Reaction of Amino Substituted Heterocycles with One Heteroatom in a Five-membered Ring as Enamines. A Revision [1]

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2-Aminoheterocycles (pyrrole, furan, and thiophene) exist in solution in the amino form of type **1** and **5**. They undergo protonation at the exocyclic nitrogen in DMSO/TFA and protonation at position 5 in TFA. However when the electrophile is different from proton the 2-aminoheterocyles do not react as enamines (*C*-acylation is never observed), but their behavior is typical of aromatic amines, giving rise to *N*-acylated product of type **9**.

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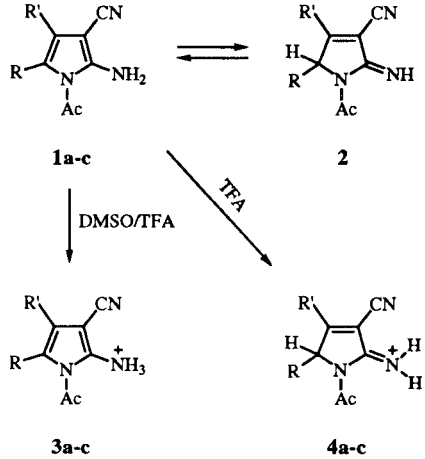
In the course of our researches on nitrogen heterocycles of biological interest we needed aminopyrroles as useful synthons. Therefore we became interested in investigations on the synthesis, the structure and reactivity of 2- and 3-aminopyrroles. We have recently reported ^1H and ^{13}C nmr data demonstrating that 2- and 3-aminopyrroles, showing a similar behavior, exist in the amino form and undergo ring protonation in trifluoroacetic acid (TFA) and protonation at the exocyclic nitrogen in dimethyl sulfoxide/trifluoroacetic acid (DMSO/TFA) [2,3]. In this paper we report the behavior of 2-aminopyrroles of type **1** in different solvents and acid conditions, and some investigations on their reactivity. The required derivatives **1a-c** were obtained by a modification of known procedures [4] that allowed their isolation in preparative yields. Their nmr spectra were measured in different solvents and protonation was achieved under different acid conditions, either by adding two equivalents of TFA to the DMSO solutions or dissolving directly the compounds into TFA. The ^1H and ^{13}C nmr data for derivatives **1a-c**, reported in Tables 1 and 2, demonstrate that either in deuteriochloroform and in dimethyl sulfoxide the free base exists exclusively in the amino form **1**. Our findings are in disagreement with those reported by Wie *et al.* [5]. In fact these authors, only on the basis of proton measurements, proposed that the imine form **2** is favored in the tautomeric equilibrium of the free amine. However in the ^{13}C nmr spectra there is no evidence for protons on the ring carbon atoms and the chemical shifts for the pyrrole carbon atoms are in the range typical for ^1H-pyrrole derivatives [6]. The nmr spectra measured in DMSO/TFA and in TFA suggest that 1-acetyl-2-aminopyrroles **1a-c** undergo protonation at the exocyclic nitrogen in the presence of two equivalents of TFA to give the ammonium salts of type **3**, whereas they undergo ring protonation in position 5 in pure TFA, as demonstrated by the appearence of doublets in the range 59.9-70.3 ppm and by the presence, in the ^1H nmr spectrum, of the pattern quartet-doublet for the coupling of CH with the methyl in position 5 in the case of derivative **4a**. However it has to be noted that the immonium protons of derivatives **4**, obtained upon protonation of the free base, appeared as two singlets at low field, because of the strong character of double bond between the exocyclic nitrogen and the carbon atom C-2, whereas they were described by Wie as a broad signal, probably because of deficiency in resolution of the nmr instruments in that period. Moreover Wie assigned to the protonated amino compound a structure compatible with a protonation at the position 3.

