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KINETIC ASPECTS OF THE DECOMPOSITION OF CLORAZEPATE POTASSIUM SALT

A. Cutie, F. M. Plakogiannis,
T. Jochsberger and S. Feifer

Brooklyn College of Pharmacy

600 Lafayette Avenue

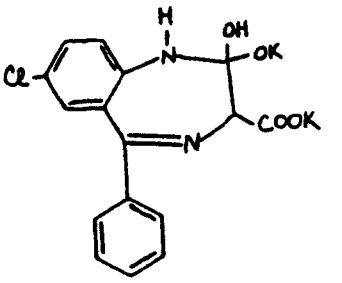
Brooklyn, New York 11216

ABSTRACT

The decomposition of clorazepate potassium salt (tranxene) in hydrocloric acid was examined at selected temperatures ranging from 6 to 78°C. The energy of activation is evaluated and possible degradation pathways are elluded to. The energy of activation was found to be about 20 Kcal/mole.

INTRODUCTION

Clorazepate (3-carboxy-7-chloro-1,3 dihydro-5-phenyl-1,4 benzodiazepine-2-one) is a relatively new antianxiety agent of the 1,4-benzodiazepine class of compounds. Its pharmacological and clinical properties have been reported by Charalampous et al.(1). The chemical structure is shown below.



Scheme I

Benzodiazepines with structures similar to clorazepate dipotassium degrade to carbostyril benzophenones and acridine derivatives (2). This note is a report of an initia' pH-temperature stability profile.

EXPERIMENTAL

Seventy milligrams per liter samples of clorazepate were dissolved in solutions of 6.2 HCl previously thermally equilibrated to 37°, 48°, 62° and 78°C. Absorbancies were immediately determined using a U.V. spectrophotometer[1] (λmax = 359 nm). The exact concentration were determined from a standard curve. Samples were periodically withdrawn, colled in an ice bath to quench reaction and their absorbancies were determined (Figure 1).

Kinetic studies at pH 1.00, 2.15 and 2.85 were carried out by the same analytic method, using a standard 0.1 N HCl[2] solution and freshly prepared phosphate buffers[3]. Table I lists rate constanst determined at various temperatures.

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[1] Perkin Elmer twin beam spectrophotometer (model 124)

