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Alkaline Hydrolysis of Quinolyl *N,N*-Dimethylthiocarbamates

Orlando D. Madoery,* Rita H. de Rossi, and Mirta M. Nasetta

O-8-(5-Z-quinolyl) *N,N*-dimethylthiocarbamates **1** (Z = NO_2, Cl, and H) were synthesized from the reaction of the 5-Z-8-quinolynol and *N,N*-dimethylthiocarbamoyl chloride. The kinetics of the hydrolysis in alkaline solution at several temperatures was measured. The observed rates are comparable to those of phenyl derivatives. The activation parameters and the Hammett relationship fit into a mechanism Bac2 for the hydrolysis, with rate-determining attack of the OH nucleophile on the C=S double bond.

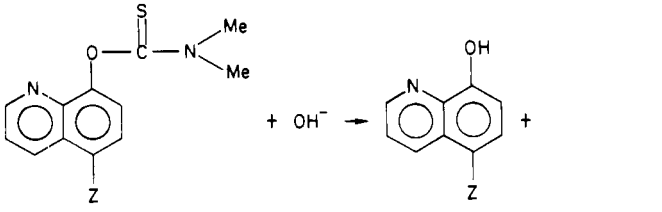
INTRODUCTION

Esters of carbamic and thiocarbamic acid have gained a great economical importance during the last few years. Due to their generally low toxicity for warm-blooded animals, their short stability in the soil, and their relatively harmless decomposition products this type of compound is used today more and more as replacement for organochlorides, mercury, and arsenic compounds (Corbett, 1974; Schlagbauer and Schlagbauer, 1972).

We have synthesized several *N,N*-dimethylthiocarbamates of substituted quinolines with potential biological activity and report here a study of their alkaline hydrolysis, since hydrolysis is one of the most important mechanisms for the transformation and degradation of carbamates (Bastide et al., 1980).

RESULT AND DISCUSSION

The alkaline hydrolysis of O-8-(5-Z-quinolyl) *N,N*-dimethylthiocarbamates (**1**) in 4:1 (v/v) water–dioxane leads quantitatively to 5-Z-8-hydroxiquinoline **2** (eq 1) as determined by UV–vis spectroscopy and the isolation of **2**.



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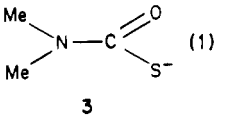

(1)

3

N,N-Dimethylthiocarbamate **3** could not be isolated because this product decomposes during the workup with acidic condition (Ewing et al., 1980).

Table I. Dependence of Observed Rate Constants k_{obsd} on the Temperature and NaOH Concentration for the Hydrolysis of 1 in Water–Dioxane 4:1 (v/v) and Ionic Strength 1 M

	10^6k_{obsd}, s^{-1} (Z = NO_2)[a]		10^6k_{obsd}, s^{-1} (Z = H)[b]		10^6k_{obsd}, s^{-1} (Z = Cl)[b]	
OH^-, M						
0.010	1.65[c]	2.90[d]				
0.053	3.17[c]	9.40[d]				
0.097	5.26[c]	11.70[d]				15.20[e]
0.189	5.93[c]	23.5[d]				
0.208				14.60[e]		18.20[e]
0.288	6.67[c]	26.7[d]				27.50[e]
0.417			3.37[d]	27.00[e]	5.50[d]	
0.508	14.70[c]	46.7[d]				
0.625			5.10[d]	45.50[c]	8.80[d]	74.30[e]
0.834			7.36[d]	56.50[e]	12.60[d]	101.00[e]
1.016	21.81[c]	93.8[d]				110.20[e]
1.042			9.40[d]	67.30[e]	14.93[d]	

[a] $[substrate]_o = 1.10^{-5}$ M. [b] $[substrate]_o = 1–2 \times 10^{-4}$. [c] T = 30 °C. [d] T = 45 °C. [e] T = 60 °C.

Table II. Second-Order Rate Constants and Activation Parameters for the Hydrolysis of 1

	10^5k_{OH}, M^{-1} s^{-1}	$\Delta H^{\ddagger}$,[a] kcal/mol	$-\Delta S^{\ddagger}$,[a] eu
Z = NO_2	1.99[b]	17.1	21.3
	8.78[a]		
Z = Cl	1.50[a]	28.3	10.8
	11.50[c]		
Z = H	0.97[a]	29.0	10.2
	6.47[c]		

[a] T = 45 °C. [b] T = 30 °C. [c] T = 60 °C.

