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1,1′-Thiocarbonyl-bis-pyrazoles

Part II.* Substituent Effects on Rates of Ethanolysis

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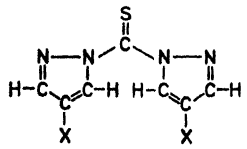
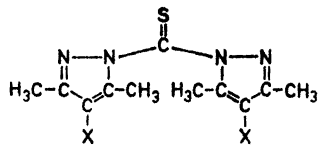
Ethanolysis of 1,1′-thiocarbonyl-bis-pyrazoles has been found to obey first order kinetics and lead to 1-ethoxythiocarbonyl-pyrazoles. The rate constants are strongly dependent on substituents, and a good linear correlation between log k and Hammett σ-values is observed, with a ϱ value of 4.8, which indicates a $B_{AC}2$ type of mechanism for the reaction.

N,*N*′-Carbonyl-bis-heteroaromatics are known to react readily with nucleophiles, and in some cases they have been found useful as reagents for transfer of carbonyl groups.[1,2] Some thiocarbonyl analogs are also known, *e.g.* the 3,5-dimethylpyrazole,[3] imidazole,[4] and benzimidazole [5] derivatives. A claim for the preparation of 1,1′-thiocarbonyl-bis-indazole [5] should be viewed with caution, since the product is described as colourless, whereas all other compounds of this class are yellow due to a distinct $n\rightarrow\pi^*$ band in the region 400—450 nm. In particular, 1,1′-thiocarbonyl-bis-imidazole has been employed for thiocarbonylation of amines [3,6] and hydrazines.[7] Walter [8] has devised a method to prepare thioamides from 1-thioacylimidazoles, which in turn are obtained from 1,1′-carbonyl-bis-imidazoles and dithiocarboxylic acids.

In general, the pyrazole derivatives are less reactive towards nucleophiles than the imidazole analogs, and the thiocarbonyl compounds are less reactive than the carbonyl analogs. Ried and Beck [3] reported that 1,1′-thiocarbonyl-bis-3,5-dimethylpyrazole (IIa) reacted with aliphatic and aromatic amines to give 1-thiocarbamoylpyrazoles and thioureas but that no reaction occurred with alcohols and phenols. We have studied the reaction of a series of 1,1′-thiocarbonyl-bis-pyrazoles (I—III) with ethanol. Compounds I a—e, IIe, and IIIa were found to react according to scheme A with a rate that was highly dependent on the substituent X, whereas the reactions of the other compounds were too slow to be studied at room temperature.

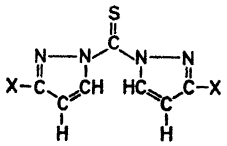
* Part I. *Acta Chem. Scand.* **22** (1968) 1655.





I, a, X = H
b, X = Cl
c, X = Br
d, X = I
e, X = NO_2

II, a–e as for I
f, X = $CO_2C_2H_5$



III, a, X = $CO_2C_2H_5$
b, X = Ph
c, X = 2′-thienyl

A: $Py_2CS + C_2H_5OH \rightarrow PyH + PyCSOC_2H_5$ (Py = 1-pyrazolyl)

IV, a–e as for I

EXPERIMENTAL

The preparation of compounds I–III has been described in Part I. For demonstration of the reaction path, one of the compounds IV was prepared in an unequivocal way:

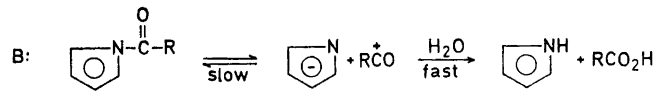
1-Ethoxythiocarbonyl-4-bromopyrazole (IVc). 4-Bromopyrazole (4.9 g) and freshly distilled ethyl chlorothionformiate [9] (4.0 g) were refluxed in benzene (150 ml) for 15 h. Evaporation and distillation under reduced pressure gave a fraction at 14 Torr and 144–146°, which crystallized from light petroleum (b.p. 40–60°) as colourless prisms, m.p. 49.5–51°, in 50 % yield. (Found: C 30.7; H 3.00; Br 34.0; N 11.9; S 13.6. $C_6H_7BrN_2OS$ (235.10) requires C 30.6; H 2.90; Br 34.8; N 11.8; S 13.6). λ_{max}: $n \rightarrow \pi^*$: 360 nm (ε=110), $\pi \rightarrow \pi^*$: 291 nm (ε=13 700) in ethanol.

The ethanol used for the solvolysis experiments was of spectroscopic grade, which was shaken with anhydrous sodium carbonate and distilled prior to use. The kinetic measurements were performed by monitoring the disappearance of the $n \rightarrow \pi^*$ absorption bands (see Part I) with an ultraviolet-visible spectrophotometer (alternatively a Hilger "Ultrascan" and a Unicam model SP 800) with an external recorder and a thermostatted cell compartment. The evaluation of the rate constants was performed according to Guggenheim,[10] and all reactions were found to obey first order kinetics. For one of the compounds, IIIa, the rate constants were measured at three concentrations, in the ratio 1:4:40, and were found to deviate by less than 1 %. Thus the reactions can be assumed to be pseudounimolecular. The ethanolysis of Ic was shown to follow scheme A, since the final spectrum of the reaction mixture exactly matched a superposition of the spectra of IVc and 4-bromopyrazole in ethanol at the same concentration. It can be safely assumed that the other systems follow the same path, at least in the first step, which is the one to which the measured rate constants apply.