Scheme 1



a R = R' = Me
b R = Ph, R' = Me
c R = H, R' = Ph

On the basis of these findings we decided to verify the position of the tautomeric equilibrium and the behavior under acid conditions of the 2-aminofuran and 2-aminothiophene derivatives already studied by Wie *et al.*

Table 1

^{1}H NMR Data (c.s. in ppm) in Different Solvents (A = DMSO, B = $CDCl_3$, C = DMSO/TFA, D = TFA) of 1-Acetyl-2-aminopyrroles

Compound	1a	1a	1b	1c	1c	3a	3b	3c	4a	4b	4c
Solvent	A	B	A	A	B	C	C	C	D	D	D
Substituent											
Ac	2.54 (s, 3H)	2.55 (s, 3H)	1.88 [a] (s, 3H)	2.58 (s, 3H)	2.56 (s, 3H)	2.56 (s, 3H)	1.89 [a] (s, 3H)	2.56 (s, 3H)	2.66 [a] (s, 3H)	2.21 (s, 3H)	2.66 (s, 3H)
NH_2	6.84 (bs, 2H)	5.96 (s, 2H)	7.15 (s, 2H)	7.34 (s, 2H)	6.19 (s, 2H)	9.22 (bs, 3H)	12.51 (vb, 3H)	10.49 (s, 2H)	9.59 (s, 1H) 10.52 (s, 1H)	9.65 (s, 1H) 10.54 (s, 1H)	9.39 (s, 1H) 10.43 (s, 1H)
R'	1.87 (s, 3H)	1.97 (s, 3H)	1.86 [a] (s, 3H)	7.33 (t, 1H) 7.44 (t, 2H) 7.67 (d, 2H)	7.36 (t, 1H) 7.42 (t, 2H) 7.57 (d, 2H)	1.89 (s, 3H)	1.87 [a] (s, 3H)	7.33 (t, 1H) 7.41 (t, 2H) 7.68 (d, 2H)	2.64 [a] (s, 3H)	2.11 (s, 3H)	7.68 (t, 2H) 7.85 (t, 1H) 8.10 (d, 2H)
H-5									5.48 (q, 1H)	6.19 (s, 1H)	5.76 (s, 2H)
R	2.20 (s, 3H)	2.25 (s, 3H)	7.265 (t, 1H) 7.35 (t, 2H) 7.43 (d, 2H)	7.15 (s, 1H)	6.60 (s, 3H)	2.21 (s, 3H)	7.28 (t, 1H) 7.36 (t, 2H) 7.44 (d, 2H)	7.08 (s, 1H)	1.84 (d, 3H)	7.19 (d, 2H) 7.48 (t, 3H)	

[a] May be reversed.

Table 2

^{13}C NMR Data (c.s. in ppm) in Different Solvents (A = DMSO, B = $CDCl_3$, C = DMSO/TFA, D = TFA) of 1-Acetyl-2-aminopyrroles

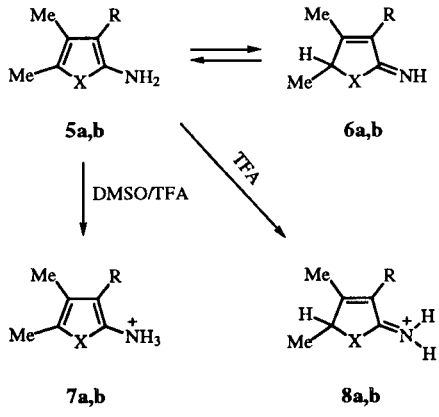
Compound	1a	1a	1b	1c	3a	3b	3c	4a	4b	4c
Solvent	A	B	A	A	C	C	C	D	D	D
Substituent										
C-2	149.4 (s)	149.6 (s)	150.2 (s)	151.5 (s)	149.5 (s)	150.6 (s)	151.9 (s)	175.7 (s)	176.1 (s)	175.0 (s)
C-3	72.4 (s)	74.7 (s)	72.7 (s)	69.6 (s)	72.6 (s)	73.2 (s)	70.1 (s)	105.4 (s)	105.0 (s)	98.95 (s)
C-4	116.2 [a] (s)	115.6 [a] (s)	120.4 [a] (s)	125.1 (s)	116.2 [a] (s)	120.8 [a] (s)	125.5 (s)	164.8 (s)	167.0 (s)	168.1 (s)
C-5	116.25 [a] (s)	116.2 [a] (s)	120.3 [a] (s)	109.4 (s)	116.3 [a] (s)	120.7 [a] (s)	109.6 (d)	70.3 (d)	77.6 (d)	59.9 (t)
Ac	27.0 (q)	26.7 (q)	27.4 (q)	23.9 (q)	26.9 (q)	27.5 (q)	24.3 (q)	24.7 (q)	25.35 (q)	24.65 (q)
	172.55 (s)	172.55 (s)	173.0 (s)	172.35 (s)	173.1 (s)	173.4 (s)	172.6 (s)	188.1 (s)	186.6 (s)	176.0 (s)
CN	116.6 (s)	118.3 (s)	116.2 (s)	116.4 (s)	116.6 (s)	116.5 (s)	117.1 (s)	109.7 (s)	108.9 (s)	111.3 (s)
R'	10.1 (q)	10.1 (q)	10.2 (q)	127.3 (d) 128.7 (d) 128.9 (d) 132.1 (d)	9.7 (q)	10.35 (q)	126.4 (d) 127.8 (d) 128.9 (d) 132.5 (s)	16.4 (q)	16.5 (q)	128.4 (s) 131.45 (d) 132.4 (d) 139.9 (d)
R	13.7 (q)	13.7 (q)	127.4 (d) 128.65 (d) 129.3 (d) 132.55 (s)		13.1 (q)	127.7 (d) 128.9 (d) 129.6 (d) 133.0 (s)		18.1 (q)	128.3 (d) 132.9 (d) 133.8 (d) 130.5 (s)	

