Tetrahedron Letters No.44, pp. 4605–4608, 1968. Pergamon Press. Printed in Great Britain.

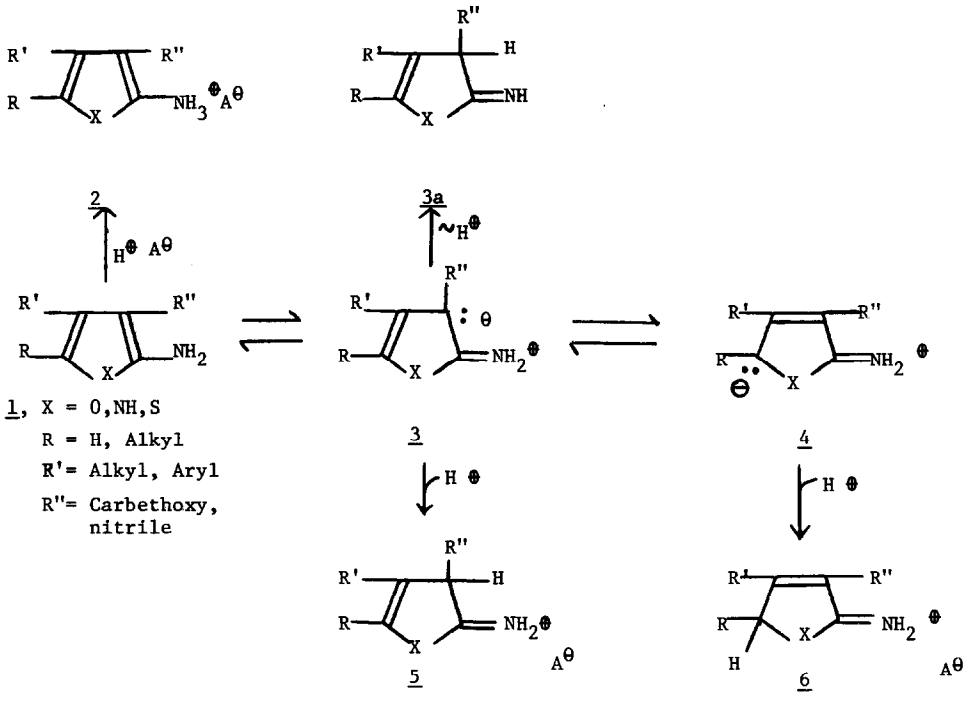
REACTION OF AMINO-SUBSTITUTED HETEROCYCLES WITH ONE HETEROATOM IN A FIVE-MEMBERED RING AS ENAMINES[1]

Chwang T. Wie, S. Sunder and C. DeWitt Blanton, Jr.[2]

School of Pharmacy, Auburn University, Auburn, Alabama 36830

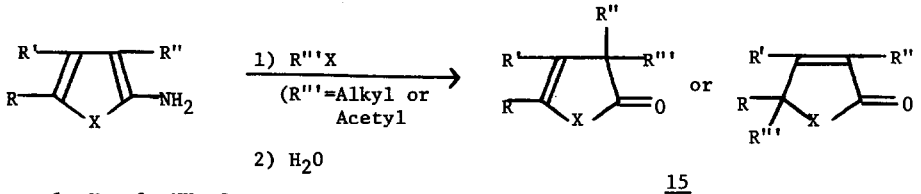
(Received in USA 27 May 1968; received in UK for publication 31 July 1968)

Although considerable literature[3] has appeared regarding the tautomerization of amino-substituted furans, pyrroles and thiophenes, no reference appears to have been made to any ability of these systems to react as enamines.[4] We have observed that a variety of 2-amino-substituted furans, pyrroles and thiophenes (1)[5] do not behave as typical aromatic amines towards an electrophilic reagent with formation of an ammonium salt (2). Instead, their reactions are characteristic of the polarized form of an enamine (3) or dienamine (4). Electrophilic addition occurs at the β- or δ-carbon atom with formation of an immonium salt (5 or 6).



