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Carbon-13 nmr data has been obtained on four hydroxy-azoloazines containing a bridgehead nitrogen atom, on the corresponding methoxide derivatives, and on selected anionic and cationic derivatives. These results have been interpreted in terms of the site of protonation of the parent hydroxy-compounds. A comparison of the anionic derivatives with those of the parent compounds demonstrate that the neutral parent hydroxy-species exist predominately in the "hydroxy form" rather than as the ionized species. The chemical shift data also provides information on the conformation of the hydroxy- and methoxy-groups in 8-hydroxy-6-methyl-*s*-triazolo[4,3-*b*]-pyridazine and 8-methoxy-6-methyl-*s*-triazolo[4,3-*b*]pyridazine.

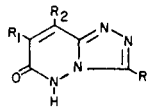
J. Heterocyclic Chem., **14**, 1403 (1977)

Introduction

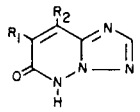
6-Hydroxy-*s*-triazolo[4,3-*b*]pyridazine (VII), 6-hydroxy-*s*-triazolo[1,5-*b*]pyridazine (II), 6-hydroxy-tetrazolo[1,5-*b*]pyridazine (XII) and their derivatives are reported to exist in the solid state in the lactam form (1,2). While not specifically stated in references 1 and 2, this conclusion is supported by ir data on the carbonyl absorption bands which appear in the region 1620-1640 cm^{-1} (1,2). The only exception is 8-hydroxy-6-methyl-*s*-triazolo[4,3-*b*]pyridazine (X) which exhibits an extremely weak band in this spectral region (3). It was concluded (3) on this basis that X exists predominately in the hydroxy form. It was observed also that the spectra of all "hydroxy" *s*-triazolo[4,3-*b*]pyridazines exhibit two broad bands in the region between 2600 cm^{-1} and 1700 cm^{-1} due to strong hydrogen bonding (3).

Methylation of 6-hydroxy-*s*-triazolo[1,5-*b*]pyridazine (II, R_1 = R_2 = H) afforded a mixture of 6-methoxy-*s*-triazolo[1,5-*b*]pyridazine (III) and 5-methyl-*s*-triazolo-[1,5-*b*]pyridazin-6(5*H*)one (IV) (2). Recently, the synthesis of mesoionic imidazo[1,2-*b*]pyridazine derivatives (XIV), methyl group migration from oxygen at C-6 to N-5 and N-1 to 6-methoxy-2-phenylimidazo[1,2-b]pyridazine (4) and formation of mesoionic-*s*-triazolo[4,3-*b*]pyridazine and derivatives (XV) (5) were reported.

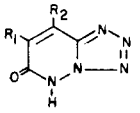
On the basis of this experimental evidence, one can



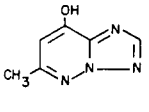
VII



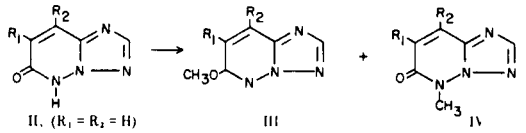
II



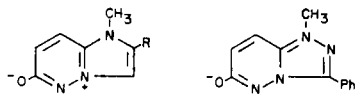
XII



X

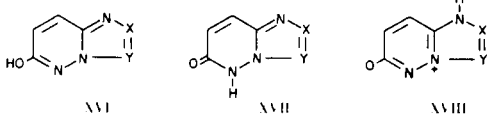


II, (R_1 = R_2 = H) III IV

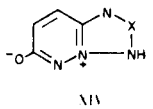


XIV, (R = H, Ph) XV

conclude that 6-hydroxy derivatives of *s*-triazolo[4,3-*b*]-pyridazine, *s*-triazolo[1,5-*b*]pyridazine, and tetrazolo[1,5-*b*]pyridazine could exist in the following tautomeric forms:



XVI XVII XVIII



XIX

X = N, Y = CH
X = CH, Y = N
X = Y = N

The carbon-13 magnetic resonance (cmr) data obtained on azoloazines with a bridgehead nitrogen and their methylated and protonated derivatives (6) have demonstrated that the site of protonation can be evaluated in the same manner as previously exhibited (7-9) in a wide variety of nitrogen heterocycles. This previous work has been extended to study the structure of the hydroxy azolopyridazines (II, VII, X, and XII) by means of cmr techniques.

