Carbon-13 NMR Investigation of the Protonation and Quaternization of Azoloazines with a Bridgehead Nitrogen

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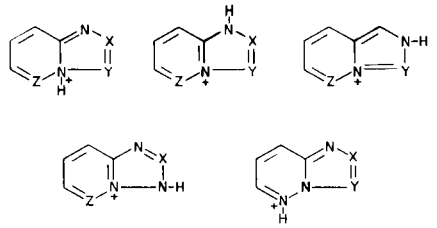
Carbon-13 nmr techniques have been employed to study imidazo[1,2-*a*]pyridine, imidazo-[1,2-*b*]pyridazine, *s*-triazolo[4,3-*b*]pyridazine, and *s*-triazolo[1,5-*b*]pyridazine and their N-1 quaternized derivatives. The data on quaternized derivatives have been analyzed to determine the tautomeric structures possible in the protonated derivatives. The data suggest that protonation at the bridgehead nitrogen does not occur in these compounds and, of the possible tautomeric forms, the N-1 tautomer predominates.

J. Heterocyclic Chem., **13**, 1057 (1976).

Introduction.

The synthesis and reactions of imidazo[1,2-*a*]pyridine derivatives were reviewed in 1961 (1). Since then a number of improved laboratory procedures for the synthesis of derivatives have been reported (2). Electrophilic substitution reactions, such as bromination, nitration, and chlorination and hydrogen deuterium exchange occur most readily at position 3 (3-5). The proton spectra of a number of derivatives of this bicyclic system have been reported and discussed (2,3,6-8). The proton spectra of imidazo-[1,2-*b*]pyridazines and *s*-triazolo[4,3-*b*]pyridazines have also been reviewed recently (9).

The protonation and quaternization of azoloazines with a bridgehead nitrogen, *i.e.*, imidazo[1,2-*a*]pyridine, imidazo[1,2-*b*]pyridazine, *s*-triazolo[4,3-*b*]pyridazine and *s*-triazolo[1,5-*b*]pyridazine can conceivably occur at N_1, N_2, N_3, N_4 and N_5.



I. X Y Z C
IV. Z X X Y C
VII. Z X X Y C
X. Z Y X X C

It has been concluded by a comparison of uv spectra (10) and proton nmr spectra (11) that quaternization and protonation of imidazo[1,2-*a*]pyridines occur at N_1. Similarly, in imidazo[1,2-*b*]pyridazine derivatives, quaternization and protonation are thought to be taking place at N_1 (12).

In the *s*-triazolo[4,3-*b*]pyridazine series the site of quaternization is dependent on the substituents attached either to the five-or-six member ring. Quaternization of the parent system and its 6- and 7-substituted derivatives occur exclusively at N_1, while quaternization of 8- and 3-substituted or 3,8-disubstituted derivatives afforded a mixture of N_1- and N_2-methylated products (12,13). The evidence was obtained on the basis of nmr spectral correlations and chemical transformations.

The consequence of quaternization at N_1 in the imidazo-[1,2-*b*]pyridazine and *s*-triazolo[4,3-*b*]pyridazine series is the greater reactivity of the six-member pyridazine ring in comparison to the parent system. Hydrogenation of the C_7-C_8 double bond and subsequent formation of 5,6,7,8-tetrahydro products were carried out under milder reaction conditions than are required for the non quaternized species (14). Easier base abstraction of the proton at position 6 followed by cleavage of the N_4-N_5 bond resulting in the formation of 1-azolyl-2-cyano substituted ethene derivatives (15) and addition of hydrazine to the N_5-C_6 double bond, followed by N_5-C_6 bond cleavage and cyclization of the intermediate hydrazone to the pyrazoline ring (16)