Each reaction was conducted four times, and the maximum deviations from the mean rate constants were always less than 2.5 % and in most cases less than 1 %.

DISCUSSION

The mechanism of this reaction can be discussed in relation to the deacylation of *N*-acylheteroaromatics, which has been studied by Staab,[11,12] Scott,[13] and Hüttel and Kratzer.[14] Staab preferred a mechanism of type $B_{AC}1$,[15] with an ionisation as the rate-determining step (B), for the neutral hydrolysis of, among others, *N*-acetyl-imidazole, *N*-acetyl-1,2,4-triazole, and *N*-acetyltetrazole.



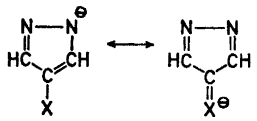
This interpretation was criticized by Scott,[13] who favoured a $B_{AC}2$ type of mechanism,[15] with a tetrahedral intermediate, for the ethanolysis of some 1-acyl- and 1-guanylpyrazoles, though without very strong evidence. Finally, Hüttel and Kratzer studied the neutral hydrolysis of a series of *N*-acetylpyrazoles and *N*-acetyl-1,2,3-triazoles. They observed a dependence of the rates on solvent polarity, which was not in agreement with path B, and also a retardation of the hydrolysis of *N*-acetylpyrazole in deuterium oxide by a factor of 3.4, which strongly supports a two-step bimolecular mechanism.

Table 1. Rate constants for ethanolysis at 25°C.

Compound	Rate constant ($min^{-1} \times 10^4$)
Ia (X = H)	9.75 ±0.05
Ib (X = Cl)	140 ±3
Ic (X = Br)	157 ±2
Id (X = I)	120 ±3
Ie (X = NO_2)	58 000 ±500
IIe (X = NO_2)	127 ±3
IIIa (X = $CO_2C_2H_5$)	723 ±7

The rate constants obtained in the present investigation are found in Table 1. At first sight, they seem to support equally well either of the two mechanisms under consideration. In the $B_{AC}1$ mechanism, electron-attracting substituents would stabilize the pyrazole anion, but they would also facilitate the formation as well as the decomposition of the tetrahedral intermediate in the $B_{AC}2$ mechanism. A decision between the two alternatives has been attempted by use of the Hammett equation.[16] It is true that its application to heterocyclic systems has not always been successful,[17–19] but several good correlations have also been reported.[18] Thus Hüttel and Kratzer [14] obtained a very good linear relation between the logarithms of the rate constants for hydrolysis of 1-acylpyrazoles and σ_p-values for substituents in position 4. For the thiocarbonyl-bis-pyrazoles it is assumed that log k for a $B_{AC}2$ mecha-

nism will correlate with σ_p-values for 4-substituents, since the reaction center is not directly conjugated with the 4 substituents but is attached to an atom so disposed. On the other hand, a $B_{AC}1$ mechanism will necessitate use of σ^--values,[20] since then the rate of the reaction will be directly affected by the strong conjugation in the pyrazole anion (C⟷D).



C D

Substituents in position 3 are *m*-related to N_1 by C_4—C_5, and *o*-related by N_2. Since the latter relation is *via* an N—N bond, which has a low double bond character, a σ_m-value should be appropriate for a $B_{AC}2$ mechanism, and possibly a σ_p-value for a $B_{AC}1$ mechanism. Linear least squares correlations have been made between the log *k*-values and six combinations of σ_m, σ_p, and σ^- (Table 2), and it is obvious that combination 4 (σ_m for position 3, σ_p for position 4) gives the best correlation, with R=0.9954 and ϱ=4.8. This result should favour a $B_{AC}2$ mechanism for the ethanolysis of the thiocarbonyl-bis-pyrazoles, which is also the most likely one in view of the structural similarity with the 1-acetylpyrazoles. The ϱ-value for the latter compounds is 2.8, which can be contrasted with 0.7 for the alkaline hydrolysis of substituted benzamides.[21] The different ϱ-values are to some extent due to different experimental conditions, but they must also reflect the greater sensitivity of acetylpyrazoles and in particular of thiocarbonylpyrazoles to polarisation by 4-substituents.

Table 2. Correlation of log *k* with Hammett σ-values.

Combination	1	2	3	4	5	6
Position 3	σ_m	σ_p	σ^-	σ_m	σ_m	σ_p
Position 4	σ_m	σ_p	σ^-	σ_p	σ^-	σ^-
R [a]	0.9436	0.9762	0.9806	0.9954	0.9765	0.9860
ϱ	5.26	4.51	2.68	4.82	2.76	2.77

[a] Correlation coefficient.

The very low rate of ethanolysis of the compounds of type II is probably due to a steric hindrance, since the normal Hammett σ-values hardly allow a polar effect of this magnitude. A considerable steric hindrance to coplanarity

is rather unlikely in view of the similarity of dipole moments and UV absorption spectra of compounds of type I and II (Part I). The effect of the methyl groups must be to cause a strong reduction of the accessible angle of approach for the ethanol molecules.

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