[a] May be reversed.

Actually the ^{1}H and ^{13}C nmr data for derivatives **5a,b**, reported in Tables 3 and 4, are in agreement with Wie's results with the usual exception of the immoniun protons, that in our measurements appear as two singlets for one proton each at 9.59-9.90 ppm, and at 9.75-10.64 ppm, respectively. These spectral data support the literature suggestion that the tautomeric equilibrium favors the amino form, whereas in DMSO/TFA and in TFA their behavior is identical to that of pyrrole derivatives, giving rise to the ammonium salts of type **7** and the immonium species of type **8**, respectively.

It could be supposed, therefore, that the hypothesis of these aminoheterocycles reacting as enamines was correct. In fact Wie described that *C*-acylation was preferred

Scheme 2



a X = O, R = CN
b X = S, R = COOEt

Table 3

^{1}H NMR Data (c.s. in ppm) in Different Solvents (A = DMSO, B = DMSO/TFA, C = TFA) of 2-Aminofuran and 2-Aminothiophene

Compound	5a	5b	7a	7b	8a	8b
Solvent Substituent	A	A	B	B	C	C
NH_2	7.04 (s, 2H)	5.97 (s, 2H)	8.11 (s, 3H)	12.11 (s, 3H)	9.59 (s, 1H)	9.90 (s, 1H)
					9.75 (s, 1H)	10.64 (s, 1H)
Me	1.83 (s, 3H)	2.14 (s, 3H)	1.83 (s, 3H)	2.10 (s, 3H)	1.82 (s, 3H)	1.82 (s, 3H)
Me	2.03 (s, 3H)	2.16 (s, 3H)	2.06 (s, 3H)	2.12 (s, 3H)	2.64 (s, 3H)	2.77 (s, 3H)
H-5					6.06 (q, 1H)	4.86 (q, 1H)
R		1.35 (t, 3H)		1.29 (t, 3H)		1.52 (t, 3H)
		4.27 (q, 2H)		4.20 (q, 2H)		4.59 (q, 2H)