EXPERIMENTAL

A. Spectroscopic Details.

All compounds were dissolved in reagent grade DMSO or DMSO-D_6. Dioxane was added (approximately 5% v/v) as the internal standard. The cmr spectra were obtained on a Varian

Table I

Chemical Shifts of Selected Azoloazine Derivatives (a)

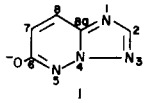
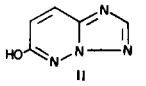
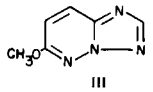
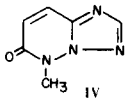
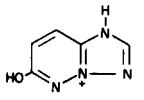
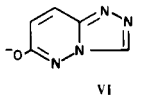
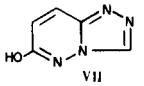
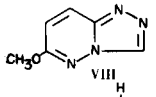
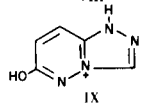
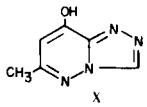
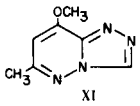
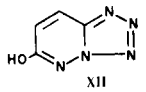
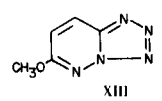
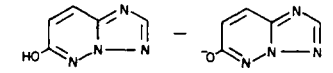
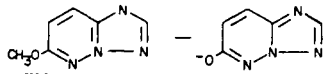
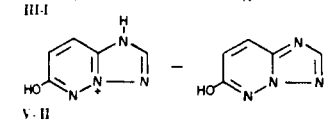
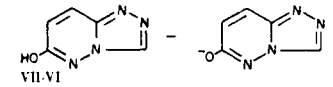
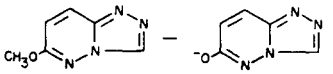
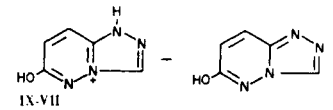
Compound	Position 2	3	6	7	8	8a
 I	147.52	--	167.03	122.20	124.76	138.30
 II	150.91	--	160.44	117.08	127.36	141.12
 III	151.17	--	160.34	117.12	127.16	141.51
 IV	148.92	--	157.29	125.47	126.63	138.08
 V	147.25	--	161.51	119.78	125.99	139.06
 VI	--	137.09	167.20	121.89	125.65	142.46
 VII	--	138.31	160.85	116.83	126.27	142.38
 VIII	--	138.83	160.93	116.63	126.17	142.49
 IX	--	138.34	162.72	122.80	124.15	140.58
 X	--	139.17	156.68	101.75	152.31	140.25
 XI	--	139.21	156.67	99.46	153.20	139.67
 XII	--	--	162.54	120.84	126.18	141.09
 XIII	--	--	162.40	120.87	126.03	141.43

Table II

Comparison of Chemical Shift Changes for Hydroxy, Methoxy and Protonated Methoxy Derivatives of *s*-Triazolo[1,5-*b*]pyridazine and *s*-Triazolo[4,3-*b*]pyridazine

Compound Pairs	Chemical Shift Changes (a) Δ2	Δ3	Δ6	Δ7	Δ8	Δ8a
 II-I	3.39	--	-6.59	-5.12	2.60	2.8
 III-I	3.65	--	-6.69	-5.08	2.40	3.2
 V-II	-3.66	--	1.07	2.70	-1.37	-2.0
 VII-VI	--	1.22	-6.35	-5.06	0.62	-0.0
 VIII-VI	--	1.74	-6.27	-5.26	0.52	0.0
 IX-VII	--	0.03	1.87	5.97	-2.12	-1.8

(a) Negative values represent shifts to higher fields.

