Tetrahedron Letters No.31, pp. 3035-3040, 1967. Pergamon Press Ltd. Printed in Great Britain.

THE SYNTHESIS AND REARRANGEMENT OF AN ALLENAMIDE

W. B. Dickinson and P. C. Lang (1)

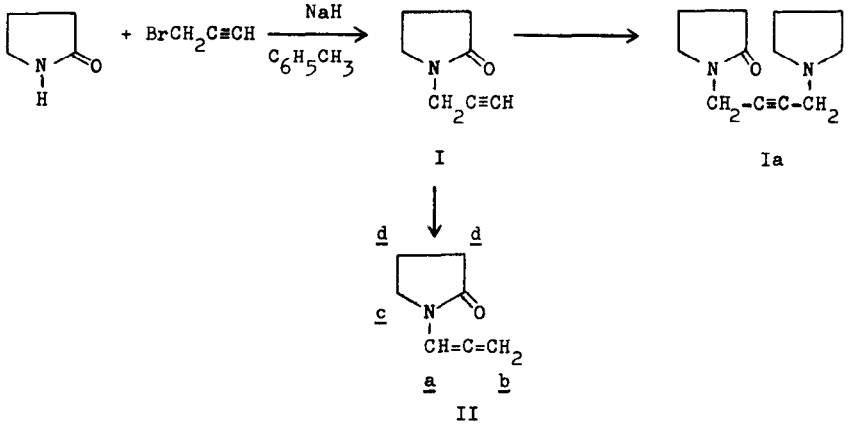
Sterling-Winthrop Research Institute

Rensselaer, New York 12144

(Received 16 May 1967)

We wish to report the preparation and characterization of an allenamide (2), i.e., 1-(1,2-propadienyl)-2-pyrrolidinone (II), and to describe its unusual base catalyzed addition-rearrangement with pyrrolidine to form 1-[(2-ethyl-1-pyrrolin-3-yl)carbonyl]-pyrrolidine (III).

Alkylation of 2-pyrrolidinone by propargyl bromide in the presence of base has been reported by Cho (3) to give 1-(2-propynyl)-2-pyrrolidinone (I), a key intermediate in the synthesis of the potent muscarinic agent oxotremorine (Ia) (3,4).

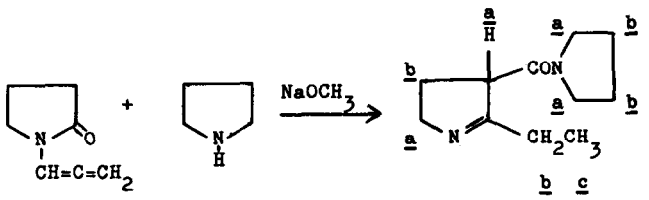


However, other workers (4) have reported difficulty in repeating this synthesis following the original procedure, in accord with our own observations. It has now been shown that the principal product of this reaction is not the expected 1-(2-propynyl)-2-pyrrolidinone (I) but is instead 1-(1,2-propadienyl)-2-pyrrolidinone (II).

Distillation of the crude product obtained using Cho's method gave a pale yellow oil, C_7H_9NO (5), b.p. 74-76° (0.08 mm), n_D^{25} 1.5402; $\lambda_{max}^{ethanol}$ 231 mμ (ε 12,789), λ_{max}^{film} 5.10 μ, 5.92 μ. The absence of absorption bands near 3.10 (≡CH) and 4.75 μ (C≡C) excluded the acetylenic structure I, while the observed bands at 5.10 (C=C=C) and 5.92 μ (-N-C=O) suggested instead the allenamide II. This structure was confirmed by n.m.r. spectroscopy (6). Peaks were centered at 431 cps (triplet, J = 6, a) and 338 cps (doublet, J = 6, b), having the chemical shifts and coupling constants characteristic of the allene moiety (7), with additional peaks at 212 cps (triplet, J = 6, c) and 170-120 cps (multiplet, d), the peak area ratio being 1:2:2:4 respectively, in good agreement with the assigned structure II.

It seems probable that the allenamide II is produced by base catalyzed isomerization of an initially formed acetylenic derivative I, since in the course of this work it was shown that authentic 1-(2-propynyl)-2-pyrrolidinone (I) (3) is rapidly converted to II by sodium hydride in toluene, by sodium methoxide in either toluene or methanol, or by pyrrolidine in dioxane.