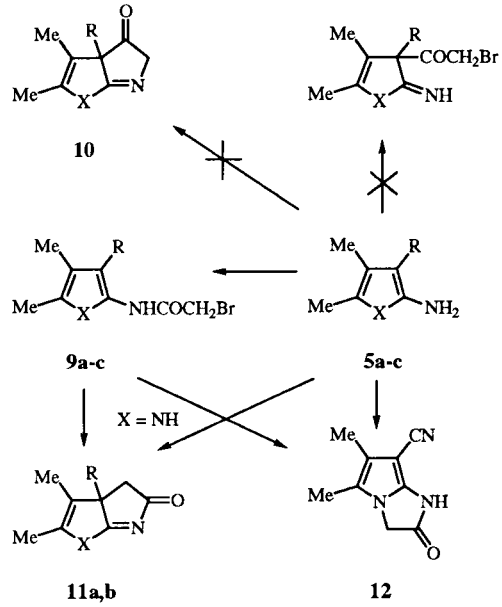
Table 4

^{13}C NMR Data (c.s. in ppm) in Different Solvents (A = DMSO, B = DMSO/TFA, C = TFA) of 2-Aminofuran and 2-Aminothiophene

Compound	5a	5b	7a	7b	8a	8b
Solvent Substituent	A	A	B	B	C	C
C-2	162.8 (s)	162.4 (s)	162.9 (s)	162.5 (s)	191.8 (s)	190.5 (s)
C-3	67.2 (s)	104.05 (s)	67.3 (s)	105.3 (s)	100.5 (s)	121.4 (s)
C-4	113.25 (s)	129.3 (s)	113.3 (s)	130.1 (s)	174.1 (s)	162.7 (s)
C-5	135.6 (s)	112.0 (s)	135.6 (s)	113.5 (s)	93.9 (d)	55.5 (d)
Me	8.7 (q)	14.5 (q)	8.7 (q)	14.75 (q)	13.2 (q)	15.7 (q)
Me	10.6 (q)	14.7 (q)	10.7 (q)	15.0 (q)	14.35 (q)	17.7 (q)
R	116.6 (s)	12.1 (q)	116.6 (s)	12.3 (q)	105.7 (s)	11.5 (q)
		58.9 (t)		59.4 (t)		63.6 (t)
		165.2 (s)		165.9 (s)		191.8 (s)

in the reaction of 2-aminofuran **5a** with bromoacetyl bromide in the presence of base. The structure **10** (X = O) was assigned to the product isolated on the basis of the chemical shift of the methylene protons. Although no details about the ratio of reactants and experimental conditions were reported, we tried to repeat the reaction of **5a**, bromoacetyl bromide and two equivalents of base, at room temperature, and indeed it was possible to isolate a product identical to that obtained by Wie (mp, ir, ^{1}H nmr). Also derivatives **5b,c** were reacted, in refluxing tetrahydrofuran, with bromoacetyl bromide and two equivalents of base and products whose elemental analyses were in agreement with cyclized compounds were isolated. In order to clarify the structure of the bicyclic products and to verify if all the 2-aminoheterocycles studied in this paper behave similarly, we tried to isolate the intermediate open chain product derived from initial acylation. When the reaction of derivatives **5a-c** with bromoacetyl bromide is carried out with one equivalent of base and at lower temperature, the bromoacetylated compounds can be isolated. On the basis of the spectral data, mainly from the chemical shifts of the nuclear carbon atoms in the ^{13}C nmr spectra, which are in the range typical for aromatic furans [7], aminothiophenes [8], and aminopyrroles [6], the structures **9a-c** were assigned to the isolated products. From these experimental data it is possible to confirm that *N*-acylation is always preferred to *C*-acylation, a behavior that however was already well established for aminothiophenes [9] and aminopyrroles [10] and that now is also

Scheme 3



a X = O, R = CN
b X = S, R = COOEt
c X = NH, R = CN

confirmed for this 2-aminofuran derivative. Moreover derivatives **9a-c** can be cyclized in the presence of base to compounds **11a-b** and **12** (when X = NH) which were identical in every respect to the products isolated by us directly from the reaction of the 2-aminoheterocycles, bromoacetyl bromide and base in excess. The structures of these compounds remain therefore unequivocally determined. Moreover compound **12** can be obtained only from the *N*-acylated precursor **9c**. Therefore it has to be concluded that a wrong interpretation of the proton nmr spectra also induced Wie to misleading conclusions on the reactivity of the 2-aminofurans and on the assignment of structure **10** to the bicyclic compound.

