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BASE-CATALYZED HYDROGEN-DEUTERIUM EXCHANGE IN SOME 5-SUBSTITUTED BENZOTHIAZOLES AND IN THIAZOLO-[4,5-*c*]PYRIDINE. EFFECT OF SUBSTITUENTS AND POLAR EFFECTS OF THE AZA GROUP

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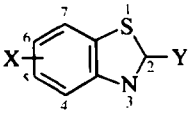
Abstract—The rates of base-catalyzed hydrogen-deuterium exchange at C-2 in some 5-substituted benzothiazoles and in thiazolo[4,5-*c*]pyridine were studied. Transmission through the thiazole ring of the effects of substituents in the benzothiazoles and of the polar effects of the aza group in the thiazolopyridine, was assessed from these data.

Several years ago Mangini[1] pointed out the similarity of an aza group with the C–NO_2 substituent, by comparing the reactivity of halogeno-heteroaromatic compounds, such as halogeno-pyridines or halogeno-quinolines with the analogous halogeno-nitrobenzenes or halogeno-nitronaphthalenes with common nucleophiles.

In principle one might expect values of σ_m and σ_p for the aza group to be found in tables of σ values for the more common substituents,[2] but this is not the case. In fact some difficulties occur in determining the polar effects of the aza group, which can easily be protonated, or undergo hydrogen bonding or internal solvation phenomena.[3]

For these reasons, the kinetic data of aza-derivatives, if compared with corresponding data for aromatic analogues, can include factors in addition to the polar effect and several discrepancies have been found in the past.[4]

We showed previously that the benzothiazole system **1** is very efficient in transmitting substituent effects from the benzo-ring to the group bonded in position 2 of the thiazole ring.[5]



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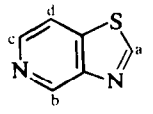
The effects are transmitted through the thiazole ring mainly by the aza in position 3, while the sulphur in position 1 does not make a significant contribution. This means that substituents in position 5 (meta in respect to the nitrogen which transmits the effects) can be considered meta to groups present in position 2; while position 6 can be considered as para. Sensitivity to substituent effects, as indicated by ρ values, is high; for example, the nucleophilic substitution of 2-halogeno-benzothiazoles[6] showed ρ values between 3 and 4 while the ρ for the acidity of some 2-carboxy-*X*-benzothiazoles[7] have a value 1·5 in methanol. The system seems to be favourable for detecting the substituent polar effect without any direct interaction between the substituent and the reaction centre. For example the effects of groups at C-4 can allow one to calculate polar σ_0 values,[8] free from direct steric effects, the centre at C-2 being more remote from the substituent than an ortho position on the benzene ring.

For the reasons explained, we investigated the reactivity of some thiazolopyridines. In this preliminary work we related the reactivity of thiazolo[4,5-c]pyridine **2** to that of some 5-substituted benzothiazoles.



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We moreover observed that the chemical, physico-chemical, and spectroscopic properties of thiazolopyridines (especially thiazolo [4,5-b]-, -[5,4-b]-, -[4,5-c]- and -[5,4-c]pyridines) are generally very little known,[9] although some of these compounds also show useful pharmacological activity.[10] For this reason, we report the IR, MS and ^{1}H-NMR of thiazolo[4,5-c]pyridine. The UV spectrum of this compound was examined by Ueda.[11]

RESULTS AND DISCUSSION

We have measured the rate of base-catalyzed hydrogen-deuterium exchange of thiazole at C_2 under standard conditions[12] for thiazolopyridine and some 5-*X*-substituted benzothiazoles (*X* = H, CH_3, Cl and

NO_2). Some pseudo first-order rate constants and the corresponding second-order rate constants are reported in Table 1.

Table 1. Pseudo first-order ($10^4 k\ sec^{-1}$) and second-order ($10^4 k$, $l\ mol^{-1}\ sec^{-1}$) rate constants for H/D exchange of 5-*X*-substituted benzothiazoles and thiazolo[4,5-c]pyridine (10^{-1} to 10^{-2} M) in CH_3OD with CH_3ONa (10^{-1} to 10^{-2} M) at 25°C

X	$10^4 k$/ sec^{-1}	$10^1[CH_3O^-]$	$10^4 k_s$/ 1 mol^{-1} sec^{-1}	log k_s	σ_m
H	0·50	4·13	1·21	$\bar{4}$·083	0·00
CH_3	0·32	4·55	0·70	$\bar{5}$·845	−0·07
Cl	0·32	0·64	5·00	$\bar{4}$·699	+0·37
NO_2	14·39	2·17	66·31	$\bar{3}$·822	+0·71
Thiazolo [4,5-c] pyridine	9·25	1·36	68·01	$\bar{3}$·833	—

The second-order rate constants in Table 1, related to the σ_m values of the substituents according to our previous conclusions, give a $\rho = 2{\cdot}2$ as shown in Fig. 1.

