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Ketoketene gem-Dithiols: Synthesis of Some Sulphur Heterocycles as Antimicrobial Agents

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Abstract □ A convenient method for the preparation of N-aryl thiazolines **4a,b**, 2,2-dichlorothiophene **5**, thiazolinones **6** and **8**, and 2,6-dihydrothiopyran 2-thione **9** derivatives is described. This depends on interaction of 3,3-dimercapto-1-(4-biphenyl)-2-propen-1-one **1** with dichloroethane, amines, trichloroacetylchloride, chloroacetamide, ethylene oxide and epichlorohydrin. Antimicrobial activity of the obtained products was studied.

Keywords □ Ketoketen gem dithiols, α-oxoteten gem-dithiols, thiazolines, sulphurheterocycles, antimicrobial activity.

Interesting pharmacological activity of thiazoles, thiopyranes and thiophenes[1-3] led the authors to study the synthesis and the various changes in the structures of these compounds in the hope of obtaining less toxic and more potent drugs utilizing gem-dithiol[4], **1** as starting material. Several reports described the synthesis of thiazolinone, thiophene, thiopyrane and thiazoline derivatives[4-7]. Here we were able to synthesize these products using new routes, simple reagents and less steps. Interaction of **1** in the form of disodium salt with 1,2-dichloroethane led to the formation of 1,3-dithiolane derivatives **2**. This when treated with some amines; aniline and 2-furfurylamine gave the products 3-s-alkylamine-3-mercapto 1-(4-biphenyl)-2-propen-1-one **3a, b**. Boiling **3a,b** in ethanol resulted in the formation of N-aryl-thiazolines **4a,b** *via* hydrogen sulphide elimination and cyclization. Treatment of **1** with trichloroacetyl chloride in basic medium gave a product of molecular formula $C_{17}H_{16}Cl_2O_2S_2$. This reaction was suggested to proceed *via* S→C thio-Claisen transformation and gave 2,2-dichloro 3-hydroxy 4(4-biphenyl)thiophene-2-thione ketone **5**, spectral and elemental analysis confirmed the structure **5** and ruled out the other possible isomer structures (cf. Table I).

In the present communication we report here a facile and new route for synthesis of thiazolinone derivative **6** *via* the reaction of **1** with chloroacetamide in dry ether followed by boiling in ethanol/sodium ethoxide solution. Condensation of **6** with benzaldehyde in ethanol and a catalytic amount of triethylamine led to the formation of 5-benzylidene 2-(4-phenzyl)-benzoyl methylene 4-oxothiazole **7**.

Ethylene oxide and epichlorohydrine reacted also with **1** in dry benzene and they serve as a suitable reagents for obtaining 3-mercapto-3-s-ethanol 1-(4-biphenyl)2-propen-1-one **8** and 5-hydroxy thiopyran-2-thion 3(4-biphenyl) ketone **9**.

Bacteriological testing and results

Seven bacterial cultures selected at random for initial screening included Gram-positive and Gram-negative bacteria and yeast of several genera having different nutritional requirements and metabolic activities. Several new compounds were tested *in vitro* at concentration 10 mg/mol. Data pertaining to the relation between structures and bacterial activity of the newly synthesized compounds are presented in Table II. It is to be noted first that most of listed compounds has marked activity against the tested microorganisms.

The tested microorganisms were:
1. *Bacillus cereus*; 2) *Sarcina lutea*; 3) *Staphylococcus aureus*; 4) *Escherichia coli*; 5) *Salmonella paratyphimurum*; 6) *Kelbsiella pneumonia*; 7) *Candida albicans*