In conclusion, the 2-aminoheterocycles studied in this paper behave as enamines, giving rise to *C*-addition under strong acid conditions, however, in our hands, when the electrophile is bromoacetyl bromide, these derivatives behave as aromatic amines. In fact under all the reaction conditions it was impossible to isolate the cyclic product resulting from initial *C*-acylation, and the first step was always the acylation of the amino group to give derivatives of type **9**. Therefore, on the basis of our evidences, it seems unlikely to ascribe an enamine-like reactivity to these 2-aminoheterocycles.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary apparatus and are uncorrected; ir spectra were determined in bromoform with a Jasco FT/IR 5300 spectrophotometer. The ^1H and ^{13}C nmr spectra were measured in DMSO solutions, unless otherwise specified, at 250 and 62.8 MHz respectively using a Bruker AC-E series 250 MHz spectrometer (TMS as internal reference); protonation was achieved by adding two equivalents of trifluoroacetic acid to the DMSO solutions or dissolving the samples directly in TFA. Mass spectra were obtained with a JEOL JMS-01 SG-2 double focusing mass spectrometer operating with an electron beam energy of 75 eV and 10 Kv accelerating voltage and with an HP 5890 Series II and HP 5989A-GC/MS apparatus.

Preparation of 1-Acetyl-2-amino-3-cyano-4-R-5-R'-pyrroles **1a-c**.

To a solution of 3-acetamidobutan-2-one [11,12], or 1-acetamido-1-phenylpropan-2-one [11,12], or ω-acetamidoacetophenone [13] (30 mmoles) in absolute ethanol (5 ml) and piperidine (0.01 ml), a solution of malononitrile (2.97 g, 45 mmoles) in absolute methanol (10 ml) was added dropwise with stirring. After being stirred at room temperature for 6 hours, the resultant solid is filtered off, washed with a little methanol and air dried.

Compound **1a** (R = R' = Me) was recrystallized from ethanol (yield 76%) mp 168° (lit [14] 166-168° from dioxane).

Compound **1b** (R = Ph, R' = Me) was recrystallized from ethanol (yield 70%), mp 179°; ir: 3420, 3310 (NH_2), 2200 (CN), 1705 (CO) cm^{-1}; ms: m/z 239.

Compound **1c** (R = H, R' = Ph) was recrystallized from ethanol (yield 80%), mp 190°; ir: 3422, 3318 (NH_2), 2195 (CN), 1725 (CO) cm^{-1}; ms: m/z 225.

2-Amino-3-cyano-4,5-dimethylfuran (**5a**).

This compound was prepared according to the literature procedure [15].

2-Amino-4,5-dimethyl-3-ethoxycarbonylthiophene (**5b**).

This compound was prepared according to the literature procedure [16].

2-Amino-3-cyano-4,5-dimethylpyrrole (**5c**).

This compound was prepared according to the literature procedure [14].

Reaction of 2-Aminoheterocycles **5a-c** with Bromoacetyl Bromide and Two Equivalents of Base.

Derivatives **5a-c** (10 mmoles) in absolute tetrahydrofuran (50 ml) were added with bromoacetyl bromide (10 mmoles) in the presence of solid potassium carbonate (10 mmoles). The reactants were refluxed, except in the case of derivative **5a** which was kept at room temperature, to the disappearence of the starting compound (tlc monitored, 12 hours). The solvent was evaporated under reduced pressure and the reaction mixture was washed with water. The resulting solid was collected, air dried and purified by column chromatography (eluent dichloromethane) to eliminate the unreacted starting material always present (10-20% yield). The reaction products were recrystallized from ethanol.

3a-Cyano-2,3-dimethyl-3a,4-dihydro-5*H*-furo[2,3-*b*]pyrrol-5-one (**11a**) (yield 15%) had mp 233-234°; ir: 2236 (CN), 1694 (CO) cm^{-1}; ^1H nmr: ppm 2.07 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 4.74 (2H, s, CH_2); ^{13}C nmr: ppm 8.48 (q), 11.1 (q), 50.3 (t), 91.3 (s), 112.6 (s), 115.8 (s), 145.0 (s), 147.5 (s), 163.0 (s); ms: m/z 176.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.20; H, 4.60; N, 16.00.