XL-100-15 spectrometer. Peak assignments were made by a combination of a single frequency decoupling for most of the protonated carbons and by means of correlation diagrams for quarternary 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 and JEOL JNM C60-HL instrument.

B. Compound Synthesis.

Methods previously described in the literature were used to prepare the following compounds:

6-Hydroxy-*s*-triazolo[4,3-*b*]pyridazine.

N. Takahayashi, *J. Pharm. Soc. Japan*, 76, 765 (1965); *Chem. Abstr.*, 51, 1192 (1957).

6-Methoxy-*s*-triazolo[4,3-*b*]pyridazine.

N. Takahayashi, *J. Pharm. Soc. Japan*, 75, 1242 (1955); *Chem. Abstr.*, 50, 8655 (1956).

6-Hydroxy-*s*-triazolo[1,5-*b*]pyridazine.

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

6-Methoxy-*s*-triazolo[1,5-*b*]pyridazine.

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

5-Methyl-*s*-triazolo[1,5-*b*]pyridazin-6(5*H*)one.

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

6-Hydroxytetrazolo[1,5-*b*]pyridazine.

T. Itai and S. Kamiya, *Chem. Pharm. Bull.*, 11, 348 (1963); *Chem. Abstr.*, 59, 8734 (1963).

6-Methoxytetrazolo[1,5-*b*]pyridazine.

N. Takahayashi, *J. Pharm. Soc. Japan*, 75, 1242 (1955); *Chem. Abstr.*, 50, 8655 (1956).

8-Hydroxy-6-methyl-*s*-triazolo[4,3-*b*]pyridazine.

C. Bulow and F. F. Weber, *Ber.*, 42, 2594 (1909).

8-Methoxy-6-methyl-*s*-triazolo[4,3-*b*]pyridazine.

French Patent 1,248,409 (1960); *Chem. Abstr.*, 56, 10160 (1962).

Anions of the species studied were obtained by adding excess concentrated sodium hydroxide to the DMSO solutions containing the neutral molecular moiety. The respective cations were likewise obtained by means of adding excess concentrated hydrochloric acid.

Results.

The ^{13}C chemical shifts of the azoloazines studied are given in Table I and portrayed graphically in Figures 1-3. A close examination of the chemical shift patterns in

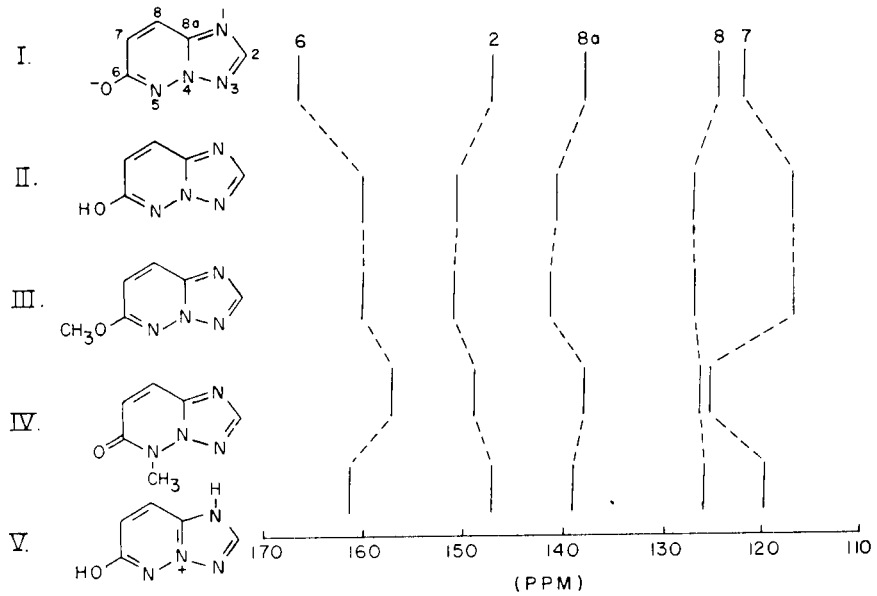


Figure 1. Correlation diagram of Carbon-13 chemical shifts for derivations of *s*-triazolo[1,5-*b*]pyridazine. All chemical shifts are taken with respect to external TMS.