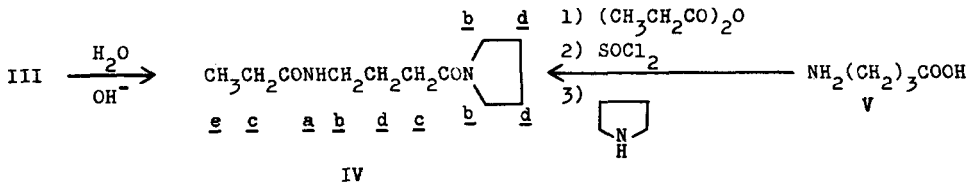
In contrast to the general reactivity of amines towards allenes (8), pyrrolidine did not react with II. However, in the presence of sodium methoxide, pyrrolidine combined exothermically with the allenamide (either preformed or generated in situ) to give a 1:1 adduct having neither γ-lactam absorption near 5.92 μ nor vinyl hydrogens in the n.m.r. spectrum. This material, which clearly was not formed by addition of pyrrolidine to any of the allenic carbon atoms of II, proved to be an unexpected rearranged adduct, 1-[(2-ethyl-1-pyrrolin-3-yl)carbonyl]pyrrolidine (III).



II III

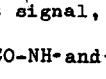
Equimolar amounts of II, pyrrolidine, and sodium methoxide in refluxing dioxane gave, after chromatography on silica gel, a yellow oil III, $C_{11}H_{18}N_2O$, b.p. 115° (0.05 mm), n_D^{25} 1.5120, mol. wt. 198 ± 10 (f.p. in dioxane); λ_{max}^{hexane} 202 mμ (ε7800), 232 mμ (shldr) (ε500); λ_{max}^{film} 6.14 μ (broad, >C=N-, -CON<); n.m.r. spectrum: 250-190 cps (broad, overlaping multiplets, a), 160-90 cps (broad, overlaping multiplets, b), 67 cps (triplet, J = 7, c), with a peak area of 7:8:3 respectively.

The structure of the adduct III was determined by its spectral and chemical properties, and by hydrolysis to an amide which has been shown to be 1-[4-(propionamido)butyryl]pyrrolidine (IV).



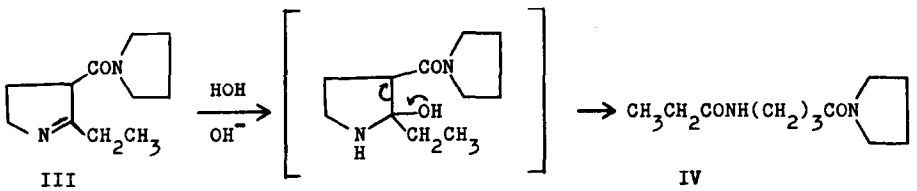
IV V

Alkaline hydrolysis of the adduct III gave, in addition to a small amount of propionic acid, a solid IV, $C_{11}H_{20}N_2O_2$, m.p. 61-62°; λ_{max}^{film} 3.07, 6.48 μ (N-H), 6.11, 6.16 μ (-CONH-, -CON<); n.m.r. spectrum: 420 cps (broad, a), 220-185 cps (overlaping multiplets, b), 155-130 cps (overlaping multiplets, c), 125-100 cps (overlaping multiplets, d), 68 cps (triplet, J = 7, e) with a peak area ratio of 1:6:4:6:3 respectively.

The presence of two amide carbonyl peaks, a single NH peak, a single C-methyl triplet signal, and the isolation of propionic acid indicated the partial structures $CH_3CH_2CO-NH-$ and  . Connecting these fragments through the divalent hydrocarbon residue C_3H_6 required by the empirical formula led to the assignment of structure IV to the hydrolysis product.

This structure was then unequivocally established through acylation of 4-aminobutyric acid (V) by means of propionic anhydride, followed by reaction with thionyl chloride-pyrrolidine to give authentic 1-[4-(propionamido)butyryl]pyrrolidine, identical in every respect to the hydrolysis product IV.