3a-Carbethoxy-2,3-dimethyl-3a,4-dihydro-5*H*-thieno[2,3-*b*]-pyrrol-5-one (**11b**) (yield 30%) had mp 163-164°; ir: 1694 (broad CO), cm^{-1}; ^1H nmr: ppm 1.26 (t, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.23 (q, 2H, CH_2), 4.39 (s, 2H, CH_2); ^{13}C nmr: ppm 12.7 (q), 13.3 (q), 14.0 (q), 54.3 (t), 60.4 (t), 128.0 (s), 131.4 (s), 131.9 (s), 141.5 (s), 161.9 (s), 164.4 (s); ms: m/z 239.

Anal. Calcd. for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85. Found: C, 55.40; H, 5.65; N, 6.00.

7-Cyano-5,6-dimethyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazol-2-one (**12**) (yield 25%) had mp 295°; ir: 3378 (NH), 2236 (CN), 1694 (CO) cm^{-1}; ^1H nmr: ppm 1.99 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 4.53 (s, 2H, CH_2), 11.65 (s, 1H, NH); ^{13}C nmr: ppm 9.6 (q), 10.5 (q), 52.6 (t), 87.7 (s), 115.4 (s), 115.7 (s), 122.9 (s), 130.5 (s), 164.1 (s); ms: m/z 175.

Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 62.01; H, 5.25; N, 24.05.

Reaction of 2-Aminoheterocycles **5a-c** with Bromoacetyl Bromide and One Equivalent of Base.

Derivatives **5a-c** (10 mmoles) in absolute tetrahydrofuran (50 ml) were added with bromoacetyl bromide (10 mmoles) in the presence of solid potassium carbonate (5 mmoles). The reactants were kept overnight at 40° in the case of derivatives **5b,c**, and at 0° for 1 hour, in the case of **5a**. The solvent was evaporated under reduced pressure and the reaction mixture was washed with water. The resulting solid was collected, air dried and

recrystallized from ethanol.

Compound **9a** (yield 35%) had mp 143-145°; ir: 3144 (NH), 2236 (CN), 1711 (CO) cm^{-1}; ^1H nmr: ppm 2.02 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 4.14 (s, 2H, CH_2), 11.61 (s, 1H, NH); ^{13}C nmr: ppm 8.5 (q), 10.9 (q), 28.8 (t), 61.6 (s), 113.2 (s), 115.4 (s), 142.6 (s), 148.4 (s), 164.4 (s); ms: m/z 256/258.

Anal. Calcd. for $C_9H_9N_2O_2Br$: C, 42.05; H, 3.53; N, 10.90. Found: C, 42.13; H, 3.67; N, 11.01.

Compound **9b** (yield 60%) had mp 119-121°; ir: 3225 (NH), 1657 (broad CO), cm^{-1}; ^1H nmr: ppm 1.34 (t, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 4.32 (q, 2H, CH_2), 4.40 (s, 2H, CH_2), 11.50 (s, 1H, NH); ^{13}C nmr: ppm 11.9 (q), 13.8 (q), 14.0 (q), 29.1 (t), 60.5 (t), 113.5 (s), 123.7 (s), 128.8 (s), 144.2 (s), 163.7 (s), 164.8 (s); ms: m/z 319/321.

Anal. Calcd. for $C_{11}H_{14}NO_3SBr$: C, 41.26; H, 4.41; N, 4.37. Found: C, 41.45; H, 4.37; N, 4.52.

Compound **9c** (yield 45%) had mp 248-250°; ir: 3265 (NH), 2224 (CN), 1667 (CO) cm^{-1}; ^1H nmr: ppm 1.25 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 3.40 (s, 2H, CH_2), 10.21 (s, 1H, NH), 10.61 (s, 1H, NH); ^{13}C nmr: ppm 9.4 (q), 10.4 (q), 29.1 (t), 82.4 (s), 113.9 (s), 116.2 (s), 121.2 (s), 131.1 (s), 165.3 (s); ms: m/z 255/257.

Anal. Calcd. for $C_9H_{10}N_3OBr$: C, 42.21; H, 3.94; N, 16.41. Found: C, 42.44; H, 4.02; N, 16.33.