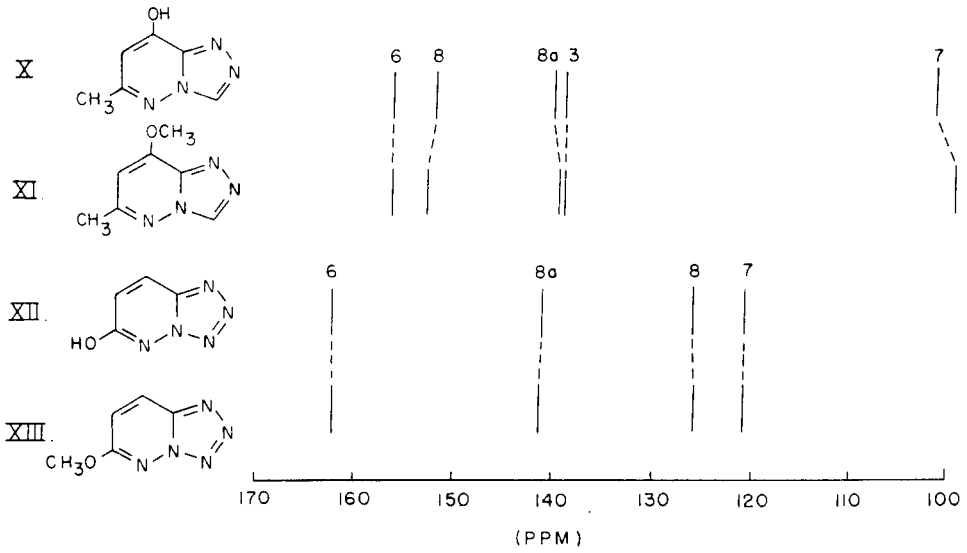


Figure 2. Correlation diagram for Carbon-13 chemical shifts for derivations of *s*-triazolo[4,3-*b*]pyridazine.

Figures 1 and 2 of derivatives of *s*-triazolo[1,5-*b*]pyridazine and *s*-triazolo[4,3-*b*]pyridazine provides information regarding the effects of protonation and methylation of I and VI. The chemical shift changes portrayed in Figures 1 and 2 are tabulated in Table II. These data illustrate the chemical shift change relative to the anionic species for the hydroxy, methoxy and protonated hydroxy derivatives of I and VI. It is significant to note that whereas change occurs in the resonance positions of II vs I and VII vs VI, the chemical shifts of the II-III and VII-VIII molecular pairs are essentially the same. In Figure 3, one observes that the chemical shifts of the pair XII-XIII likewise do not exhibit significant variations. In the case of the X-XI pair no appreciable chemical shift change is noted at C-3, C-6, and C-8a whereas the C-7 and C-8 positions are perturbed with the largest effect observed at C-7.

The molecular pair-wise comparisons of the anions (I and VI) of the hydroxide derivatives (II and VII) and methoxy derivatives (III and VIII) of *s*-triazolo[1,5-*b*]-pyridazine and *s*-triazolo[4,3-*b*]pyridazine as well as the pair-wise shift comparisons of the protonated (V and IX) species of II and VII are given in Table II. The similarities in chemical shift changes in the I-II, I-III and VII-VI, VIII-VI pairs is indicative of similar chemical structures.

Discussion.