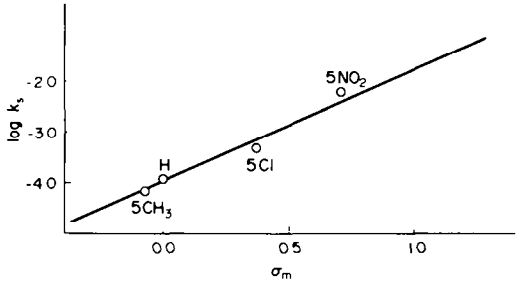

Fig. 1. The slope of σ_m-log k_s plot is $\rho = 2{\cdot}2$.

By comparison with data for the corresponding 5-substituted benzothiazoles one can evaluate the transmission of polar effects of the aza group through the thiazole ring in thiazolo[4,5-c]pyridine.

Certain facts should be noted. First, the sensitivity of the H/D-exchange reaction to the substituent in the benzo ring is relatively high, as indicated by ρ value; in fact when passing from 5-methyl to 5-nitrobenzothiazole the rate constants vary by a factor of two powers of ten. The reaction is hence suitable for evaluating the substituent effect. Second, the reactivity of thiazolo[4,5-c]pyridine is practically the same as that of 5-nitrobenzothiazole, indicating in the cases here examined a nearly complete equivalence between an aza and a C-NO_2 group, in accordance with Mangini's assumption.[1]

At present the base-catalyzed hydrogen-deuterium exchange of the 6-derivatives analogous are in progress.

EXPERIMENTAL

The IR spectrum (KBr disc) was recorded on a Perkin-Elmer 577 infrared spectrophotometer. The ^1H NMR spectra were recorded on a JEOL JNM-C-60 HL spectrometer using TMS as internal standard. The MS were obtained using a Hitachi Perkin-Elmer RMU-6D mass spectrometer with a direct inlet system. The temperature of the probe was 200°C and the energy of the ionization was 70 eV. Accurate mass measurements were carried out by the peak matching method.

Thiazolo[4,5-c]pyridine. This compound was synthesized following Takahashi, Ueda and Ichimoto's method[13] modified for direct conversion of 3-nitro-4-chloropyridine into 3-nitro-4-mercaptopyridine according to Kruger and Mann's method.[14]

Many of the fragmentations described are supported by the presence of metastable ions (m*), and others are indicated for to the benzolthiazoles[15] (fragment "a"), pyridines (fragment "b"), thiophenes and thiazoles[16] (fragment "c") fragmentations.

The ^{13}C NMR of thiazolo[4,5-c]pyridine and 5-substituted benzothiazoles is being studied.

Benzothiazole. The comercial product, supplied by Merck-Schuchardt, was distilled twice in vacuo for use in the kinetic measurements of isotopic exchange.

5-Methylbenzothiazole, 5-chlorobenzothiazole and 5-

Table 2. ^1H NMR chemical shifts ($\delta \pm 0{\cdot}02$ ppm; 60 MHz; TMS) and coupling constant (Hz) for thiazolo[4,5-c]pyridine (0·25 M) at 40°C in various solvents

Solvent	H_a(s)	H_b(s)	H_c(d)	H_d(d)	$J_{c,d}$
CCl_4	9·31	8·88	8·44	7·76	
$CDCl_3$	9·41	9·01	8·55	7·88	
CD_3OD	9·33	9·27	8·47	8·12	5·25
DMSO-d_6	9·57	9·42	8·60	8·27	
CD_3COCD_3	9·34[a]		8·55	8·12	

[a] In this case, for the "a" and "b" protons a singlet was observed.

Table 3. *m/e* values and relative intensities of the peaks by electron impact fragmentation of thiazolo[4,5-c]pyridine

28·0(8·8); 31·0(0·8); 32·0(3·0); 34·0(0·9); 36·0(1·1); 37·0(5·5); 38·0(13·8); 39·0(2·3); 40·0(1·4); 41·0(2·6); 44·0(4·2); 45·0(12·7); 47·0(1·0); 49·0(2·3); 50·0(4·9); 51·0(2·2); 52·0(5·0); 54·0(1·0); 56·0(1·9); 57·0(3·4); 58·0(2·6); 59·0(1·0); 62·0(1·0); 63·0(1·6); 64·0(7·0); 65·0(2·3); 68·0(8·4); 69·0(10·4); 70·0(1·9); 75·0(2·1); 76·0(2·6); 80·0(1·3); 81·0(12·6); 82·0(60·2); 83·0(7·4); 84·0(3·0); 85·0(1·3); 92·0(2·9); 103·0(0·9); 108·0(1·3); 109·0(34·8); 110·0(2·7); 111·0(1·7); 135·0(2·3); 136·0(100·0); 137·0(10·1); 138·0(5·1);