Cyclization Reaction of Compounds **9a-c**.

Derivatives **9a-c** (10 mmoles) were dissolved in absolute tetrahydrofuran and added with solid potassium carbonate (5 mmoles). The reaction mixture was kept at 40° in the case of **9a**, and under reflux in all the other cases, for 20 hours (steam bath). The solvent was evaporated under reduced pressure and the reaction mixture was washed with water. The resulting solid was collected, air dried and purified by column chromatography (eluent dichloromethane:ethyl acetate 9:1) to eliminate the unreacted starting material always present (5-7% yield). The bicyclic compounds **11a,b** and **12** (50%, 50%, and 46% yields, respectively) were recrystallized from ethanol and resulted to be identical to those obtained in the reaction with two equivalents of base (mp, tlc, ir, nmr).

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REFERENCES AND NOTES

[1] Presented in part at Eleventh Symposium on Chemistry of Heterocyclic Compounds, Prague, August 1993, abstract P1.

[2] G. Cirrincione, A. M. Almerico, P. Diana, S. Grimaudo, G. Dattolo, E. Aiello, and F. Mingoia, Fourteenth International Congress of Heterocyclic Chemistry, Antwerp, August 1993, abstract OP-MI-3.

[3] G. Cirrincione, G. Dattolo, A. M. Almerico, E. Aiello, R. A. Jones, and W. Hinz, *Tetrahedron*, **43**, 5225 (1987).

[4] R. W. Johnson, R. J. Mattson, and J. W. Sowell, Sr., *J. Heterocyclic Chem.*, **14**, 383 (1977).

[5] C. T. Wie, S. Sunder, and C. DeWitt Blanton, Jr., *Tetrahedron Letters*, 4605 (1968).

[6] G. Cirrincione, A. M. Almerico, E. Aiello, and G. Dattolo, Aminopyrroles in Pyrroles. Part Two, in The Chemistry of Heterocyclic Compounds, Vol **48**, R. A. Jones, ed, John Wiley & Sons, New York, NY, 1992, p 403.

[7] F. M. Dean and M. V. Sargent, in Comprehensive Heterocyclic Chemistry, Vol **4**, C. W. Bird and G. W. H. Cheeseman, eds, Pergamon Press, 1984, p 564.

[8] R. K. Norris, Aminothiophenes and Their Derivatives in Thiophene and Its Derivatives. Part Two, in The Chemistry of Heterocyclic Compounds, Vol **44**, S. Gronowitz, ed, John Wiley & Sons, New York, NY, 1986, p 738.

[9] R. K. Norris, Aminothiophenes and Their Derivatives in Thiophene and Its Derivatives. Part Two, in The Chemistry of Heterocyclic Compounds, Vol **44**, S. Gronowitz, ed, John Wiley & Sons, New York, NY, 1986, p 687.

[10] G. Cirrincione, A. M. Almerico, E. Aiello, and G. Dattolo, Aminopyrroles in Pyrroles. Part Two, in The Chemistry of Heterocyclic Compounds, Vol **48**, R. A. Jones, ed, John Wiley & Sons, New York, NY, 1992, p 486.

[11] This *N*-acetyl-α-aminoketone was prepared according to the procedure described by H. D. Dakin and R. West, *J. Biol. Chem.*, **78**, 91 (1928), taking care of **removing the solvent by steam distillation** to avoid the formation of the *N,N*-diacetyl-α-aminoketone.

[12] R. H. Wiley and O. H. Borum, *J. Am. Chem. Soc.*, **70**, 2005 (1948).

[13] F. Wolfheim, *Chem. Ber.*, **47**, 1442 (1914).

[14] U. I. Shvedov, M. V. Mezentseva, and A. N. Grinev, *Khim. Geterotsikl. Soedin.*, 1217 (1975); *Chem. Abstr.*, **84**, 59299 (1976).

[15] K. Gewald, *Chem. Ber.*, **99**, 1002 (1966).

[16] K. Gewald, E. Schinke, and H. Bottcher, *Chem. Ber.*, **99**, 94 (1966).