Table I

CMR Data Azoloazines With a Bridgehead Nitrogen

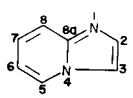
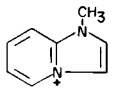
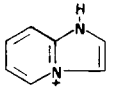
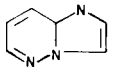
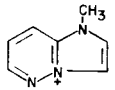
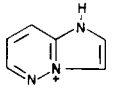
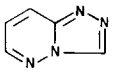
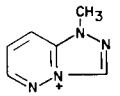
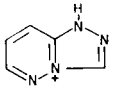
Compound	Chemical Shifts (a)													
	2	Δ2	3	Δ3	5	Δ5	6	Δ6	7	Δ7	8	Δ8	8a	Δ8a
 I	134.05		113.41		126.91		124.59		112.19		117.62		145.60	
Imidazo[1,2-*a*]pyridine														
 II	126.51	(+7.54)	114.72	(-1.31)	129.32	(-2.41)	117.08	(+7.51)	133.27	(-21.08)	111.42	(+6.20)	139.16	(+6.44)
 III	122.51	(+11.54)	115.38	(-1.97)	129.29	(-2.38)	117.12	(+7.47)	133.59	(-21.40)	112.06	(+5.56)	139.18	(+6.42)
 IV	133.49		116.69				143.79		117.33		125.50		138.40	
Imidazo[1,2-*b*]pyridazine														
 V	126.80	(+6.69)	118.16	(-1.47)			148.06	(-4.27)	129.65	(-12.32)	121.54	(+3.96)	135.79	(+2.61)
 VI	123.22	(+10.27)	118.11	(-1.42)			146.88	(-3.08)	126.63	(-9.30)	122.88	(+2.62)	136.50	(+1.90)
 VII			139.04				146.57		121.20		124.61		143.31	
s-Triazolo[4,3-*b*]pyridazine														
 VIII			138.70	(+0.34)			149.93	(-3.36)	128.83	(-7.63)	121.20	(+3.41)	140.67	(+2.64)
 IX			139.24	(-0.20)			148.64	(-2.07)	125.72	(-4.52)	122.98	(+1.63)	142.25	(+1.06)

Table I (continued)

Compound	2	Δ2	3	Δ3	5	Δ5	6	Δ6	7	Δ7	8	Δ8	8a	Δ8a
	152.50						144.55		123.04		125.92		144.05	
s-Triazolo[1,5-*b*]pyridazine	148.74	(+3.76)					146.44	(-2.91)	126.16	(-3.12)	124.62	(+1.30)	142.07	(+1.98)

(a) Relative to external TMS. Δ values taken with respect to parent compound in each series. Positive values refer to upfield shifts.

are only the most pronounced examples.

The growing body of knowledge regarding the chemistry of azoloazines and their quaternized derivatives has prompted us to examine the carbon-13 nmr (cmr) spectra of imidazo[1,2-*a*]pyridine, imidazo[1,2-*b*]pyridazine, *s*-triazolo[4,3-*b*]pyridazine, *s*-triazolo[1,5-*b*]pyridazine, and protonated and methylated derivatives. In this paper we attempt to correlate the cmr data with available chemical data.

EXPERIMENTAL

A. Spectroscopic Details.

All compounds were dissolved, without further purification, in reagent grade DMSO or DMSO-d_6. Dioxane was added (approximately 5% v/v) as internal standard. The cmr spectra were obtained on a Varian XL-100-15 spectrometer. Peak assignments were made by a combination of single frequency proton decoupling for most protonated carbons and by means of correlation diagrams for quaternary carbons and those methine resonance positions that could not be clearly assigned by decoupling techniques. Proton spectra were obtained on a Varian EM-390 instrument.

B. Compound Synthesis.

Methods described in the literature were used to prepare the compounds studied.

Imidazo[1,2-*a*]pyridine and 1-Methylimidazo[1,2-*a*]pyridinium Iodide.

A. M. Roe, *J. Chem. Soc.*, 2195 (1963).

Imidazo[1,2-*b*]pyridazine and 1-Methylimidazo[1,2-*b*]pyridizinium Iodide.

J. Kobe, B. Stanovnik, and M. Tišler, *Tetrahedron*, **24**, 239 (1968).

s-Triazolo[4,3-*b*]pyridazine.

