Diazo-, Azo-, and Azidoazoles. IV. Influence of Substituents on the 2-Azidoimidazole/Imidazo[1,2-*d*]tetrazole Equilibrium

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The effect of various common groups on the equilibrium **3** ⇌ **4** is discussed based on the Hammett substituent constants and the values of field and resonance constants calculated by Hansch, *et al.* *N*-Chloroacetyl, dichloroacetyl and trichloroacetyl derivatives of 2-azidoimidazole were also prepared. The shifting of equilibrium to the tetrazole form does not depend on the whole electron-attracting effect of a group, but it is mainly governed by its resonance electron-withdrawing ability.

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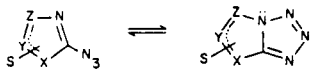
The azapentalenic systems have been the subject of a number of studies aimed at assessing their possible aromatic nature (1a-d). In an earlier work (2), we suggested the use of the azido/tetrazole equilibrium in the azole series (**1** ⇌ **2**) as a measure of the relative thermodynamic stability of 3a-azapentalenic systems (**2**), a stability which will be largely related to the higher or lower aromaticity of these bicyclic systems.

Scheme 1

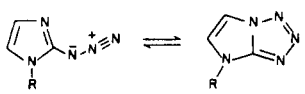


1 2

X, Y or Z = N or CH

On the other hand, all azidoazoles of type **1** which are known have spectroscopic properties typical of azido derivatives, but very recently (2-3) it was found that *N*-acetyl-2-azidoimidazole (**3**, R = acetyl) is an important exception, because this compound exists as a tautomeric mixture of the azide form and the tetrazole form. To explain this fact and to relate it to the above comments on

Scheme 2



3 4

the stability of azapentalenic systems, it appeared appropriate to study the effect of different groups on the referred equilibrium **3**⇌**4**.

Table I shows the nmr spectra of the various compounds which were synthesized. If together with the compounds shown in Table I we consider 2-azidoimidazole and its derivatives R = acetyl, R = methyl and R = 2,4-dinitrophenyl prepared by us at an earlier data (2), we then obtain data which will permit us to relate the equilibrium constant to the nature of the R group.

If we accept the simplification that the relative steric effects must not be very important, the influence that each substituent will have on the equilibrium will be a function of its electron-withdrawing or electron-donating ability.

Table II shows the values of Hammett constants σ_m and σ_p (4) corresponding to the groups used by us, or, in default thereof, to related groups; the third column includes the differences σ_p-σ_m which represent, to a first approximation, a qualitative measure of the resonance electron-withdrawing ability of the various substituents; the fourth and fifth columns give the values calculated by Hansch, *et al.*, (4) for field (*F*, inductive effect) and resonance (*R*, mesomeric effect) constants (5). The groups in the Table were arranged (approximately) according to this latter parameter.

As can be seen from Table II, we can establish a direct qualitative relationship between R (or σ_p-σ_m) and K_T values, if the case R = tosyl is excepted. The explanation of this exception lies perhaps in the high *F* value for this substituent. A reasonable assumption would be to think that the resonance electron-withdrawing groups (see **5**) favour the formation of the bicyclic system, while the highly electron-withdrawing groups by the inductive effect

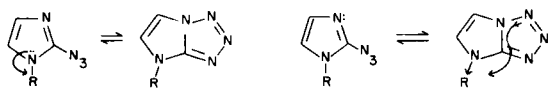
Table I

Nmr Spectra (a) of **3** ⇌ **4** in Dimethylsulfoxide-d_6

	3	**4**	$K_{35}°$
R = $SO_2\phi Me$ (b)	H_4 = 6.90 (d) H_5 = 7.53 (d) J_{45} = 1.9 H_A = 7.90 (d) H_X = 7.51 (d) J_{AX} = 8 Me = 2.40		
R = COOEt	H_4 = 6.89 (d) H_5 = 7.37 (d) J_{45} = 1.8 CH_2 = 4.37 (q) CH_3 = 1.31 (t) J_{Et} = 7.3	H_4 = 7.97 (d) H_5 = 8.32 (d) J_{45} = 2.8 CH_2 = 4.46 (q) CH_3 = 1.38 (t) J_{Et} = 7.3	0.16
R = CHO	H_4 = 7.01 (d) H_5 = 7.52 (d) J_{45} = 1.8 CHO = 9.02	H_4 = 7.98 (d) H_5 = 8.15 (d) J_{45} = 2.8 CHO = 9.19	~0.03
R = CONHϕ	H_4 = 6.94 (d) H_5 = 7.50 (d) J_{45} = 1.8 NH = 8.64 ϕ = 7.44 (m)		

(a) Chemical shifts in δ; coupling constants in hertz. (b) Sample temperature = 15°.

Scheme 3



5 6

(through space and sigma bonds, see **6**) play the opposite role.

