Kinetics of Hydrolysis of Acylals of Aspirin: Hydrolysis of (1′-Ethoxy)ethyl 2-Acetoxybenzoate

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Abstract □ A derivative of aspirin, (1′-ethoxy)ethyl 2-acetoxybenzoate, was synthesized and its hydrolysis was studied in aqueous solution. The rate of hydrolysis was followed spectrophotometrically and found to be: *(a)* first order with respect to the compound, *(b)* independent of pH, *(c)* very sensitive to solvent polarity, and *(d)* an isotope effect (k_{D_2O}/k_{H_2O}) near unity. Based on these results, the hydrolysis of the derivative appears to proceed by a classical S_N1-type mechanism.

Keyphrases □ Aspirin derivatives, (1′-ethoxy)ethyl 2-acetoxybenzoate—synthesis and hydrolysis □ (1′-Ethoxy)ethyl 2-acetoxybenzoate (aspirin derivative)—synthesis and hydrolysis

The oral administration of aspirin has been shown to induce gastric irritation and bleeding (1–3). It is believed (1) that this effect is due to a local irritation of the mucous membranes by the very acidic aspirin particles.

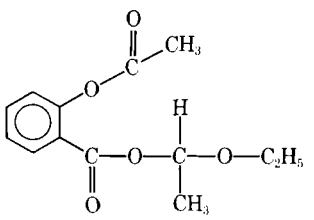
It was indicated (1) that present aspirin products containing alkaline additives to reduce the gastric irritation have the disadvantages of either high sodium content or limited buffer capacity.

In an attempt to mask reversibly the acidic carboxylic group of aspirin and hopefully to reduce its local irritation, (1′-ethoxy)ethyl 2-acetoxybenzoate (I) was synthesized and its rate of hydrolysis was studied. In aqueous solution, Compound I cleaves extremely rapidly, generating aspirin.

EXPERIMENTAL

Compound I was prepared according to the following procedure. To 3.0 g of aspirin in a 100-ml stoppered, round-bottom flask, 50 ml of freshly distilled dichloromethane, 30 ml of freshly distilled ethyl vinyl ether[1], and 10 ml of dichloromethane saturated with hydrogen chloride gas were added. The reaction mixture was stirred at room temperature for 2 hr. The solvents were then removed at 40° using a rotary evaporator, leaving a viscous oil.

Alternatively, and more conveniently, the hydrogen chloride gas was replaced with 0.1 ml of a 0.4% solution of *p*-toluenesulfonic acid in benzene. At the completion of the reaction, the remaining p-toluenesulfonic acid was neutralized with 1 equivalent of pyridine. The solvents were then removed at ≤40° using a rotary evaporator, leaving a viscous oil. The NMR and IR spectra and the elemental analysis were consistent with the structure of I; NMR ($CDCl_3$): δ 6.93–8.15 (m, 4, ArH), 6.13 [q, 1, —O—C*H*(CH_3)—O—], 3.35–3.95 (m, 2, —O—C*H*$_2$—CH_3), 2.31 (s, 3, —CO—CH_3), 1.46 [d, 3, —O—CH(C*H*$_3$)—O], and 1.20 (t, 3, —CH_2C*H*$_3$); IR (neat): 3050 (ArH), 2920 (aliphatic C—H), 1770 [CH_3—C(=O)—O—], 1720 [Ar—C(=O)—O—], 1300 and 1190 (C—O, ester), 1070 and 1030 (C—O, ether), and 750 and 700 (ArH) cm^{-1}.



I

Anal.—Calc. for $C_{13}H_{16}O_5$: C, 61.85; H, 6.39. Found: C, 61.58; H, 6.11.

The rate of hydrolysis was measured spectrophotometrically at 285 nm by measuring the formation of aspirin and was found to be first order with respect to the compound over the pH range studied.

Table I—Half-Lives of Hydrolysis of I at 25° and Ionic Strength of 0.1

pH	$t_{1/2}$, sec[a]
3.25	3.2
4.00	3.1
5.23	3.5
6.28	3.5

[a] Each half-life is an average of four determinations.

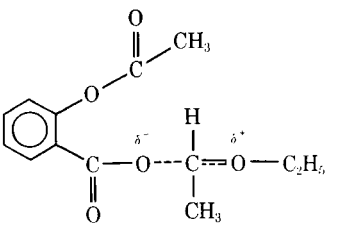
Table II—Dependency of First-Order Rate Constants for Hydrolysis of I on the Dielectric Constant of the Solution

Dioxane, %	Dielectric Constant (ε)	k_{obs}, sec^{-1}
0	78.6	0.23
5	74	—
10	70	0.111
25	56.3	0.046
50	34.3	0.0027

RESULTS AND DISCUSSION

The facts that the rate of hydrolysis is independent of pH (Table I) and markedly dependent on the dielectric constant (Table II) and that the ratio of k_{D_2O}/k_{H_2O} is unity[2] would strongly suggest that the hydrolysis of I proceeds by an S_N1-type mechanism (4, 5). The rate-limiting step in the hydrolysis reaction is probably the C—O bond cleavage as shown in Scheme I.