Evidence for the electrophilic addition to the carbon atom with formation of the immonium salt (6) was readily obtained by n.m.r. spectroscopy. (In these initial studies, the salts (5 or 6) were not isolated for characterization.) The n.m.r. spectrum of 2-amino-3-cyano-4,5-dimethylfuran (7) in dimethylsulfoxide (d_6) supports the literature[3] suggestion that the tautomeric equilibrium favors the amino form (1). However, in trifluoroacetic acid, or sulfuric acid, n.m.r. spectra indicate that this compound (7) behaves as a dienamine with electrophilic addition at C_5 (6), since the peaks for the C_5-methyl group exist as a doublet and the C_5-proton as a quartet (Table I). Six additional 2-amino-substituted heterocyclic compounds have been examined (Table I) and similar results were recorded. Compounds substituted with a methyl group at the five position (7,9,10,12,13) gave clear indication of electrophilic addition by their characteristic splitting patterns. The proton ratios for 8 and 11 suggested electrophilic addition at position five. Since the n.m.r. data indicated that these heterocyclic systems are reacting as enamines (dienamines), we believe it is significant to note that an isosteric aromatic compound, p-toluidine (14), does not possess an n.m.r. spectrum suggesting electrophilic addition to a polarized enamine form. (The ammonium salt is evidently formed.) It is also interesting to note that the n.m.r. spectrum of the 1-acetyl-pyrrole derivative (13) suggest that the keto (imine) form (3a) of the tautomeric equilibrium is favored in deuteriochloroform.

Recognition of the enamine behavior for substituted 2-aminofurans, as well as for 2-aminothiophenes and 2-aminopyrroles, should prove of considerable value to synthetic chemistry. For example, under appropriate reaction conditions, one may expect facile C-acylation or C-alkylation at the β- or δ-carbon. This observation should also contribute a convenient procedure for the preparation of novel substituted γ-lactones, γ-lactams or γ-thiolactones (15).



1, X = O, NH, S

15

In our laboratory, we have been particularly interested in furopyrroles, thienopyrroles and pyrrolopyrroles (indole isosteres). C-Acylation of an appropriately substituted 2-amino-heterocyclic system with bromoacetyl bromide has given encouraging results for a simple synthesis of these ring systems. For example, treatment of 2-amino-3-cyano-4,5-dimethylfuran (7)

TABLE I
Nmr Data [a]

Compound[b]	Solvent (or electrophile)[c]	Chemical Shift (δ), Multiplicity[d], Number of Hydrogens	
7, 2-amino-3-cyano-4,5-dimethylfuran	A.	6.42, b, 2; 2.05, s, 3; 1.9, s, 3.	B. 9.7, b, 2; 6.0, q, 1; 2.58, s, 3; 1.8, d, 3.
	C.	9.2, d, 2; 6.5, q, 1; 3.19, s, 3; 2.3, d, 3.	
8, 2-amino-3-cyano-4-methylfuran	A.	6.8, m, 2; 4.28, q, 1; 2.07 and 1.55, methyl, d, 3	B. 9.8, b, 2; 5.75, s, 2; 2.62, s, 3.
9, 2-amino-3-carbethoxy-4,5-dimethylthiophene	D.	6.05, b, 2; 4.28, q, 2; 2.15, d, 6; 1.35, t, 3.	B. 10.4, b, 2; 4.90, q, 1; 2.74, s, 3; 4.60, q, 2; 1.85, d, 3; 1.48, t, 3.
10, 2-amino-3-carbethoxy-4-phenyl-5-methylthiophene	B.	7.55, m, 5; 5.4, q, 1; 4.3, q, 2; 1.65, d, 3; 1.05, t, 3.	
11, 2-amino-3-carbethoxy-4-phenylthiophene	A, D.	7.21, s, 5; 7.02, b, 2; 5.97, s, 1; 4.00, q, 2; 0.90, t, 3.	B. 10.3, b, 2; 7.55, s, 5; 4.90, s, 2; 4.25, q, 2; 1.10, t, 3.
12, 2-amino-3-cyano-4,5-dimethylpyrrole	A.	9.28, b, 1; 5.05, s, 2; 1.95, s, 3; 1.89, s, 3.	B. 8.9, b, 1; 7.85, d, 2; 4.85, q, 1; 2.5, s, 3; 1.6, d, 3.
13, 1-acetyl-2-amino-3-cyano-4,5-dimethylpyrrole	D.	6.98, b, 1; 2.55, s, 3; 2.25, s, 3; 2.15, s, 1; 1.98, s, 3.	B. 10.0, b, 2; 5.50, s, 1; 2.7, d, 6; 1.8, d, 3.
14, p, toludine	B.	8.9, s, 3; 7.25, s, 4; 2.3, s, 3.	

