Kinetics of the Detritiation of a Series of 4- and 5-Substituted 2-([^{3}H]acetyl)thiophenes[1]

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A series of 4- and 5-substituted 2-([^{3}H]acetyl)thiophenes have been prepared and the kinetics of the hydroxide-catalysed detritiation studied at 25.0 °C. The second-order detritiation rate constants parallel those observed for the corresponding *meta*- and *para*-substituted acetophenones but as the reaction constant ρ is higher (1.61) the range of reactivity is much wider than that witnessed for the acetophenones.

Despite the fact that both aromatic and aliphatic ketones have been extensively used in studies of proton-transfer reactions[2,3] relatively little work has been carried out on the heterocyclics. Such studies could be of use in at least three different ways. Firstly, a comparison with the results obtained for other ketones would allow one to assess more fully the importance of heteroatom effects. Secondly, the effects of metal complexation with the heteroatom and hence on the reactivity of the ketone could be investigated; so far the only available results refer to the work carried out by Cox[4] on 2-acetylpyridine. Finally, in view of the relatively large number of ring systems available it would seem worthwhile studying the possibility of intramolecular catalysis.[5] Investigations of this kind have tended to concentrate on six-membered ring systems[6] and the observed effects have been found to be relatively small.

As far as rates of ionisation are concerned the acetophenones are amongst the most extensively studied ketones,[7-9] both halogenation (particularly bromination) and tritium-hydrogen exchange techniques having been used. They therefore form a good starting point for comparing the behaviour of heterocyclic ketones. In the present paper we report results for the hydroxide-catalysed detritiation of some 15 4- and 5-substituted 2-([^{3}H]acetyl)thiophenes and compare our findings with those obtained for the acetophenones.

Table 1. Hydroxide-catalysed detritiation rate constants for some 4- and 5-substituted 2-([^{3}H]acetyl)thiophenes at 25.0 °C together with comparable data for some *meta*- and *para*-substituted acetophenones

	Acetylthiophenes		Acetophenones[7]	
Compound No.	X	$10^3k^{T}_{OH^-}$/ $M^{-1}\ s^{-1}$	X	$10^3k^{T}_{OH^-}$/ $M^{-1}\ s^{-1}$
(1)	5-MeSO$_2$	79.3 ± 2.0		
(2)	5-NO$_2$	78.2 ± 1.8	*p*-NO$_2$	35.0
(3)	5-CN	60.0 ± 1.3	*p*-CN	23.7
(4)	5-I	7.9 ± 0.13	*p*-I	9.4
(5)	5-Br	8.77 ± 0.06	*p*-Br	9.1
(6)	5-Cl	8.15 ± 0.03	*p*-Cl	9.0
(7)	5-MeS	4.20 ± 0.02		
(8)	H	5.04 ± 0.09	H	5.4
(9)	5-Ph	5.03 ± 0.13		
(10)	5-Me	2.69 ± 0.02	*p*-Me	3.55
(11)	5-Et	2.69 ± 0.06		
(12)	5-OMe	1.35 ± 0.03	*p*-OMe	2.47
(13)	4-Me	4.12 ± 0.09	*m*-Me	4.53
(14)	4-Pr^i	3.96 ± 0.1		
(15)	4-Br	13.6 ± 0.05	*m*-Br	11.0

Experimental

Synthesis and Purification of Compounds.—Compounds (1) and (7),[10] (2),[11] (4),[12] (5), (6), (8), and (10),[13] (8) and (13),[14] (9),[15] (11),[16] (12),[17] (14),[18] and (15)[19] were prepared and/or purified according to the literature methods. (See Table 1 for numbering of compounds). The products gave correct analyses and n.m.r. spectra.

5-*Cyano*-2-*acetylthiophene* (3).—A mixture of 5-iodo-2-acetylthiophene (14.4 g) and copper(I) cyanide (5.7 g) was refluxed in dry pyridine (80 ml) for 2.5 h. After removal of pyridine *in vacuo*, the residue was extracted with boiling benzene, and the cold benzene filtered from the tar. Distillation of the benzene left a residue that was extracted with boiling ethanol [in which the copper(I) salts were insoluble], the ethanol solution was evaporated, and the residue chromatographed on silica gel (eluant, benzene–ethyl acetate 4:1) to give the nitrile: m.p. 79—80 °C (from light petroleum–benzene).

