REACTION OF METHYL 3-PHENYL-3-CHLORO-2-OXO-PROPIONATE WITH 2-MERCAPTO- AND 2-HYDROXY-ETHANOLAMINES: THE PRODUCTS AND SOME OF THEIR TRANSFORMATIONS

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It was found that the nature of the SH and OH groups in 2-mercapto- and 2-hydroxyethanolamines plays a decisive role in the reactions between these compounds and methyl 3-phenyl-3-chloro-2-oxopropionate, the products comprising 1,4-thiazine and 1,4-oxazane derivatives, respectively. Some of the reactions of these products were investigated.

In a previous report [1] we showed that 3-phenyl-3-chloro-2-oxopropionic acid derivatives reacted with thioglycol and dithioglycol in benzene to yield oxathiine- and dithiinecarboxylic acid derivatives, which form components of the well-known fungicides plantvaks and vitavaks [2].

The present work sets out to study the reaction between methyl 3-phenyl-3-chloro-2-oxopropionate (I) and 2-mercapto- and 2-hydroxyethanolamines, and some of the reactions which the products themselves undergo. Because of the considerable reactivity of 2-oxopropionic acid derivatives toward bases [3] the synthesis methods described in the literature for obtaining 1,4-thiazine derivatives from the reaction between α-chloroketones and 2-mercaptoethanolamines in the presence of strong bases [4] could not be employed.

It was found that α-chloroketone I reacted with 2-mercaptoethanolamine in the presence of catalytic amounts of 4-toluenesulfonic acid, affording methyl 2-phenyl-5,6-dihydro-1,4-thiazine-3-carboxylic acid (II), which in acetic anhydride solution converted into the corresponding crystalline N-acetyl derivative III.

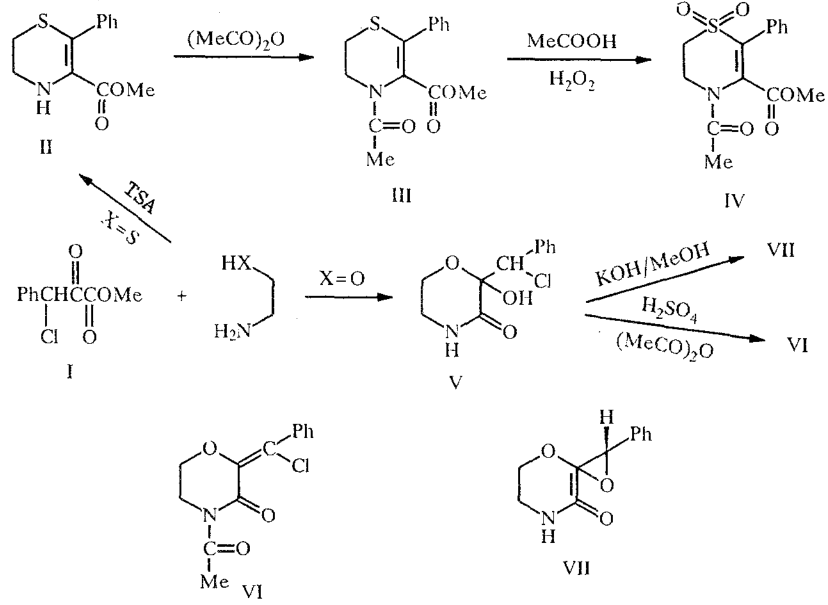

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TABLE 1. Physical Properties and Spectral Data for Compounds II-VII

Compound	Empirical formula	mp, °C	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm [solvent]	Yield, %
II	$C_{12}H_{13}NO_2S$	—	1600 (C=C); 1720 (C=O); 3240 (N—H)	3,20 (2H, t, CH_2S); 3,30 (3H, s, CH_3O); 3,73 (2H, t, CH_2N); 7,13 (5H, s, C_6H_5) [CCl_4]	66*
III	$C_{14}H_{15}NO_3S$	137...138	1590 (C=C); 1665, 1710 (C=O)	3,0...3,23 (2H, m, CH_2S); 3,26 (3H, s, CH_3O); 3,73...3,96 (2H, m CH_2N); 7,26 (5H, s C_6H_5) (DMF-D_7)	86*
IV	$C_{14}H_{15}NO_5S$	200...201	1140, 1160, 1310 (SO2); 1610 (C=C); 1690, 1730 (C=O)	2,30 (3H, s CH_3CO); 3,46 (3H, s, CH_3O); 3,63...3,90 (2H, m, CH_2SO_2); 4,30...4,56 (2H, m, CH_2N); 7,23 (5H, s, C_6H_5) (DMSO-D_6)	100
V	$C_{11}H_{12}ClNO_3$	164...167	1670 (C=O); 3200 (N—H); 2500...3310 (OH)	3,10...3,37 (2H, m, CH_2N); 3,75...4,02 (2H, m, CH_2O); 5,16 (1H, s, CH); 6,66...7,66 (7H, m C_6H_5, NH, OH) (DMF-D_7)	75
VI	$C_{13}H_{12}ClNO_3$	117...118	1615 (C=C); 1700 broad band (C=O)	2,26 (3H, s, CH_3); 3,73...3,99 (2H, m, CH_2N); 4,07...4,33 (2H, m CH_2O); 7,16 (5H, s, C_6H_5) (DMSO-D_6)	92
VII	$C_{11}H_{11}NO_3$	140...142	1690 (C=O); 3070 (epoxide ring) 3220 (NH)	3,23...3,50 (2H, t, CH_2N); 3,86...4,13 (2H, t, CH_2O); 4,46 (1H, s CH); 7,30 (5H, s, C_6H_5); 8,46 (1H, br.s, NH) (DMSO-D_6)	54

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*Yield calculated from the quantity of water collected in a Dean−Stark trap.