Table I. Physical data of the synthesized compounds

Comp. No.	IR/ $cm^{-1}(\nu)$	^{1}H-NMR (δ)	Molecular formula	mp. ℃	Solvent crystn.	Colour	Elemental analysis% Calc./found. C	H	N	S	Cl
1	1685(C=O), 2540(SH)	5.3(s, 1H, SH), 7.1(s, CH=C) 7.4-7.8(m, 9H, C_6H_5-C_6H_4)	$C_{15}H_{12}O\ S_2$ (272.28)	121	Benzene	yellow	66.16 66.2	4.41 4.4	0.00 –	23.52 23.8	– –
3a	2565(SH), 3400(NH)	3.3(d, 2H, CH), 3.8(d, 2H, CH_2), 7(s, 1H, CH=C), 7.3-8 (9H, C_6H_4), 8.2(s, 1H, NH)	$C_{23}H_{21}NOS_2$ (391.39)	193	ethanol	Orange	70.58 70.6	5.37 5.4	3.57 –	16.38 16.4	
3b	3450(NH), 2560(SH)		$C_{21}H_{19}NO_2S_2$ (381.35)	86	benzene	Brown	66.14 66.1	4.98 5.0	3.67 –	16.81 17.0	
4a	1650(C=O), 2950(CH_2)	7.2-8(m, 14H, C_6H_5-C_6H_4 +C_6H_5), 7.0(s, 1H, CH=C)	C23H_{19}NOS (357.32)	265	benzene	Brown	77.31 77.5	5.32 5.1	3.92 –	8.97 9.0	
4b	1645(C=O), 2940(CH_2)	2.4-2.6(q, 4H, CH_2 thiaz.) 6-6.7(t, 3H, Furan), 7.1 (s, 1H-CH=C)	$C_{21}H_{17}NO_2S$ (347.29)	107	ethanol	Brown	72.62 72.6	4.89 4.8	4.03 –	9.23 10.00	
5	3600(OH), 1675(C=C), 1430(-C=S)	7.2-7.8(m, 9H, C_6H_5-C_6H_4) 12.6(s, 1H-OH)	$C_{17}H_{10}Cl_2O_2S$ (381.19)	278	benzene	Orange	53.56 53.6	2.62 2.6	– –	16.82 16.9	18.60 18.6
6	1690(C=O), 1720(C=O), 3200(NH)	3.6(d, 2H, CH_2, thiaz) 7.0(s, 1H, CH=C) 7.2-8 (m, 9H, C_6H_5-C_6H_4), 11.8(1H, NH)	$C_{17}H_{13}NO_2S$ (295.24)	225	ethanol	Yellow	69.15 69.1	4.40 4.4	4.74 –	10.85 10.8	
7	1670(C=O), 1730(C=O), 3300(NH)	7.2-8.1(m, 14H, C_6H_5 +C_6H_5-C_6H_4)	$C_{24}H_{17}NO_2S$ (383.32)	263	ethanol	Yellow	75.20 75.2	4.43 4.5	3.65 –	8.36 8.4	
8	3500(OH), 1680(C=O), 2535(SH), 2850-2800 (CH_2)	3.2-3.4(2d, 4H, 2CH_2), 12.2 (s, 1H, OH), 7.2-7.9(m, 9H, C_6H_5-C_6H_4), 5.2(s, 1H, SH)	$C_{17}H_{16}O_2S_2$ (316.30)	232	ethanol	Yellow	64.55 64.5	5.06 5.00	– –	20.27 20.4	
9	1675(C=O), 1440(C=S), 3520(OH), 2950(CH_2)	2.9-3.1(2d, 4H, 2CH_2), 4.9(s, 1H, thiopyran-3H), 7.2-8(m, 9H, C_6H_5-C_6H_4), 13.4(s, b, 1H, OH)	$C_{18}H_{16}O_2S_2$ (328.31)	283	ethanol	Yellow	65.85 65.8	4.87 4.9	– –	19.53 19.6	

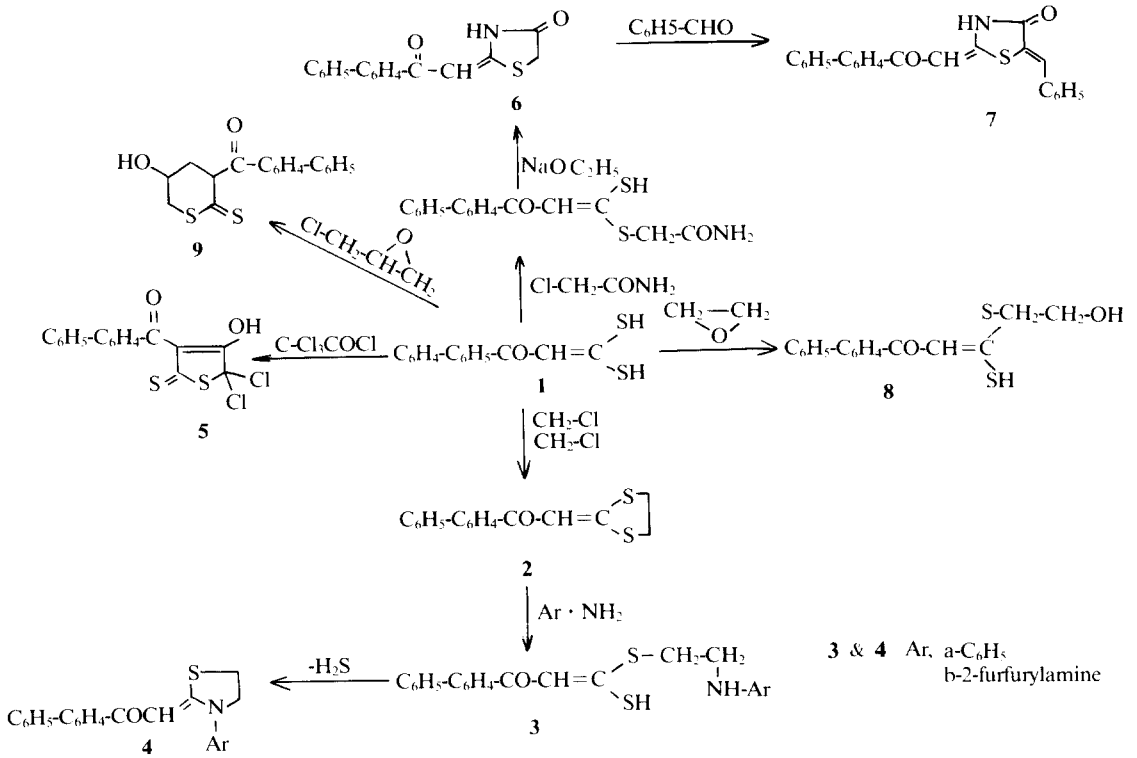
Table II. Antimicrobial activity of synthesized products