Tritiation Procedure.—Typically some 50 mg of substrate was dissolved in a small volume (*ca.* 3 ml) of dioxane, a pellet of NaOH added followed by tritiated water (10 μl, 50 Ci ml^{-1}), and the mixture kept in a sealed tube for up to 48 h at room temperature. The solution was then withdrawn and injected into a separating flask containing 200 ml of water and 15 ml of chloroform. The chloroform layer was separated off, dried (anhydrous Na$_2$SO$_4$) and the chloroform itself gently removed by passing a stream of nitrogen. The product was then taken up in [^{2}H$_6$]DMSO, the activity determined, and both the ^{1}H and ^{3}H n.m.r. spectra recorded. In all cases specific tritiation in the acetyl group was achieved.

Kinetic Measurements.—The detritiation studies were carried out in the same way as for the acetophenones.[7] Usually the sodium hydroxide concentration was varied ten-fold; quoted second-order rate constants ($k^{T}_{OH^-}$) are the mean of 3—5 determinations.

Results and Discussion

The application of the Hammett equation to five-membered heterocyclic compounds is not without difficulty.[20] One possibility is to consider the heteroatom as replacing a –CH=CH– link in the benzene ring and to equate the 2,5- and 3,4-positions with the *para*- and *meta*-positions, respectively, of

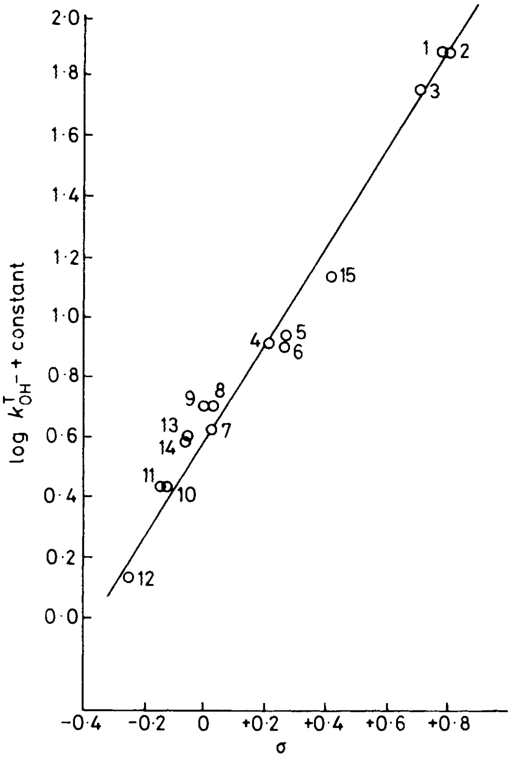

Figure. Plot of log $k^{T}_{OH^-}$ against σ for the 4- and 5-substituted 2-([^{3}H]acetyl)thiophenes. Numbers correspond to those given in Table 1

Table 2. Reaction constants (ρ) in H_2O at 25.0 °C for various heterocyclic acids

Compound	ρ	Reference
4- and 5-X-Pyrrole-2-carboxylic acids	1.65	22
5-X-Furoic acid	1.40	22
4- and 5-X-Thiophene-2-carboxylic acids	1.20 (*ca.* 1.0)[25]	23, 24
Selenophene-2-carboxylic acids	1.23	26
Tellurophene-2-carboxylic acids	1.20	27

the benzene ring. Alternatively, new σ values could be defined depending on the nature of the ring and the position of substituents with respect to both the reaction centre and the heteroatom.

The present results (Table 1) show that although acetylthiophene and acetophenone have virtually the same rate constants the effect of substitution at both the 4- and 5-position in the acetylthiophene is a good deal more marked than is the case for *meta*- and *para*-substitution in the acetophenones. This can be seen most clearly in the Hammett plot (Figure), which can be constructed by using σ_m values for the 4-substituents and σ_p values for the 5-substituents. An excellent correlation is observed, with a reaction constant ρ of 1.61 ± 0.06, considerably higher than the value (1.03) obtained for the corresponding acetophenones. This enhanced reaction constant has its counterpart in the equilibrium ionisation process (Table 2) where values in excess of unity are invariably found. Similar effects are observed when other properties, *e.g.*, infrared frequencies[21] ν(C=O) are investigated. Clearly the -S- group is superior to the -CH=CH- in transmitting electronic effects.

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