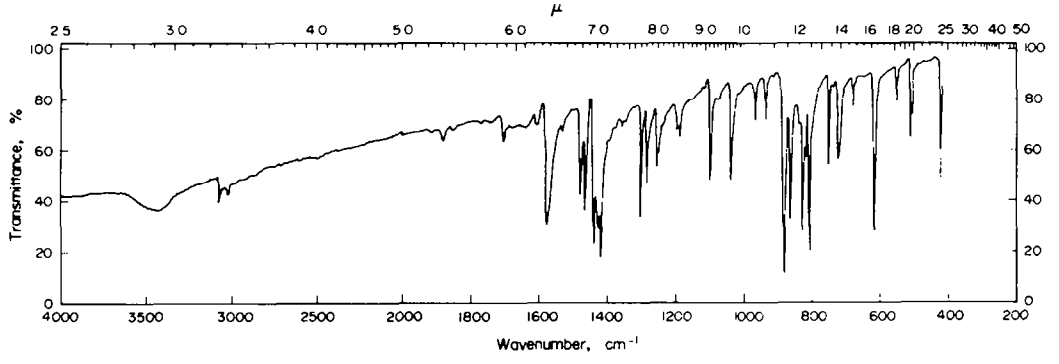

Fig. 2. IR of thiazolo[4,5-c]pyridine.

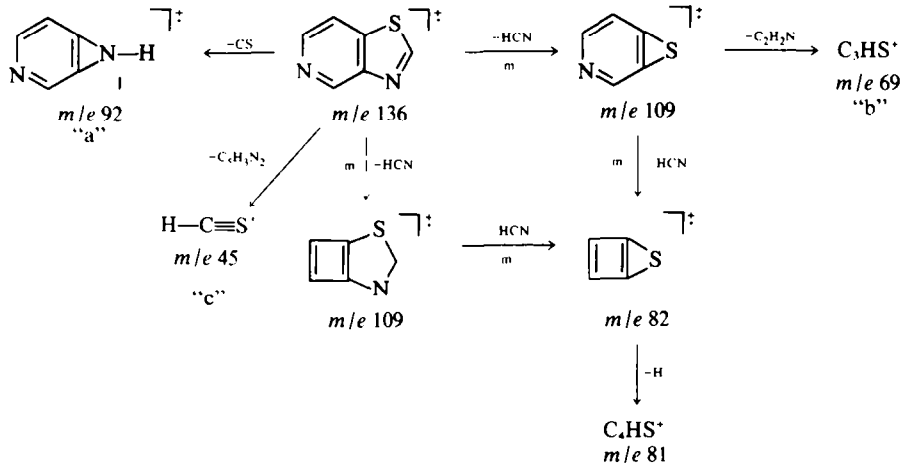

Fig. 3. The electron impact fragmentation pattern of thiazolo[4,5-c]pyridine.

nitrobenzothiazole. These compounds were prepared as reviewed by Todesco.[5-17]

Kinetic measurements of hydrogen-deuterium exchange. In a typical experiment, a solution of the substrate in CH_3OD and a solution of CH_3ONa in CH_3OD were kept in a water bath at 25°C (±0·1) for 2 h. After this time the solution of the CH_3ONa was added to the solution of the substrate. The resulting concentration of the substrate was 10^{-1} to 10^{-2} M and that of the CH_3ONa was 10^{-1} to 10^{-2} M. After suitable intervals the samples were withdrawn and poured into a mixture of water, ice, and methylene chloride. The organic layer was rapidly removed, dried over anhydrous sodium sulphate and the solvent was evaporated *in vacuo* without heating. The solid residue was dissolved with 0·5 ml of the appropriate deuterated solvent and the measurements of the extent H/D exchange were provided by NMR.[12] In the graphical derivation of the rate constants of Table 1, the pseudo first-order rate equation ($\ln c/c_0 = -kt$) was used. The initial concentration c_0 being substituted with A_0/n (A_0 is the intensity of the NMR signals of n non-exchangeable protons, in the substrate, selected as reference) and the concentration c being replaced by A (intensity of the NMR signal at time t for the proton signal under consideration). From these pseudo first-order rate constants, divided by [CH_3O^-], the second-order rate constants of Table 1 were obtained. In the graphical derivation of the ρ value of Fig. 1, the equation $\log k_x/k_H = \rho\sigma_m$ was used.

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