To check this assumption we have prepared the three *N*-chloroacetyl derivatives of 2-azidoimidazole, the nmr spectra and azido/tetrazole equilibrium constants of which are shown in Table III.

While to the best of our knowledge no experimental values of the Hammett constants of groups chloroacetyl, dichloroacetyl, and trichloroacetyl are reported in the literature, it is logical to assume that the introduction of new chlorine atoms will alter preferentially the inductive attracting nature of the group, without the value of *R* changing too much (6).

The KT values obtained agree with the above. Thus, on changing from R = acetyl to R = trichloroacetyl, KT decreases in such a manner that in the latter compound the tetrazole form can hardly be detected.

In conclusion, it can be stated that the substituents which reduce the aromaticity of the imidazole ring, due to their resonance electron-withdrawing ability, favour the formation of the bicyclic system, and the optimum case is that where a high mesomeric effect is accompanied with a moderate inductive effect. According to literature data, the acetyl group is the best, among the more common groups, that combines these two characteristics.

EXPERIMENTAL

Melting points were determined on a Buchi apparatus and are uncorrected. Boiling points were determined at the indicated pressure on a Buchi furnace. The magnetic resonance spectra have been recorded on a Perkin-Elmer R-12B.

2-Azidoimidazole.

2-Azidoimidazole was obtained by adding an aqueous sodium azide solution to a freshly prepared solution of imidazole-2-diazonium sulfate (7): 1.32 g. of 2-aminoimidazole sulfate dissolved in 20 ml. of 2*M* sulfuric acid at -10° were diazotized with a solution of 0.75 g. of sodium nitrite in a small volume of water; then a saturated aqueous sodium azide solution was added dropwise (in the hood) until gas evolution ceased.

The resulting solution was neutralized with sodium bicarbonate and five extractions with a similar volume of ether were carried out. The ethereal solution was dried over magnesium sulfate, and the solvent removed to leave the expected product, dec. 140° (7), with a 90-95% yield.

2-Azido-1-tosylimidazole.

2-Azidoimidazole (272.5 mg., 2.5 mmoles) and tosyl chloride (190 mg., 1 mmole) were refluxed in 150 ml. of methylene chloride for 48 hours under an anhydrous nitrogen atmosphere, protecting the mixture from the light. The suspension was cooled to *ca.* 0°, filtered under nitrogen (the insoluble material consisting of 2-azidoimidazole hydrochloride and some recovered 2-azidoimidazole), and the methylene chloride solution concentrated with a rotavapor, protecting it from the moisture with a phosphorus pentoxide tower (8). The residue was treated with 20 ml. of carbon tetrachloride, filtered under nitrogen, and the solvent removed *in vacuo* as mentioned above, giving 145 mg. (55% yield based upon tosyl chloride) of 2-azido-1-tosylimidazole, dec. 98°.

Anal. Calcd. for $C_{10}H_9N_5O_2S$: C, 45.62; H, 3.44; N, 26.60. Found: C, 45.48; H, 3.26; N, 26.62.

2-Azido-1-(ethoxycarbonyl)imidazole.

2-Azidoimidazole (109 mg., 1 mmole) was dissolved in 50 ml. of methylene chloride at reflux, 48 μl. (0.5 mmoles) of ethyl chloroformate were added, and smooth reflux under dry nitrogen maintained for 24 hours, protecting the mixture from the light. The insoluble material (2-azidoimidazole hydrochloride) was recovered, while the filtrate was concentrated with a rotavapor. The residue was dissolved in 10 ml. of carbon tetrachloride and filtered under nitrogen. Finally, the solvent was removed *in vacuo* giving an oil (85% yield referred to chloroformate), b.p. 150-152° (furnace) at 1 mm.

2-Azido-1-formylimidazole.

2-Azidoimidazole (109 mg., 1 mmole) was dissolved in 50 ml. of methylene chloride and an equivalent amount of acetic formic anhydride (9) was added. The solution, magnetically stirred, was

Table II

Hammett Substituent and *F-R* Constants *versus* Experimental Equilibrium Constant

	σ_m	σ_p	σ_p-σ_m	F	R		$K_{35°}$ (DMSO)
COMe	0.38	0.50	0.12	0.32	0.20	COMe	0.48
$SO_2\phi$	0.61	0.70	0.09	0.56	0.18	$SO_2\phi$Me	
COOEt	0.37	0.45	0.08	0.33	0.15	COOEt	0.16
CHO	0.35	0.42	0.07	0.31	0.13	CHO	0.03
CONHMe (a)	0.35	0.36	0.01	0.34	0.05	CONHϕ	
picryl (b)	0.26	0.30	0.04	0.24	0.08	DNP (c)	
H	0.00	0.00	0.00	0.00	0.00	H	
Me	-0.07	-0.17	-0.10	-0.04	-0.13	Me	

(a) No values are reported in the literature for CONHϕ. However, having in mind that the phenyl group is somewhat less electron donating than a methyl group (4), it is likely that, for instance, R for group CONHϕ is slightly higher than 0.05. (b) No values are reported for 2,4-dinitrophenyl, while it appears logical to assume for it slightly lower F and R values than for picryl. (c) 2,4-dinitrophenyl.