The similarity in ring carbon chemical shifts in the II-III, VII-VIII, and XII-XIII species seems anomalous if

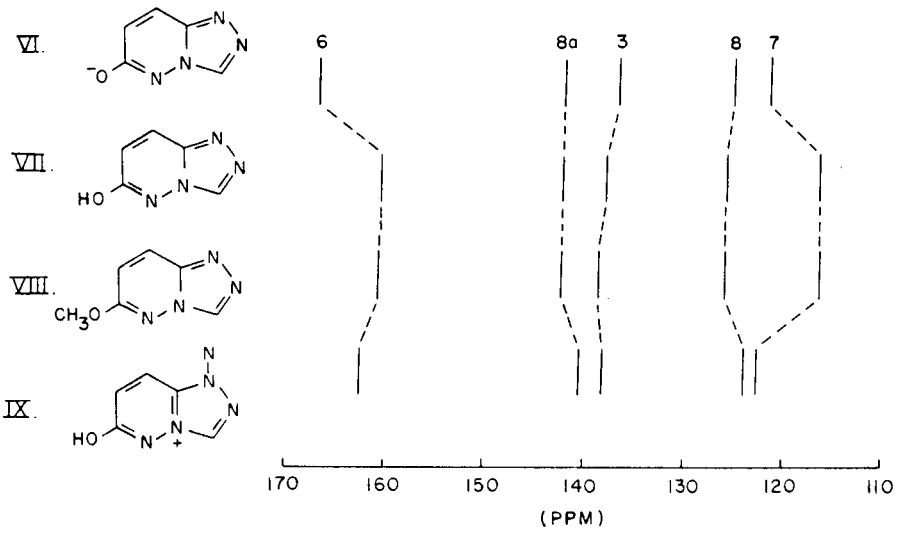


Figure 3. Correlation diagrams for Carbon-13 chemicals for 6-methyl derivatives of s-triazolo[4,3-*b*]pyridazine and derivatives of tetrazolo-[1,5-*b*]pyridazine.

one assumes that the hydroxy derivatives exist primarily in the anionic form. An examination of the cmr data of the anionic species, I and VI, as compared to II-III and VII-VIII, respectively given in Table II suggests that this assumption cannot be valid. Chemical shift changes of 6.59 and 6.69 ppm to higher field are observed for the C-6 resonance position in the I-II and I-III pairs respectively, while upfield shifts of 6.35 and 6.27 ppm are observed for the VII-VI and VIII-VI pairs. Upfield shifts at C-1 of 12.7 and 9.4 ppm have been reported for phenol and anisole, respectively when compared to the sodium pheolate salt (10). Hence, the data on the compounds studied in this work suggested that the hydroxy derivatives exist predominantly in the -OH form. This conclusion has since been reinforced by means of x-ray crystallographic data which demonstrates that the hydroxy form exists in solid 6-hydroxy-*s*-triazolo[4,3-*b*]pyridazine (11). Since the chemical shift variation of C-1 in phenol and anisole is substantial (3.3 ppm) (10), one would not intuitively anticipate the C-6 resonance positions to be equivalent (within approximately 0.1 ppm) in the hydroxy-methoxy pairs investigated (II-III, VII-VIII, and XII-XIII). The observed chemical shift similarities in the azoloazine hydroxy-methoxy pairs investigated are apparently not due to substituent affects alone.

The data portrayed in Figure 1 also provide interesting information regarding the prototropic structure of the cationic species V. The tabulated data in Table II for the protonation shifts in II are within 0.1 ppm of the protonation values observed at C-2, C-8, and C-8a in the parent ring system (s-triazolo[1,5-*b*]pyridazine) (6). The tabulated chemical shift changes at C-6 and C-7 given in Table II are of similar sign and comparable magnitude to the corresponding shift changes reported in reference 6. The data thus suggests that protonation of V occurs predominately at N-1 but one cannot, as previously discussed (6), rule out the possibility of minor contributions from the N-3, N-5, and perhaps N-4 tautomeric species. The chemical shift changes observed upon protonation of VII are similarly consistent with those observed previously (6) for methylation and protonation of *s*-triazolo[4,3-*b*]pyridazine. The data on the pair VII-IX indicates that protonation of VII occurs primarily at N-1 and rules out any significant contribution from the N-2 tautomeric form. However, as previously noted (6), the chemical shift data does not eliminate the possibility of a modest contribution from the N-5 tautomer although the steric hindrance of the hydroxyl group at C-6 might be expected to reduce the population of this species as compared to the parent ring system (*s*-triazolo[4,3-*b*]pyridazine).