Repetitive scanning of the UV–vis spectra during the alkaline hydrolysis give perfect isosbestic points at λ 270 and 320 nm (Z = H), λ 290 and 380 (Z = NO_2), and λ 270 and 340 (Z = Cl), indicating a simple 1:1 reaction.

The observed pseudo-first-order rate constant k_{obsd} depends linearly on the OH^- concentration in the range studied. Similar results were obtained at two temperatures for each compound studied. The data are summarized on Table I. From the slopes of the linear plot (not shown) we calculated the second-order rate constants k_{OH}. These values, together with the activation parameters are summarized on Table II.

Two mechanisms have been suggested for the hydrolysis of carbamic and thiocarbamic esters (Williams, 1972; Mindl et al., 1980): the ElcB and the Bac2 mechanisms. The

Departamento de Biología Aplicada, Facultad de Ciencias Agropecuarias, Universidad Nacional de Córdoba, C.C.509-Córdoba, 5000 Argentina (O.D.M. and M.M.N.), and Instituto de Investigaciones en Fisicoquímica de Córdoba (INFIQC), Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Argentina (R.H.d.R.).

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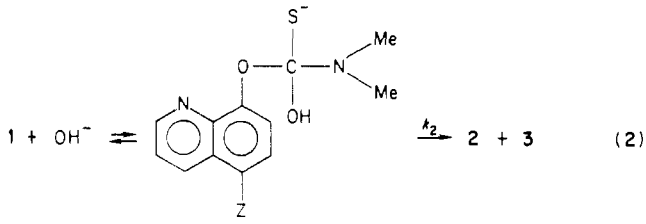
Bac2 mechanism which involves a tetrahedral intermediate is the one that take place with N,N-disubstituted compounds. This mechanism using 1 as an example is described in eq 2.



(2)

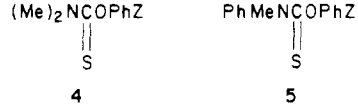
The effect of the substituent on the observed second-order rate constant can be correlated by the Hammett equation (eq 3).

$$\log k_{OH} = 1.25\sigma + 5.07 \qquad (r = 0.994) \qquad (3)$$

The ρ value of approximately 1 obtained for various Z substituents in the leaving group is consistent with hydroxide ion attack on the ester, followed by 8-hydroxyquinoline elimination, (Williams and Naylor, 1971; Ryan and Humphray, 1966). This value is in agreement with that expected for a Bac2 mechanism (Sartore, 1977).

The effect of temperature on the rate constant for the hydrolysis of 1 was studied and the values of entropy and enthalpy are indicated in Table II. The negative activation entropy is consistent with the proposed mechanism. Similar values have been reported for the hydrolysis of *N,N*-dimethylcarbamates (Christenson, 1964) and for N,N-disubstituted thiocarbamates (Sartore et al., 1977).

The quinolyl thiocarbamates studied are somewhat less reactive than the corresponding aryl derivatives 4. Although we did not find in the literature data regarding the rate of hydrolysis of compounds of the type 4, we can get a rough estimate from the data reported for 5 (Sartore, 1977).



4 5

The rate of hydrolysis of compound 5 with Z = H or NO_2 at 67, 5 °C in water–ethanol 4:1 (v/v) are $2.66.10^{-4}$ M^{-1} s^{-1} and $21.4.10^{-4}$ M^{-1} s^{-1}, respectively. The effect of changing a phenyl group by a methyl group may be estimated assuming $\rho = 1$ and from the values of σ_I of phenyl (0.1) (Taft et al., 1959; Ehrenson et al., 1973) and methyl (–0.05), this leads to a ratio $k_{Me}/k_{Ph} = 0.708$.

Thus the estimated rate constants for compound 4 are 2×10^{-4} M^{-1} s^{-1} for Z = H and 15.10^{-4} M^{-1} s^{-1} for Z = NO_2. These two values can be compared with the values corresponding to the hydrolysis of 1 at the same temperature which are calculated from the data reported on Table II, namely $1.52.10^{-4}$ M^{-1} s^{-1} (Z = H) and $5.78.10^{-4}$ M^{-1} s^{-1} (Z = NO_2).