Table III

Nmr Spectra (a) of Chloroacetyl Derivatives

		Deuteriochloroform	Acetone-d_6			Dimethylsulfoxide-d_6		
		3	3	4	K_T	3	4	K_T
R = $COCH_2Cl$	H_4	6.88 (d)	6.86 (d)	7.97 (d)	0.09 (0°)	6.95 (d)	8.17 (d)	0.33 (20°)
	H_5	7.40 (d)	7.45 (d)	8.10 (d)		7.56 (d)	8.41 (d)	
	CH_2	4.69	4.96	5.14		5.02	5.19	
	J_{45}	2.0	2.0	2.7		1.9	2.7	
R = $COCHCl_2$	H_4	6.90 (d)	6.94 (d)	8.04 (d)	~0.03 (0°)	7.00 (d)	8.35 (d)	0.24 (20°)
	H_5	7.42 (d)	7.53 (d)	8.21 (d)		7.67 (d)	8.49 (d)	
	CH	7.04	7.37	7.89		7.48	8.03	
	J_{45}	2.0	2.0	2.9		1.9	2.8	
R = $COCCl_3$	H_4	6.95 (d)	6.96 (d)					
	H_5	7.72 (d)	7.73 (d)			(b)	(b)	
	J_{45}	2.0	2.0					

(a) Chemical shifts in δ; coupling constants in hertz. (b) Decompose in dimethylsulfoxide.

maintained at 30° under nitrogen for 3 hours, then quickly washed with aqueous sodium bicarbonate, and finally stored over anhydrous magnesium sulfate. After filtering, the solution was evaporated to dryness and the residue dissolved in 15 ml. of carbon tetrachloride and filtered. Evaporation *in vacuo* gave the expected product (103 mg., 75% yield), b.p. 120-122° (furnace) at 1 mm.

2-Azido-1-(*N*-phenylcarbamoyl)imidazole.

2-Azidoimidazole (1 mmole) and phenyl isocyanate (108 μl., 1 mmole) were refluxed in 50 ml. of methylene chloride for 5 hours. The solution was concentrated, the residue dissolved in 20 ml. of carbon tetrachloride and the solution filtered under nitrogen. Evaporation of solvent *in vacuo* gave 205 mg. (90%) of product. Recrystallization in carbon tetrachloride/hexane affords an analytical sample, m.p. 63-64°.

Anal. Calcd. for $C_{10}H_8N_6O$: C, 52.63; H, 3.53; N, 36.83. Found: C, 52.82; H, 3.41; N, 36.65.

Chloroacetyl Derivatives.

2-Azidoimidazole (1 mmole) was dissolved in 50 ml. of methylene chloride and 0.5 mmoles of corresponding acid chloride were added. A smooth refluxing under dry nitrogen was maintained for 4 hours (monochloracetyl), 2 hours (dichloracetyl) and overnight (trichloroacetyl). The resulting mixtures were filtered under nitrogen and the filtrates concentrated with a rotavapor using a phosphorus pentoxide tower (10). The residues were dissolved in 10 ml. of carbon tetrachloride and treated as above, yielding the corresponding derivatives of 2-azidoimidazole: monochloroacetyl, m.p. 77-78°, 50% referred to acyl chloride; dichloroacetyl, b.p. 135-137° (furnace) at 1 mm, 65%; trichloracetyl, dec. 80°, 40%.

1-Acetyl-2-azidoimidazole has also been prepared by this method, alternatively to the system described by us previsouly (2).

REFERENCES AND NOTES

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(2) R. Granados, M. Rull and J. Vilarrasa, *J. Heterocyclic Chem.*, **13**, 281 (1976).

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(5) C. G. Swain and E. C. Lupton, *J. Am. Chem. Soc.*, **90**, 4328 (1968).

(6) In a fairly similar case, that of groups methylsulfonyl, difluoromethylsulfonyl and trifluoromethylsulfonyl, the values of F are, respectively, 0.54, 0.70 and 0.73, and those of R, 0.22, 0.22 and 0.26 (4).

(7) E. Meléndez and J. Vilarrasa, *An. Quim.*, **70**, 966 (1974).

(8) The product is very sensitive to moisture. Special care is needed, otherwise hydrolysis occurs during the work-up.

(9) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley Interscience, New York, 1967, p. 4.

(10) These compounds, particularly the trichloroacetyl derivative, are very easily hydrolyzed.