N. Takahyashi, *J. Pharm. Soc. Japan*, **76**, 765 (1956); *Chem. Abstr.*, **56**, 1192 (1957).

1-Methyl-*s*-triazolo[4,3-*b*]pyridizinium Iodide.

M. Japelj, B. Stanovnik, and M. Tišler, *J. Heterocyclic Chem.*, **6**, 559 (1969).

s-Triazolo[1,5-*b*]pyridazine.

S. Polanc, B. Vercek, B. Sek, B. Stanovnik, and M. Tišler, *J. Org. Chem.*, **39**, 2143 (1974).

Protonated derivatives were obtained by addition of concentrated hydrochloric acid to the DMSO solution of the neutral species.

Results.

The chemical shifts of the compounds studied are given in Table I. In each case the parent compound is used to obtain the quaternization shifts, ΔC, at each position. In the case of the imidazo[1,2-*a*]pyridine (I) and its derivatives (II) and (III), one notes that quaternization, *i.e.*, methylation and protonation, produces an upfield shift at the adjacent carbons (C-2 and C-8a) which is consistent with quaternization data reported from our laboratory on

other heterocyclic species (17-20). Position C-3, which is a β-carbon to the quaternized nitrogen, is shifted downfield as expected (17-20). The Δ-values observed at C-5, C-6, C-7, and C-8 reflect cross-ring substituent effects that persist not only in the systems contained in Table I but also in all other quaternized azaindenes studied (21) as well as in purine ring systems (18-20). It is significant to note that the Δ-values for C-6 and C-7 move in opposite directions in II and III with the value for C-7 unusually large (-21.08 and -21.40 ppm, respectively). The Δ-value at C-5 exhibits the smallest cross ring perturbation. With the exception of the Δ-values at C-2, the chemical shift perturbations in II and III are remarkably similar.

An examination of the chemical shifts in imidazo[1,2-*b*]-pyridazine (IV) and V and VI reveals that quaternization produces upfield Δ-values at C-2 and C-8a but the Δ-shift values are significantly reduced at the latter position. The β-shift values (Δ3) in V and VI are nearly identical and are consistent in magnitude and sign with anticipated values. The Δ values at C-8 are positive, as they were in II and III, though of reduced magnitude. On the other hand Δ-values at C-6 are now negative. Again, the largest Δ-values in the six-member ring are found at C-7, but it is interesting to note that the magnitude of all Δ-values in the six-member rings of V and VI are less than one-half of the comparable values in II and III. This factor is apparently due to the presence of the additional nitrogen at C-5 which moderates the cross-ring substituent effects. Similar results are observed for the Δ-values in the six-member rings of VIII, IX, and XI when compared to the values in II and III. The fact that the Δ-values at C-3 in VIII and IX have opposite signs is probably not significant since the absolute magnitude of the values are quite small. The anticipated 1-2 ppm Δ-value for β-carbons (for C-3) in VIII and IX is not observed. It is also interesting to note that the Δ-value for C-2 in XI, while exhibiting the expected positive value for an α-carbon, is approximately one-third of the observed value in III.

Discussion.