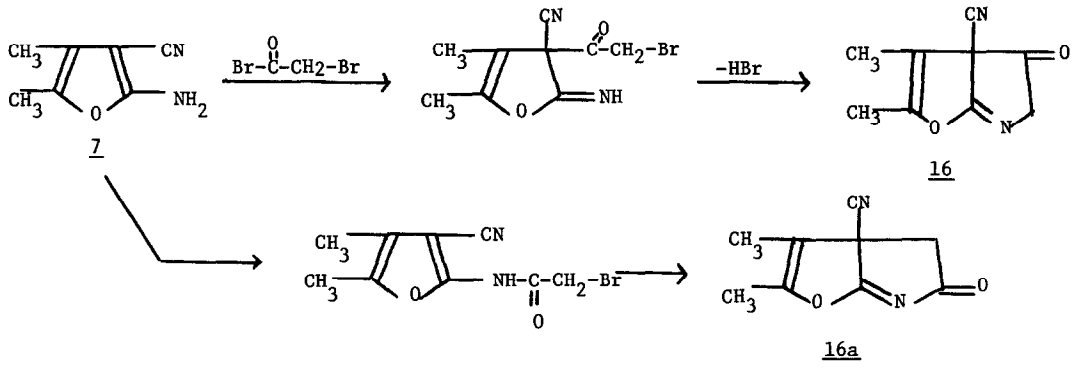
[a] Nuclear magnetic resonance spectra were obtained with a Varian HR-60 Spectrometer (IL), unless stated otherwise.

[b] Structural assignment as indicated by nmr spectrum.

[c] A = DMSO d_6. B = CF_3COOH. C = H_2SO_4. D = $CDCl_3$.

[d] s = singlet. d = doublet. t = triplet. q = quartet. m = multiplet. b = broad.

with bromacetyl bromide, in the presence of anhydrous potassium carbonate and tetrahydrofuran, has given 2,3-dimethyl-3a,4-dihydro-3a-cyano-4-oxo-5H-furo[2,3-b]pyrrole (16) in yields of 30-40%, m.p. 231-233° (Anal. calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.55; N, 15.91. Found C, 61.30; H, 4.62; N, 15.73), ν^{KBr} 2250, 1698, 1650 cm^{-1}; n.m.r. in dimethylsulfoxide ($DMSOd_6$) at 60 Mc, singlet at 4.70 δ (2H, methylene group) and two singlets at 2.17 and 2.07 δ (6H, two methyl groups).[6] Structure 16, which should result from C-acylation and cyclization by elimination of hydrogen bromide, was assigned in preference to structure 16a, which should be ob-



tained if N-acylation occurred, followed by C-alkylation. The basis for this conclusion was the location of the methylene peak at 4.70 δ. Had the methylene been located between a carbon and a carbonyl, the peak would appear at about 2.50 δ rather than at 4.70 δ.[6]

Preliminary results suggest that one may expect the enamine reaction to occur less readily for thiophenes as this heterocycle has a higher resonance energy. Under present conditions, N-acylation occurs for 2-aminothiophene rather than C-acylation. It is possible that the N-acylated product from bromoacetyl bromide may be subjected to an enamine type C-alkylation to give desired indole isostere(16a; -O- replaced by -S- or -NH). These studies will be the subject of a later communication.

REFERENCES

1. This work was supported by research grant MH-10673 from the National Institutes of Health, U.S. Public Health Service, Bethesda, Maryland.
2. To whom inquiries may be addressed. Present address: School of Pharmacy, University of Georgia, Athens, Georgia, 30601
3. A.R. Katritzky and J.M. Lagowski, "Advances in Heterocyclic Chemistry," Vol. 2, A.R. Katritzky, ed., Academic Press, New York, N.Y. 1963, p. 3.
4. For review articles on Enamines: (a) J. Szmuszkovicz, "Advances in Organic Chemistry", Vol. 4, R.A. Raphael, Ed., Interscience Publishers, New York, N.Y., 1963, p. 1; (b) K. Blaha and O. Cervinka, "Advances in Heterocyclic Chemistry," Vol. 6, A.R. Katritzky and A.J. Boulton, Ed., Academic Press, New. York, N.Y., 1966, p. 147.
5. (a) K. Gewald, Z. Chem., 1, 349 (1961); (b) K. Gewald, E. Schinke and M. Bottcher, Chem. Ber., 99, 94 (1966); (c) K. Gewald, Chem. Ber., 99, 1002 (1966).
6. Nmr spectrum and interpretation obtained from Simon Research Laboratory, Elgin, Illinois. Tetramethylsilane was used as the internal standard.