Structure IV having been positively established, the pyrrolidine-allenamide adduct III from which it was derived by addition of one equivalent of water could be identified as 1-[4-(1-pyrrolin-3-yl)carbonyl]pyrrolidine (III), a structure which

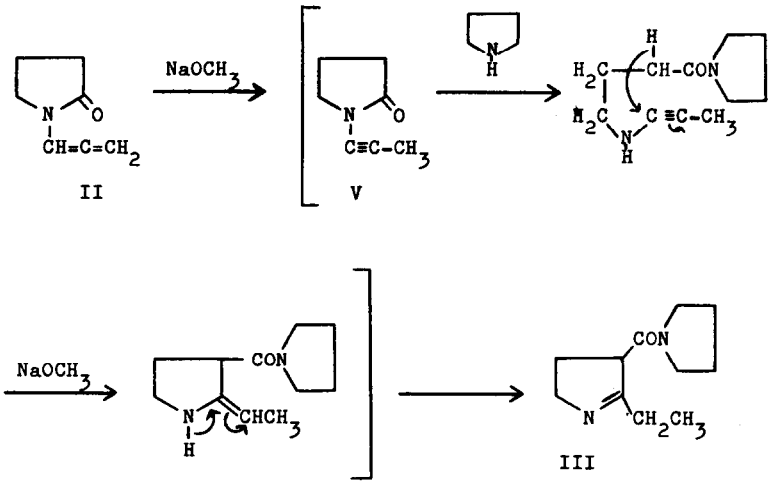


III IV

accommodates the observed u.v. end-absorption at 202 mμ, the broad, intense double bond absorption near 6.14 μ (>C=N-, -CON<), the C-methyl triplet signal ($\underline{CH_3}CH_2$-), the lack of vinyl or NH protons, and the peak area ratio of 7:8:3.

The hydrolysis of III is regarded as a process analogous to the well-known base catalyzed cleavage of β-ketoesters and β-ketoacids.

Although the precise sequence of events in this addition-rearrangement is as yet unknown, formation of III may be visualized as an isomerization of the allenamide II to a reactive N-(1-propynyl)amide V which undergoes ring scission by pyrrolidine. Recyclization <u>via</u> amide α-carbanion (9) addition to the acetylenic bond (10) followed by proton transfer leads to III as shown in the sequence:



That III is not isomerized to an α,β-unsaturated amide under these conditions reflects the poor conjugative capability of the amide function, and is in accord with the observations of Witkop (11a) and others (11b) that there are probably no authentic secondary 2-pyrrolidines known.

Acknowledgements: We are grateful to Dr. S. Archer for his continued support and encouragement. We are also indebted to Dr. R. K. Kullnig and Miss K. Martini for assistance in interpreting the spectral data, to Mr. M. Priznar for the u.v. determinations, and to Mrs. M. Becker and Mrs. E. Bohl for technical assistance.

References

1. Taken in part from the Ph.D. thesis of P. C. Lang, submitted to the Rensselaer Polytechnic Institute, Troy, N. Y., 1966. Present address: General Aniline & Film Corp., Rensselaer, N. Y.

2. S. Nakanishi and E. V. Jensen, J. Org. Chem., 27, 702 (1962), have applied the term enamide to N-acyl enamines. By analogy, the name allenamide is suggested for the type of allene derivative described here.

3. A. K. Cho, W. L. Haslett, and D. Jenden, Biochem. Biophys. Res. Commun. 5, 276 (1961).

4. (a) A. Bebbington and D. Shakeshaft, J. Med. Chem. 8, 274 (1965).
(b) J. L. Archibald, J. Med. Chem. 8, 390 (1965).

5. All compounds reported gave satisfactory elemental analyses. We are indebted to Mr. K. D. Fleischer and his staff for these determinations.

6. Spectra were measured in approximately 10% solution in $CDCl_3$ on a Varian A-60 spectrometer. Chemical shifts are in cycles per second from internal tetramethylsilane as zero. Coupling constants are in cycles per second, the underlined letters giving the peak assignment to the appropriate protons.

7. E. J. Snyder and J. D. Roberts, J. Am. Chem. Soc. 84, 1582 (1962).

8. H. Fischer, The Chemistry of Alkenes, ed. by S. Patai, Interscience Publishers, New York, N. Y., 1964, p. 1079.

9. P. G. Gassman and B. L. Fox, J. Org. Chem. 31, 982 (1966).

10. G. Eglinton and M. C. Whiting, J. Chem. Soc. 1953, 3052.

11. (a) B. Witkop, J. Am. Chem. Soc. 76, 5597 (1954).
(b) R. Bonnett and D. E. McGreer, Can. J. Chem., 40, 177 (1962).