Comp. No.	Diameter of inhibition zone in mm Gram (+ve) bacteria 1	2	3	Gram (−ve) bacteria 4	5	6	7
3a	18	14	15	13	16	16	12
3b	16	16	18	14	10	22	14
4a	12	12	16	22	18	20	14
4b	15	16	12	20	15	14	17
5	13	12	14	13	–	24	–
6	18	16	14	17	12	18	12
7	18	–	–	–	–	12	14
8	17	14	16	20	14	26	22
9	18	18	20	22	12	18	24

EXPERIMENTAL

All melting points are uncorrected and determined on "Electrothermal melting point apparatus", IR spectra were measured on "Unicam SP 1000 infrared spectrophotometer", ^{1}H-NMR spectra were recorded on "Varian EM390-90 MHz spectrometer" and the chemical shifts are expressed in ppm ($CDCl_3$). The activity of the tested compounds against microorganisms was determined at the microbiology department at National Organization for Drug Control and Research, Giza, Egypt.

3,3-dimercapto 1-(4-biphenyl)2-propen-1-one **1** and **2** is prepared according to the knwon methods in



the literature[4]. (121°C).

Action of amines on 2 to give 3a,b

A mixture of equimolar ratio of **2** (0.01 mol) and the required amines, aniline and/or 2-furfurylamine (0.01 mol) in water (100 m*l*) was stirred at room temperature for 6 hours. Leaving the reaction mixture over night at room temperature gave **3a,b** (cf Table I). (Yield; 76 & 68%).

Synthesis of thiazoline derivatives, 4a,b

Heating **3a,b** (0.01 mol) in ethanol (100 m*l*) under reflux till complete evolution of hydrogen sulphide (cap. 2 hours) afforded the required N. substituted 2-(4-biphenyl vinylketone) thiazoline **4a,b** (Yield; 66 & 62%).

Synthesis of 2,2-dichloro 3-hydroxy 5-thione 4-(4-biphenyl) thienyl ketone, 5

A mixture of **1** (0.01 mol), sodium ethoxide (0.022 mol) and trichloroacetylchloride (0.011 mol) in dry benzene (100 m*l*) was stirred at room temperature for 3 hours, then heated under reflux for 4 hours. Excess benzene distillated to just dryness, then acidified with cold dilute hydrochloric acid (20%) to give **5**. Recrystallization from benzene obtained a pale yellow crystals (physical data, cf. Table I). (Yield 81%).

Condensation of 1 with chloroacetamide: synthesis of thiazolinone derivative, 6

3 Mercapto 3-S-acetamide 1-(4-biphenyl)2-propen-1-one (prepared from **1** *via* its reaction with chloroacetamide in ether while stirring at 5-10°C). (0.01 mol) in absolute (Merck) and sodium ethoxide (0.01 mol) were heated under reflux till complete evolution of hydrogen sulphide (cap. 3 hours). After cooling, cold water was added while stirring. Leaving the solution at room temperature over night afforded the required product 5-(4-biphenylmethylene ketone)-thiazolin (3H)3-one **6** (physical data cf. Table I). (Yield; 77%).

Condensation of 6 with benzaldehyde: Synthesis of 7

A mixture of **6** (0.01 mol) and benzaldehyde (0.01 mol) in ethanol (100 m*l*) and catalytic amount of triethylamine was heated under reflux for 3 hours. After cooling and pouring into ice-cold water, the

separated solid was collected and recrystallized from ethanol to give **7** as a pale yellow crystals. (physical data cf Table I). (Yield; 86%).

Action of ethlene oxide and epichlorohydrine on 1: Synthesis of 8 and 9

To **1** (0.01 mol) in dry benzene (100 m*l*) ethylene oxide and/or epichlorohydrin (0.01 mol) was added. The reaction mixture was then stirred at room temperature for 5 hours, then heated under reflux for 2 hours. After leaving the reaction mixture aside over night, the separated solid was recrystallized from ethanol to give **8** and **9** respectively. (physical data, cf Table I). (Yield; 84%).

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