New Compounds: Addition Products of Heterocyclic Chalcones

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Abstract □ Michael-type adducts, 1,3-heterocyclic-3-mercaptopropan-1-ones, were prepared by the base-catalyzed reaction of heterocyclic chalcones with thiols. These new compounds were found to be active as fungicides.

Keyphrases □ Chalcones, heterocyclic—addition products, 1,3-heterocyclic-3-mercaptopropan-1-ones synthesized as potential fungicides □ 1,3-Heterocyclic-3-mercaptopropan-1-ones—synthesized as potential fungicides □ Fungicides, potential—synthesis of Michael-type adducts, 1,3-heterocyclic-3-mercaptopropan-1-ones

Some addition products of heterocyclic chalcones with thiols were prepared in view of potential biological properties. Bronchodilatory (1), coronary spasmolytic (2–5), bacteriostatic (6), tuberculostatic (7), staphylostatic (8), and anthelmintic (9) activities have been reported for heterocyclic chalcones; recently, these compounds also showed an inhibitory effect on the suprarenal gland cortex of the rat (10).

The intermediate chalcones (1,3-heterocyclic-2-propen-1-ones) were prepared by the conventional (11) aldehyde–ketone base-catalyzed condensation. In turn, these chalcones were used for the Michael-type adducts, 1,3-heterocyclic-3-mercaptopropan-1-ones (Table I). A base-catalyzed ethanolic solution refluxed for 2–3 hr gave good yields of the adducts.

Several of the compounds showed fungicidal properties.

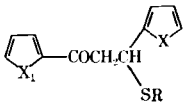

Table I—1,3-Heterocyclic-3-mercaptopropan-1-ones

Compound	X	X_1	R	Melting Point	Formula	Analysis, %	
						Calc.	Found
I	O	O	Phenyl	63–64°	$C_{17}H_{14}O_3S$	C 68.45	68.45
						H 4.73	4.71
						S 10.73	11.05
II	O	O	*p*-Tolyl	95–96°	$C_{18}H_{16}O_3S$	C 69.22	69.40
						H 5.16	5.26
						S —	—
III	O	S	*p*-Chlorophenyl	77–78°	$C_{17}H_{13}ClO_2S_2$	C 58.56	58.91
						H 3.76	3.86
						S 18.35	18.64
IV	O	S	*p*-Tolyl	75–76°	$C_{18}H_{16}O_2S_2$	C 65.85	65.82
						H 4.91	5.12
						S —	—
V	O	S	*o*-Aminophenyl (12)	74°	—		
VI	S	S	3,4-Dichlorophenyl	96–97°	$C_{17}H_{12}Cl_2OS_3$	C 51.31	51.02
						H 3.24	3.62
						S 24.17	24.23
VII	S	S	*p*-Bromophenyl	91–92°	$C_{17}H_{13}BrOS_3$	C 49.87	50.07
						H 3.20	3.16
						S 23.51	23.69
VIII	O	S	*p*-Bromophenyl	76–78°	$C_{17}H_{13}BrO_2S_2$	C 51.92	52.25
						H 3.33	3.23
						S 16.27	16.54
IX	S	O	*p*-Chlorobenzyl	61–62°	$C_{18}H_{15}ClO_2S_2$	C 59.59	59.42
						H 4.17	4.14
						S —	—
X	O	O	3,4-Dichlorophenyl	73–74°	$C_{17}H_{12}Cl_2O_3S$	C 55.78	55.44
						H 3.53	3.42
						S 8.74	8.93
XI	O	O	*p*-Bromophenyl	90–91°	$C_{17}H_{13}BrO_3S$	C 54.12	53.81
						H 3.47	3.42
						S 8.48	8.61
XII	O	O	*p*-Methoxyphenyl	66–67°	$C_{18}H_{16}O_4S$	C 65.85	66.18
						H 4.91	4.92
						S 9.75	10.00
XIII	S	O	1-Octyl	44–45°	$C_{19}H_{26}O_2S_2$	C 65.10	65.13
						H 7.48	7.42
						S —	—
XIV	S	O	1-Dodecyl	55–57°	$C_{23}H_{34}O_2S_2$	C 67.96	67.94
						H 8.43	8.52
						S —	—
XV	S	O	*p*-Bromophenyl	93–95°	$C_{17}H_{13}BrO_2S$	C 51.92	51.95
						H 3.33	3.23
						S —	—