Considering only electronic effects, one would have expected the hydrolysis of quinolyl derivatives 1 to be faster than that of phenyl derivatives 4. The fact that it is slower may be explained by the higher steric compression in the tetrahedral intermediate since the quinolyl group is bulkier than the phenyl group.

EXPERIMENTAL SECTION

Substrates. Substituted O-8-(5-quinolyl) *N,N*-dimethylthiocarbamates 1 were prepared by the method of Newman and Hetzel (Newman and Hetzel, 1971) from dimethylthiocarbamoyl chloride and the substituted 8-hydroxyquinoline 2.

Table III. Mass, Proton NMR, and IR Spectra of Compounds 1

Z = NO_2	Z = H	Z = Cl
Mass Spectra, 20 eV		
277 (48)	232 (11)	266 (11)
233 (18)	188 (6)	222 (28)
88 (55)	88 (79)	88 (78)
72 (100)	72 (100)	72 (100)
NMR Spectra (Cl_4C), δ		
3.7 (s, 3 H)	3.6 (s, 3 H)	3.6 (s, 3 H)
3.8 (s, 3 H)	3.5 (s, 3 H)	3.5 (s, 3 H)
7.6–8.4 (m, 5 H)	7–8.5 (m, 6 H)	7–9 (m, 5 H)
IR Spectra (KBr), cm^{-1}		
1290 (C=S)	1515 (C=S)	1479 (C=S)
1120 (COAr)	1124 (COAr)	1116 (COAr)

A solution prepared by dissolving in water 2 and equimolecular quantities of potassium hydroxide was stirred at room temperature. Then, a solution of dimethylthiocarbamoyl chloride in dry tetrahydrofuran was added dropwise. After the addition was completed the stirring was continued for an additional 10 min. The reaction mixture was shaken with benzene, and the benzene layer was separated, dried, and concentrated to give the crude product that was recrystallized from ethanol. 1 (Z = H): mp 126–127 °C. Anal. Calcd for $C_{12}H_2N_2OS$: C, 62.07; H, 5.16. Found: C, 61,85; H, 5.41. 1 (Z = Cl): mp 146 – 147 °C. Anal. Calcd for $C_{12}H_{11}N_2OSCl$: C, 54.05; H, 4.12. Found: C, 53.83; H, 4.38. 1 (Z = NO_2): mp 161–162 °C. Anal. Calcd for $C_{12}H_{11}N_3O_3S$: C, 52.00; H, 3.96. Found: C, 52.00; H, 4.16.

The structures assigned to the thiocarbamates were confirmed by IR, NMR, and mass spectroscopy; the data are summarized in Table III.

Other reagents were of analytical reagent grade or were purified by distillation or recrystallisation.

Apparatus. A Bausch and Lomb Model Spectronic 21 spectrophotometer was used for all spectroscopic measurements. The NMR spectra were run in a Varian T-60 spectrometer and the mass spectra on a Finnigan Model 3.300. The elemental analysis was carried out in UMYMFOR, Facultad de Ciencias Exactas Físicas y Naturales, Universidad Nacional de Buenos Aires, Argentina.

Isolation and Identification of Reaction Products. To a solution of O-8-(5-nitroquinolyl) *N,N*-dimethylthiocarbamate (0.05 g) in dioxane (40 mL) was added a solution of sodium hydroxide 0.097 M (160 mL). The mixture was stirred for 10 h at 30 °C, the solution was extracted with four portions of chloroform, and the resulting extract was evaporated to dryness. The product obtained (0.015 g) had the same NMR as the starting thiocarbamate. The aqueous layer was acidified and extracted with chloroform. After evaporation of the chloroform 0.035 g of 8-hydroxy-5-nitroquinoline was obtained. The other quinolynols were similarly obtained. Identification was made with the melting point and UV–vis absorption spectra.

Kinetic Method. The kinetic method is the same as that used in previous work (de Rossi and de Vargas, 1981).

The rate of hydrolysis of *N,N*-dimethylthiocarbamates 1 was studied in 4:1 (v/v) water–dioxane at ionic strength 1 M with NaCl as compensating electrolyte.

