case to an N-acylamine oxide which should regenerate the starting active ON-ester: $R\underset{\underset{O}{\|}}{C}O-N= \rightleftharpoons R\underset{\underset{O\ O}{\|\ \downarrow}}{C}-N=$

Protected O(α-aminoacyl)N,N-diethylhydroxylamine offers a new type of an activated amino acid ester for a dipeptide synthesis. Coupling of benzyloxycarbonylamino acids with N,N-diethylhydroxylamine produced the intermediary O-acyl-N,N-dialkyl esters (IV), and reaction with an amino acid ester or salt in ethanol or ethanol - water solution gave the N-protected dipeptides (V) (70-80%).

$$Cbz\text{-}NHCH(R)COOH + HON(C_2H_5)_2 \xrightarrow{DCC} Cbz\text{-}NHCH(R)COON(C_2H_5)_2 \quad (IV)$$

$$(IV) + R'\text{-}CH(NH_2)COOX \longrightarrow Cbz\text{-}NHCH(R)CONHCH(R')COOX \quad (V)$$

IV, R=H: m.p. 81-82°; R=CH_2OH: m.p. 95-96°; R=$CH_3SCH_2CH_2$: oil

V, R=H, R'=H, X=C_2H_5: m.p. 76-78°.

R=H, R'=H, X=H: m.p. 179-80°.

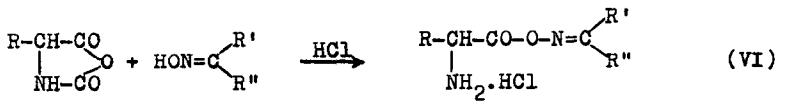
R=H, R'=CH_3, X=H: m.p. 183-84°.

R=H, R'=$C_6H_5CH_2$, X=H: m.p. 156-57°.

The reaction proceeds slowly (for some days) at room temperature without remarkable interaction with the solvent (the active ester being recovered after certain time intervals).

O(α-Aminoacyl)oximes, a type of compounds similar to III, were obtained from N-carboxyanhydrides and oximes of acetone,

of cyclohexanone and of acetophenone, in the presence of an equivalent of hydrogen chloride.



(VI)

L-VI, R=$C_6H_5CH_2$, R'=R"=CH_3; m.p. 172-73°,

$[\alpha]_D^{20}$ = -18.4 (c=12.5 in water).

L-VI, R=$C_6H_5CH_2$, R'-R"= -$(CH_2)_5$-; m.p. 165-67°,

$[\alpha]_D^{20}$ = -22.4 (c=6.2 in water).

DL-VI, R=$C_6H_5CH_2$, R'=C_6H_5, R"=CH_3: m.p. 160-61°.

L-VI, R=$C_6H_5CH_2$, R'=C_6H_5, R"=CH_3: m.p. 158-59°,

$[\alpha]_D^{20}$ = +36° (c=4.16 in ethanol).

VI, R=H, R'=CH_3, R"=CH_3; m.p. 147-48°.

Work is proceeding on applying this procedure to related compounds.

REFERENCES

1. S. Bittner, Y. Knobler, and M. Frankel, Israel J. Chem. 1, 240 (1963).
2. Y. Knobler, S. Bittner, and M. Frankel, J. Chem. Soc., 1964, 3941.
3. W.P. Jencks, J. Amer. Chem. Soc., 80, 4581 (1958); Ibid. 80, 4585 (1958).
4. L.A. Carpino, C.A. Giza, and B.A. Carpino, J. Amer. Chem. Soc., 81, 955 (1959).
5. T.C. Bruice and L.R. Fedor, J. Amer. Chem. Soc., 86, 739 (1964).
6. M. Goodman and K.C. Stueben, J. Amer. Chem. Soc., 81, 3980 (1959).