[2] Fischer Scientific

[3] Harloco Chemical

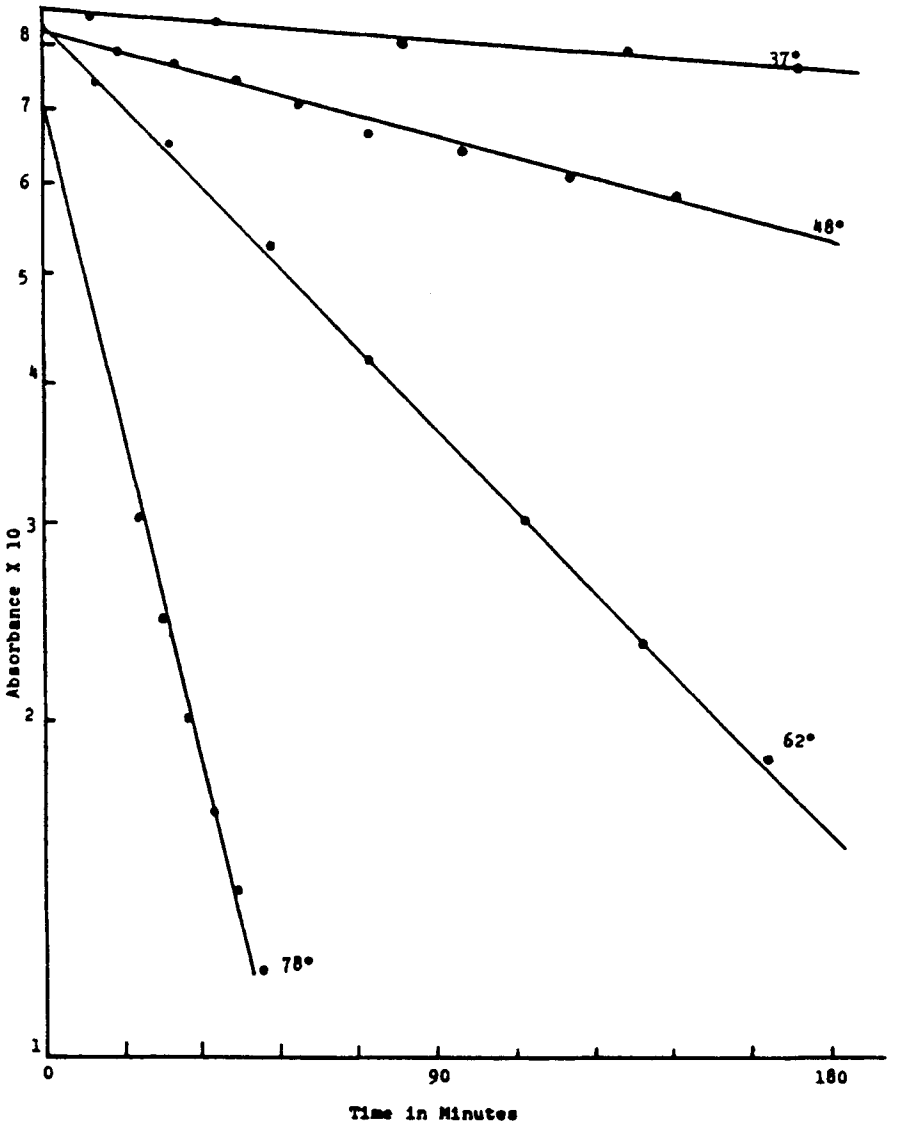


FIGURE I. First Order Decomposition Rates of Tranxene (6M HCl)

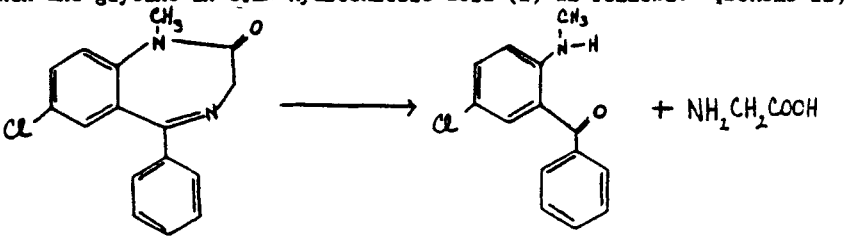
TABLE I

Observed first order rate constants k x 10^2 (hr^{-1}) for the disappearance of clorazepate in aqueous solutions.

pH	6°	24°	37°	48°	78°
1.00	0.23	0.9	2.53	6.42	54.0
2.15	0.13	0.96	1.69	5.18	68.7
2.85	0.44	1.56	6.35	___	___

RESULTS AND DISCUSSION

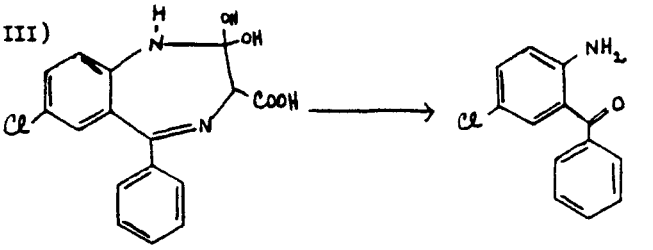
It has been shown that diazepam undergoes hydrolysis to 2-methyl-5-chlorobenzophenon and glycine in 6.2N hydrochloric acid (2) as follows: (Scheme II)



(Scheme II)

It is proposed in the present study that clorazepate undergoes a similar degradation in 6.2 N HCl to a derivative of nordiazepam (3) shown below:

(Scheme III)



(Scheme III)

Activation energies for clorazepate are reported in Table II. The energy of activation in 6.2 N HCl (Figure 2) was found to be 20 KCal/mole. This value agrees well with Katutzky and Jones (4) and Ogata (5), who have reported Ea values between 19–25 Kcal/mole for the breakage of an amide linkage.