The presence of a sulfide sulfur in 1,4-thiazine III enabled its sulfonic derivative IV to be obtained by treating it with hydrogen peroxide in acetic acid.

It is worth noting that in the PMR spectrum of sulfonic derivative IV the 1,4-thiazine ring proton signals were shifted ~0.6 ppm downfield compared to the analogous signals in compounds II and III due to the strong electron-acceptor capability of the SO_2 group, while the chemical shifts of the other proton-containing groups (C_6H_5, OCH_3, $COCH_3$) remained virtually unchanged.

In contrast to 2-mercaptoethanolamine a completely different situation arose when α-chloroketone I was reacted with 2-hydroxyethanolamine. The reaction proceeded exothermically with the formation of a crystalline product. No methoxycarbonyl group signal was observed in the PMR spectrum of the reaction product, while a broad singlet signal was exhibited at 8.35 ppm, corresponding in integral strength to a single proton. These facts, coupled with the appearance of new $\nu_{C=O}$ and ν_{N-H} valence vibration bands at 1670 and 3220 cm^{-1} in its IR spectrum, suggested that the reaction between α-chloroketone I and 2-hydroxyethanolamine proceeded via initial attack of the hydroxyl group at the ketone group of α-chloroketone I with the intermediate formation of a semiketal, followed by subsequent cyclization through intramolecular amidation at the ester group and the formation of 2-hydroxy-2-(α-chlorobenzyl)-3-oxo-1,4-oxazane (V).

The OH group valence vibration in the IR spectrum of compound V appeared as a very broad, blurred absorption band in the 3310-2500 cm^{-1} region, which can probably be interpreted as the formation of a chelate-type hydrogen bond. Other chemical reactions also corroborated the structure of compound V. For example, when it was acetylated using acetic anhydride in the presence of sulfuric acid, dehydration involving the OH group and the methine proton, besides the reaction at the N−H group, gave rise to 2-(chlorobenzylidene)-3-oxo-4-acetyl-1,4-oxazane (VI). Additional confirmation of the presence of a hydroxyl group and an α-chlorobenzyl fragment at position 2 of the oxazane ring in compound V was provided by the formation of spiroepoxide VII when compound V was treated with alcoholic KOH solution.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument (pastes in Vaseline). PMR spectra were obtained using a Varian T-60 (60 MHz), internal standard TMS. Melting points were determined on a Boetius heating plate.

Elemental analysis data for compounds II-VII was in line with calculated values with respect to C, H, N, S, and Cl.

Physical properties and spectral characteristics for the compounds are shown in Table 1.

Methyl Ester of 2-Phenyl-5,6-dihydro-1,4-thiazine-3-carboxylic Acid (II). A mixture of equimolar quantities of α-chloroketone I and 2-mercaptoethanolamine were boiled in benzene with a Dean–Stark trap in the presence of catalytic amounts of toluenesulfonic acid. On completion of the reaction the benzene was evaporated off, yield compound II in the form of a dense mass.

Methyl Ester of 2-Phenyl-5,6-dihydro-4-acetyl-1,4-thiazine-3-carboxylic Acid (III). A sample of 0.02 moles of compound II was dissolved in acetic anhydride and the solution was kept at 20°C for 24 h. The resultant precipitate of ester III was filtered off and crystallized from ethanol.

Methyl Ester of 1,1-Dioxido-2-phenyl-4-acetyl-5,6-dihydro-1,4-thiazine-3-carboxylic Acid (IV). To a solution of 0.01 mole of compound III in 50 ml of CH_3COOH at 20°C were added 10 ml of 30% H_2O_2. The mixture was heated to 80°C and stirred at this temperature for a further 3 h. The precipitated crystals of ester IV were filtered off and crystallized from CH_3COOH.

2-Hydroxy-2-(α-chlorobenzyl)-3-oxo-1,4-oxazane (V). To a solution of 0.049 moles of ethanolamine in 25 ml of absolute methanol were added at 16-21°C (water cooling) 0.049 moles of methyl 3-phenyl-3-chloro-2-oxopropionate. After the reaction mixture had been kept at room temperature for 12 h, the precipitated crystals of oxazane V were filtered off and washed several times with water, then ether.

2-(Chlorobenzylidene)-3-oxo-4-acetyl-1,4-oxazane (VI). A mixture of 0.004 moles of compound V, 30 ml of acetic anhydride, and 4-5 drops of sulfuric acid was kept at room temperature for 72 h. After the acetic anhydride had been evaporated in vacuum, the residue was treated with water. Oxazane VI was then crystallized from isopropyl alcohol.

8-Oxo-2-phenyl-1,4-dioxa-7-azaspiro[2,5]octane (VIII). To a solution of 0.5 g of KOH in 25 ml of absolute methanol was added at 0°C 0.008 moles of compound V. After the reaction mixture had been stirred for 1 h at the same temperature, it was kept for a further 12 h at room temperature. The precipitated crystals of epoxide VII were filtered off and washed with water.

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