The Δ-values for II and III, given in Table I, provide information not only as to the effects of quaternization of I but, in the case of III, clear evidence that protonation occurs at N-1 rather than N-4. This conclusion is reached by comparison of the Δ-values in II and III. In the case of the *N*-methyl derivatives (II) of imidazo[1,2-*a*]pyridine, the Δ-values at C-2 and C-8a are positive (+7.54 and +6.44, respectively) as expected (19,20) for carbons adjacent to the site of *N*-methylation while C-3 moves to lower field (-1.31 ppm) reflecting a shift change associated with a carbon located at a β-position relative to the site of quaternization. Identical relative shift changes are observed at C-2, C-3, and C-8a in III. The fact that Δ6 in III is positive cannot be used to argue that protonation has occurred at N-4 since, if that were the case, Δ2 and Δ3 would of necessity reverse sign as well as magnitude. Furthermore, it is noted that Δ6 in II is positive and of almost identical magnitude to that found in III and, hence, reflects significant cross-ring efforts due to quaternization at N-1. While the variations in absolute magnitude of Δ-values at C-2 and C-3 in II and III may appear to be rather large, similar variations in the magnitude of methylation and protonation shifts have been previously reported (19-20). It is significant to note, however, that the shift changes at C-2 and C-3 in II and III are essentially invariant; *i.e.*, $\frac{\Delta 2_{III}}{\Delta 3_{II}} = 1.53$ and $\frac{\Delta 3_{III}}{\Delta 3_{II}} = 1.50$, and, hence, reflect differences associated with methylation as compared to protonation. The cross-ring quaternization effects at individual carbon atoms in II and III seem to indicate that the six-member ring in imidazo[1,2-*a*]pyridine is insensitive to the nature of the substituent at N-1. However, the magnitude and sign of these Δ-values indicate that a relatively large variation in electronic structure is produced by quaternization of N-1. Position C-7 exhibits an unusually large downfield shift and the data suggest that the decrease in electron density usually accompanied by a downfield shift (22) is especially large at this position. It is interesting to note that the sign of the Δ-values alternate at C-5, C-6, C-7 and C-8.

The arguments employed for compounds II and III can now be applied to V and VI in order to determine the site for protonation of imidazo[1,2-*b*]pyridazine. A comparison of Δ-values at C-2, C-3 and C-8a for compounds II and V clearly indicates that a nitrogen at position 5 affects the chemical shift values at these positions but, with the exception of C-8a, has little affect on the respective Δ-values. However, the Δ-value at C-6 has reversed sign. The comparable values for Δ2, and Δ3, and Δ8a in III and VI represent compelling evidence that protonation has occurred at N-1 in VI. The possibility for protonation of IV at N-4 is eliminated by arguments similar to those made for III. The fact that Δ6 is negative in V (-4.27 ppm) and is of comparable value in VI (-3.08 ppm) provides sufficient evidence to demonstrate that protonation has occurred predominately at N-1 rather than N-5. However, the data do not strictly eliminate the possibility of the N-5 tautomeric species. This is suggested by the fact that at C-6, C-7, C-8 and C-8a, the Δ-values in VI are less than those found in V while no significant discrepancy is observed in II and III. However, the data indicate that the N-1 moiety is the predominant structure. It is also interesting to note that the magnitudes of the Δ-values at C-6, C-7 and C-8 in V and VI are approximately half those observed in II and III. The large (-12.32 ppm) Δ-value at

C-7, however, suggests a possible correlation with the greater reactivity noted earlier (14) in six-member ring resulting from methylation at N-1 of IV and VII.

The chemical shift data for *s*-triazolo[4,3-*b*]pyridazine (VII) and its *N*-methylated (VIII) and protonated derivatives (IX) can be used to explore the effects of quaternization of the parent species. One should, however, compare the Δ-values of VIII and those of V in order to ascertain if the addition of a nitrogen at position 2 produces significant cross-ring perturbations in the Δ-values. The Δ-values at C-8a are nearly identical (+2.61 and +2.64 ppm in V and VIII, respectively) while the variation in Δ-values at C-8 is 0.55 ppm. The variations at position C-6 and C-7 are somewhat higher, particularly at C-7 (-12.32 *vs* -7.63 ppm). The small change in Δ3 was not anticipated to be positive in value, nor of the magnitude observed and the value is probably due to subtle changes in electronic structure that are not strictly comparable between IV and VII. Evenso, the close correlation of the Δ-values at C-8a and C-6 in V and VIII provides useful data for evaluation of the Δ-values in IX. The fact that the Δ-values at C-6 and C-8a in II and III were essentially identical, whereas significant differences are observed for these chemical shift changes in VIII and IX, indicates that several tautomeric forms may exist for IX. The small, negative Δ-value at C-3 suggests that the N-2 and N-4 tautomeric forms do not make major contributions as such structures would produce positive Δ-values of several ppm. On the other hand, the N-5 tautomeric form would affect the Δ-value at C-6 and this parameter is shifted 1.3 ppm to higher field in IX than the corresponding value in VIII. These data suggest that the N-5 tautomer may make a significant contribution to the prototopic structures of IX. While the data do not permit quantitative estimates of various tautomeric forms the data suggest that the N-1 and N-5 tautomers predominate.