The presented data show that *transient* blocking of the very



Scheme I

[1] Aldrich Chemical Co.

[2] The half-lives in seconds for the hydrolysis of I in deuterium oxide and water are 3.2, 3.3, and 3.2 and 3.2, 3.1, and 3.2, respectively.

acidic carboxylic group of aspirin may be achieved by making derivatives similar to Compound I. One possible advantage of a compound such as I is that the mucous membranes of the stomach are in contact with a neutral molecule. As I dissolves, however, it will rapidly hydrolyze, generating aspirin in solution. The mechanism of hydrolysis of I was shown to proceed by a classical S_N1-type reaction.

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Selenium Heterocycles X: Synthesis and Antibacterial Activity of Pyridyl-1,2,3-thiadiazoles and Pyridyl-1,2,3-selenadiazoles

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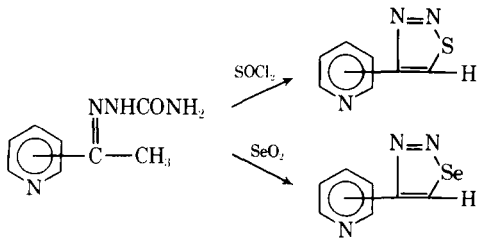
Abstract □ Three isomeric 4-pyridyl-1,2,3-selenadiazoles and their corresponding diselenafulvines were prepared. 4-(3-Pyridyl)-1,2,3-thiadiazole and its dithiafulvene were also synthesized. The hydrochloride salts of all compounds prepared showed significant antibacterial activity.

Keyphrases □ Selenium heterocycles—synthesis and antibacterial activity of pyridyl-1,2,3-thiadiazoles and pyridyl-1,2,3-selenadiazoles □ Pyridyl-1,2,3-thiadiazoles and selenadiazoles—synthesized and screened as antibacterial agents □ Selenadiazoles, pyridyl-1,2,3—synthesized and screened as antibacterial agents □ Antibacterial agents, potential—synthesis and screening of pyridyl-1,2,3-thiadiazoles and pyridyl-1,2,3-selenadiazoles

Recently, the synthesis of 1,2,3-selenadiazoles by selenium dioxide oxidation of aldehyde or ketone semicarbazones having an α-methyl or methylene group was reported (1–4). It was also shown that 1,2,3-selenadiazoles and base afforded 1,4-diselenafulvenes (5).

DISCUSSION

In the present work, the three isomeric 4-pyridyl-1,2,3-selenadiazoles were prepared. Also, 4-(3-pyridyl)-1,2,3-thiadiazole was prepared in high yield by reaction of thionyl chloride and 3-acetylpyridine semicarbazone (Scheme I). All thia- and selenadiazoles prepared (Tables I and II) were converted to the corresponding dithia- and diselenafulvenes by reaction with potassium hydroxide in ethanol (Scheme II).



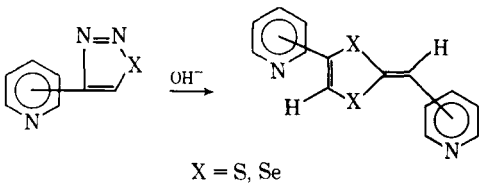
Scheme I

Some of the 1,3,4-thiadiazole derivatives have shown antibacterial and antiviral activities (6, 7). Also, 1,2,3-selenadiazole and some of its derivatives were found to have significant antibacterial activity (5). In the search for new potent antibacterial agents, it was of interest to study the antibacterial activity of the pyridyl thia- and selenadiazoles closely related to these compounds. All compounds (Tables I and II) were tested against *Bacillus subtilis* NCTC 3610, *Staphylococcus aureus* ATCC 6538, *Klebsiella pneumoniae* ATCC 10031, and *Sarcina lutea* ATCC 9341. Nitrofurazone was used as a control. Standard paper disks of 6 mm diameter were immersed in solution and placed on inoculated assay medium surface[1].

The antibacterial activity of all compounds that were dissolved in acetone at the concentration 0.5% were insignificant. However, the hydrochloride salts (prepared by dissolving the base in dilute hydrochloric acid and drying at room temperature in the dark) at a concentration of 0.5% in distilled water (and nitrofurazone dissolved in dimethylformamide at the same concentration) were active (Table III).

EXPERIMENTAL[2]

4-(2-Pyridyl)-1,2,3-selenadiazole (I)—2-Acetylpyridine semicarbazone (4.4 g, 0.025 mole) was dissolved in 50 ml of boiling



Scheme II

[1] Antibiotic Assay Medium; British Pharmacopoeia, 1968.

[2] Melting points were taken on a Kofler hot-stage microscope and are uncorrected. The IR spectra were recorded using a Leitz spectrograph. UV spectra were obtained with a Varian Techtron 635 instrument. The mass spectra were recorded on a Varian Mat 111 instrument.