According to Carstensen et al (6) the stability of diazepam derivatives with substitution in position one increases with increasing pH. Therefore clorazepate having no substitution at position one is unstable and the principal reason for its instability is the structural element (Scheme I). It is apparent from Tables I and II that its degradation follows more than one pathway at higher temperatures and different pH's. Under the experimental conditions of 6.2 N HCl the appearance of the benzophenone seems to be favored and the U.V. data supports this claim.

Table I and II seem to indicate that other pathways may be simultaneously taking place at different pH's. For example at 37°C the rate at pH 2.15 is less than that of pH 1.0 and pH 2.85. These alternate pathways are currently under investigation.

Table II

Activation Energies for the decomposition of clorazepate at different pH's

pH	Ea (Kdal/mole)
1.00	14.6
2.15	16.7
2.85	14.4
6.2N HCl	20.0

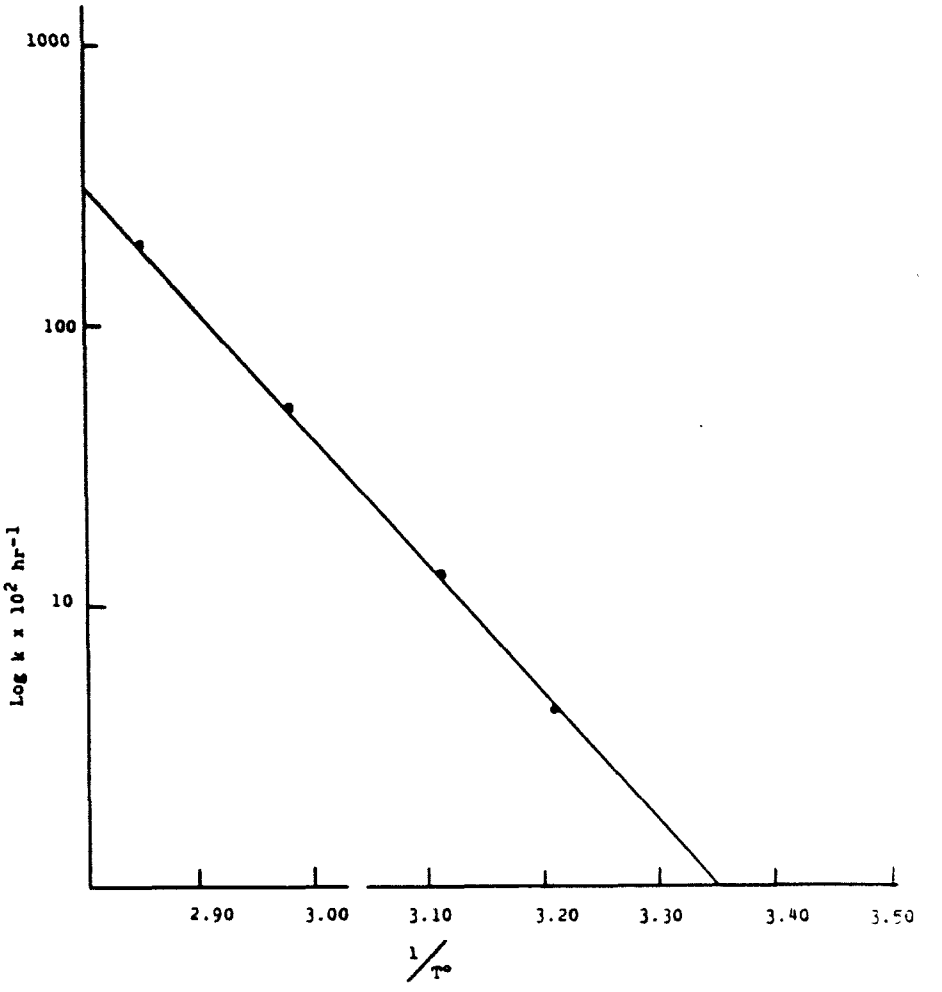


FIGURE II. Arrhenius Plot for the Decomposition of Tranxene in the presence of 6.2N HCl

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