Kinetic measurements were initiated by addition of 1 mL of a stock solution of 1 in dioxane to a temperature equilibrated solution containing the other ingredients. Reaction rates were followed spectrophotometrically by measuring the increase in the absorption at the λ_{max} of the quinolynol 2, λ 450 nm (Z = NO_2), λ 370 nm (Z = Cl) and 360 nm (Z = H). All reactions are first order in substrate as well as in hydroxide ion and all rate measurements were

carried out with the hydroxide ion concentration more than 50 times the substrate concentration.

Pseudo-first-order rate constants were obtained from linear regression analysis of ln $(A_\infty - A_t)$ vs. time data. The plots were linear for over three half-lives for compound 1 (Z = Cl and Z = H) but the NO_2 derivative gave a downward curvature after about two half-lives. Then the infinite value was calculated on the basis of the initial concentration of the substrate and the extinction coefficient of 2 (Z = NO_2).

Thermodynamic activation parameters were obtained by standard procedures. (Bunnett, 1974).

Registry No. 1 (Z = NO_2), 97073-93-3; 1 (Z = Cl), 97073-94-4; 1 (Z = H), 97073-95-5; dimethylthiocarbamoyl chloride, 16420-13-6.

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Tocopherols and Tocotrienols in Finnish Foods: Meat and Meat Products

Vieno Piironen, Eeva-Liisa Syväoja, Pertti Varo, Kari Salminen, and Pekka Koivistoinen*

This study is part of a comprehensive survey carried out to determine the tocopherol and tocotrienol contents of Finnish foods. Tocopherols and tocotrienols from 40 commodities of meat, animal fats, edible offals, and meat products were analyzed by a high-performance liquid chromatographic method. α-Tocopherol was the predominant compound, but small amounts of α-tocotrienol and γ-tocopherol were also found in almost every sample. Some samples also showed small peaks with retention values identical with those of β-tocopherol and β-tocotrienol. The α-tocopherol content of meat samples ranged from 0.16 to 0.84 mg/100 g of fresh weight, of fat samples from 0.52 to 2.68 mg, of offal samples from 0.23 to 1.37 mg, and of meat product samples from 0.14 to 0.74 mg. There was a clear seasonal variation in the α-tocopherol contents of the meat, fat, and liver of both cows and steers. The α-tocopherol content of meat products followed the fat content. The estimated daily intake of α-tocopherol from meat and edible offals is about 0.8 mg per capita.

The vitamin E content of meat and edible offals is reported to be low or moderate. The α-tocopherol content of raw meat is usually below 0.5 mg/100 g and that of edible offals no more than 1.0 mg/100 g (Paul and Southgate, 1978; McLaughlin and Weihrauch, 1979; Bauernfeind, 1980; Souci et al., 1981). Animals do not synthesize tocopherols or tocotrienols, and the vitamin E content of animal products is therefore influenced by diet.

Only α-tocopherol and small amounts of other tocopherols, but no tocotrienols, have been found in meat and offals (McLaughlin and Weihrauch, 1979; Bauernfeind, 1980). γ-Tocopherol has been shown to be absorbed about as efficiently as α-tocopherol, but it disappears faster from tissues than α-tocopherol (Bieri and Poukka Evarts, 1974). Behrens and Madere (1983), on the other hand, have suggested that the absorption, transport, and tissue-uptake mechanisms of tocopherols are specific for α-tocopherol and that small amounts of α-tocopherol are sufficient to displace γ-tocopherol.

In this study the most important meats, edible offals, animal fats, and meat products commonly consumed in Finland were analyzed for tocopherols and tocotrienols. The study is part of a comprehensive survey carried out to determine the tocopherol and tocotrienol contents of Finnish foods (Piironen et al., 1985; Syväoja et al., 1985a; Syväoja et al., 1985b; Syväoja et al., 1985c; Syväoja et al., 1985d).

EXPERIMENTAL SECTION

Sampling. Samples were taken at the end of the indoor feeding season in the spring of 1982 (late April–early May) and again at the end of the grazing season in fall 1982 (late Sept–early Oct). Some commodities were collected only once.

Meat, offal, and fat samples were collected from two slaughterhouse chains that together represent 80–90% of

Department of Food Chemistry and Technology, University of Helsinki, SF-00710 Helsinki 71, Finland (V.P., P.V., P.K.), and Valio Finnish Co-operative Dairies' Association, Research and Development Department, Kalevankatu 56 B, SF-00180 Helsinki 18, Finland (E.-L.S., K.S.).

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