Only the protonated derivative (XI) of *s*-triazolo[1,5-*b*]-pyridazine (X) was studied as the 1-methyl derivative is not available. The Δ-values at C-2 and C-8a in XI indicate that protonation occurs at N-1 but one cannot eliminate the possibility that the N-3 tautomer also contributes to the prototopic structure. The nitrogen at position three eliminates the source of information as to the likelihood of protonation at N-4. As previously noted, the C-6 Δ-value suggests that the C-5 tautomer may also exist in solution. While data do not permit one to quantify the contribution from the possible tautomeric structures (N-1, N-3, N-4, or N-5) it is clear that contributions arise from the N-1, N-3, and N-5 protonated species. The ^{13}C-data provide no information as to the possible existence of the N-4 protonated species.

An examination of the Δ-values at C-7 in the compounds studied reveals an interesting trend in the methylated derivatives when comparing II and V and VIII. The unusually large Δ-value at C-7 in II is reduced by a factor of 2 due to substitution of a nitrogen at position C-5 and represents a significant perturbation of the cross-ring substituent affects produced by methylation of I at N-1. The additional substitution of a nitrogen at position C-2 (in VIII) produces another approximate 2-fold reduction in the Δ-value (as compound to V) suggesting the complex nature of the various inductive and resonance effects which combine to produce the substituent perturbations noted. The significant variations in the Δ-values for the protonated species VI and IX, as compared to the concommitant methylated derivatives (V and VIII), suggest that significant contributions are made by the N-5 tautomer for V and IX. The data provide no evidence for significant contributions arising from the N-4 tautomer. The data on XI suggest probable contributions from N-1, N-3, N-5 and do not permit us to rule out the possibility for an N-4 tautomeric form although, based on data for the remainder of the molecular species studied, such a contribution is not highly probable. Hence, the cmr data support the conclusion noted earlier (10-12) that quaternization of I and IV occurs at N-1 but the data further demonstrate that the N_5 tautomeric form of VI also makes a nontrivial contribution. A similar conclusion is reached for IX. The fact that quaternization of 3- and 8-substituted or 3,8-disubstituted derivatives of VII provides mixtures of the N_1 and N_2 methylated products (12,13) reflects steric effects at C-8 which hinder N_1-methylation due to a strong *peri*-interaction between the substituent and the incoming methyl group. In the parent species (VII), however, quaternization occurs at N_1 and possibly N_5 with no evidence derived from cmr data that the N_2 tautomer is formed (23). The cmr data thus suggest that the N-1 tautomeric form exists in all protonated species studied with contributions also from the N-5 and N-3 as well.

The cmr data thus obtained have proven useful for delineating significant substituent effects which provide information of significance in suggesting chemical reactivity of the species in question. Furthermore, the application of protonation and methylation studies to systems containing bridgehead nitrogens has proven effective in studies involving these unusual molecular species and has demonstrated the applicability of the quaternization effects on carbon-13 chemical shifts of nitrogen heterocycles.

Acknowledgment.

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(21) R. J. Pugmire, J. C. Smith, B. Stanovnik, and D. M. Grant, manuscript in preparation.

(22) See References 17 and 18 for discussion of factors influencing carbon-13 chemical shifts.

(23) Mechanistic studies of the borohydride reductions of azolopyridazines, *i.e.*, imidazo[1,2-*b*]pyridazine, *s*-triazolo[4,3-*b*]pyridazine and tetrazolo[1,5-*b*]pyridazine, have established that azolopyridazines should first form an immonium ion by protonation of the nitrogen at position 5. See P. K. Kadaba, B. Stanovnik and M. Tišler, *J. Heterocyclic Chem.*, **13**, (1976), in press. These results are supportive of the results obtained from our cmr data.