A comparison of the chemical shifts of the hydroxy-methoxy pair X-XI points out an interesting anomaly in the data of these two molecular species as compared to the other three such molecular pairs (II-III, VII-VIII and XII-XIII) which were studied. Whereas insignificant variation in chemical shifts are observed at all carbons in the latter three molecular pairs, such is not true at C-8 and particularly C-7 in X and XI. The upfield shift of 2.3 ppm at C-7 in XI, as compared to X, is significant. In considering the cmr data for anisole and phenol, one observes that the *ortho* position in anisole is shifted 1.7 to 2.9 (12) ppm to higher field as compared to phenol. This upfield shift can be explained on the basis of differences in the steric interaction of the substituent with the C-2 proton. In a series of 2-alkylsubstituted anisoles, Buchanan, *et al.*, (13) found that the resonance position of C-6 moves upfield *ca.* 3 ppm due to alkyaltion at C-2. These authors suggest a possible rationale for this effect as a closer spatial

approach of the methoxy carbon to C-6 as a result of increased steric crowding at C-2 and a resultant γ-steric interaction (13,14). This type of steric crowding is even more pronounced in data reported by Highet and Edwards (15) in 1-methoxynaphthalene where the C-2 carbon is moved further upfield (by approximately 6 ppm) than one would expect from simple substituent considerations. A possible explanation is the interaction of the peri-hydrogen (at C-8) with the methoxy group which would force the methoxy group into a *trans*-configuration (relative to C-8) and thus increase the steric crowding at C-2 as well as at C-8. Support for this conclusion is obtained by noting that C-8 moves 1.8 ppm upfield in 1-methoxy as compared to the 1-methyl derivative of naphthalene (16), apparently due to increased steric crowding of C-8 by the methoxy group.

The preceding chemical shift data can be used in conjunction with chemical evidence to rationalize the chemical shifts observed at C-7 in X and XI. Hayashi, *et al.*, (17) reported that *N*-oxidation of monoalkoxypyridazines with alkoxy groups attached to position C-3 always occurs at the remote nitrogen, N-1, rather than the proximate nitrogen (N-2). Otomasu, *et al.*, (18) have investigated the geometrical arrangement of alkoxy substituents relative to the *N*-oxide group in pyridazines by means of dipole moment measurements. These authors presented evidence for a "*cis*"-arrangement, *i.e.*, a conformation in which the attached alkoxy group is oriented toward the proximate nitrogen atom. Such an arrangement is sterically less perturbed than the "*trans*"-conformation with the alkoxy group oriented toward the hydrogen at C-4 or an out of plane orientation. Such a *trans* orientation is probably favored for both the hydroxyl and methoxy groups in X and XI, respectively, since the absence of a hydrogen at position N-1 eliminates the sterically unfavorable *peri*-interaction. Hence, the hydroxyl group in X will probably preferentially orient to the *cis*-position and such an orientation may even be enhanced by means of intramolecular hydrogen bond formation with the electronegative nitrogen N-1 (10). Based on the experimental data cited in References 17 and 18, the *cis*-orientation of the methoxy group at C-8 in XI may still predominate. However, steric effects of the less favored *trans*-orientation would be expected, based on chemical shift data cited in References 12-16, to shift C-7 to higher field if the *trans*-form made a significant contribution to the ring conformation of the methoxy group. The 2.3 ppm upfield shift at C-7 in XI, as compared to X suggests that the methoxy group is less readily accommodated in the *cis*-form than the hydroxy derivative and that the population of the *trans*-form thus substantially increases relative to X.

The cmr data reported on the hydroxy derivatives of azoloazines thus have been useful in demonstrating that the molecular species exist primarily in the hydroxy form rather than the ionic state. The chemical shift data also are consistent with other experimental data regarding the *cis*-orientation of the hydroxy group in X and further demonstrates the power of carbon-13 spectroscopy in the investigation of chemical structural problems.

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