EXPERIMENTAL

All adducts listed in Table I were prepared by the following procedure as exemplified by 1,3-di-(2-furyl)-3-(*p*-bromomercapto)-propan-1-one.

p-Bromothiophenol (5.0 g, 0.0264 mole) was added to 5.0 g (0.0265 mole) of 1,3-di-(2-furyl)-2-propen-1-one in 100 ml of ethanol, followed immediately by 5 drops of the catalyst triethylamine. After refluxing for 2 hr on a steam bath, the solution was cooled. The precipitate that formed was collected and recrystallized from ethanol–water to give a white crystalline material, mp 90–91°, in almost quantitative yield.

Anal.—Calc. for $C_{17}H_{13}BrO_3S$: C, 54.12; H, 3.47; Br, 21.18; S, 8.48. Found: C, 53.81; H, 3.42; Br, 21.02; S, 8.61.

Other intermediates used were 1-(2-furyl)-3-(2-thienyl)-2-propen-1-one, 1-(2-thienyl)-3-(2-furyl)-2-propen-1-one, and 1,3-di-(2-thienyl)-2-propen-1-one.

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COMMUNICATIONS

Influence of Peroxide Impurities in Polyethylene Glycols on Drug Stability

Keyphrases □ Polyethylene glycols—peroxide impurity, corticosteroid stability □ Antioxidants—butylated hydroxytoluene, propyl gallate □ Colorimetric assay—peroxide concentrations

To the Editor:

The poor stability of an experimental topical corticosteroid formulated in polyethylene glycol 300 was found to be due to the high concentration of peroxides in the vehicle. Removal of the impurity from the vehicle led to an increase in stability of the steroid at elevated temperatures. Boon and Mace (1) reported that degradation of tripelennamine hydrochloride in polyethylene glycol 300 was dependent on the concentration of ethylene oxide in polyethylene glycol; when the concentration of ethylene oxide exceeded 0.1%, there was measurable loss of the active constituent.

Higher molecular weight polyethylene glycols and polyethylene glycol esters, *i.e.*, polyethylene glycol 400, polyethylene glycol 1500, and polyethylene glycol 6000 distearate, used to solubilize the steroid before its incorporation into an ointment formulation (petrolatum base), all contained peroxides as impurities and the steroid showed poor stability. Except for one sample of polyethylene glycol 1500, samples of polyethylene glycols from different manufacturers all contained peroxides. In one instance, a small quantity of hydrogen peroxide had been added by the manufacturer to maintain a water-clear product.

Although the identities of the peroxides present as impurities were not determined, they are believed to consist of various organic peroxides rather than hydrogen peroxide *per se*. The concentrations of peroxide in polyethylene glycols of different molecular weights and polyethylene glycol 6000 distearate are reported in Table I. In the colorimetric assay used, the glycol sample was added to an acidified potassium iodide solution and the iodine liberated was titrated against standard thiosulfate solution.

The level of peroxide in polyethylene glycols increased with aging. Studies in these laboratories showed that the presence of selected antioxidants and water (5–10%) in the vehicle helped to decrease the concentration of peroxides. Thus, of eight antioxidants tested, butylated hydroxytoluene and propyl gallate were the most successful in this respect, and pretreatment of the vehicle with 0.005–0.05% of either agent was effective. The decomposition of peroxides under the influence of water or antioxidants was slow at room temperature but was accelerated by heating. Both the concentration of antioxidant and the duration of heating (60–80°) required for the removal of peroxide were dependent on the initial con-