SYNTHESIS OF THIOXANTHENYL SUBSTITUTED HETEROCYCLES WITH POTENTIAL MOLLUSCICIDAL AND NEMATOCIDAL ACTIVITY

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The reaction of thioxanthen-9-ol with nucleophiles such as pyrazoles, succinimide, phthalimide and aminotriazoles was investigated. In the reactions, thioxanthen-9-yl is introduced in the 4-position of pyrazoles, on nitrogen in the carboximides and on amino group of aminotriazoles. The synthesized compounds were tested for molluscicidal and nematocidal activity.

The biological and pesticidal activities of thioxanthen-9-ol and its derivatives[1] as well as the important role of pyrazole compounds in the synthesis of pharmaceuticals[2,3] stimulated us to synthesize new thioxanthene derivatives in order to investigate their molluscicidal and nematocidal activities.

It has been previously reported[4] that thioxanthen-9-ol reacts with some carbanions, phenols and thiophenols to yield corresponding condensation products.

In the present work, we report on the synthesis of several new thioxanthen-9-yl substituted nitrogen heterocycles and their biological activity.

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses gave satisfactory values for C, H, N and S. IR spectra were measured on a Unicam SP-1200 spectrophotometer using KBr Wafer technique. ^{1}H NMR spectra were measured in deuterated DMSO on a Varian EM-390 spectrometer. Biological activity tests were carried out in Zoology Department, Faculty of Science, Menoufia University, Shibin El-Kom, Egypt.

Reaction of Thioxanthen-9-ol (*I*) with Nucleophiles

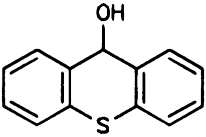
A solution of *I* (0.005 mol) and an appropriate nucleophile (0.005 mol) in a mixture of glacial acetic acid (3 ml) and ethanol (3 ml) was stirred at room temperature for the time given in Table I. The solid was filtered off and crystallized from the proper solvent. The products are listed in Table I, their IR and ^{1}H NMR spectral data are given in Table II.

Reaction of 2-(Thioxanthen-9-yl)-2-benzoylacetonitrile and Ethyl 2-(Thioxanthen-9-yl)acetoacetate with Hydrazine Hydrate

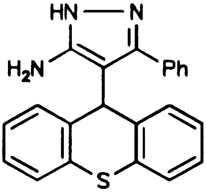
A solution of either compound (0.002 mol) and hydrazine hydrate (0.3 ml, 0.003 mol) in 1-butanol (20 ml) was refluxed for 4 h. The solvent was evaporated under reduced pressure and the products were identified by melting points and mixed melting points as *II* (77% yield) and *III* (41% yield), respectively.

RESULTS AND DISCUSSION

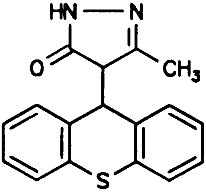
Thioxanthen-9-ol (*I*) reacts with 5-amino-3-phenylpyrazole in a mixture of glacial acetic acid and ethanol to yield a condensation product. The condensation might proceed on amino group, pyrazole NH group, or in the position 4 of pyrazole ring. IR spectrum of the product revealed the presence of NH_2 but pyrazole H-4 was not found in its ^1H NMR spectrum. Moreover, the reaction product could be prepared by condensing *I* with benzoylacetonitrile to 2-(thioxanthen-9-yl)-2-benzoylacetonitrile[4] and subsequent reaction with hydrazine hydrate. All this evidence supports structure *II* for the obtained product.



I

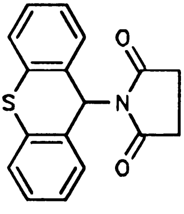


II

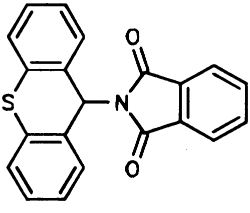


III

It has been also found that thioxanthen-9-ol reacts readily with 3-methyl-5-pyrazolone in a mixture of glacial acetic acid and ethanol at room temperature, to yield 4-(thioxanthen-9-yl)-3-methyl-5-pyrazolone (*III*). The structure of *III* could be assigned on the basis of analytical and spectral data as well as by synthesizing the same product through the reaction of ethyl 2-(thioxanthen-9-yl)acetoacetate[5] with hydrazine hydrate.



IV



V

Furthermore, the reaction of thioxanthen-9-ol with imides has been carried out. An aliphatic imide, succinimide, as well as an aromatic imide, phthalimide react readily with thioxanthen-9-ol to yield 9-succinimido- and 9-phthalimidothioxanthene, (*IV*) and (*V*), respectively.

Thioxanthen-9-ol also reacts with 3-amino-1,2,4-triazole, 1-amino-3-phenyl-1,2,4-triazole-5-thione or 1-amino-3-(4-chlorophenyl)-1,2,4-triazole-5-thione in the molar ratio 2 : 1 to yield 3-[di(thioxanthen-9-yl)amino]-1,2,4-triazole (*VI*), 1-[di(thioxanthen-9-yl)amino]-3-phenyl-1,2,4-triazole-5-thione (*VIIa*) or 4-chlorophenyl analogue *VIIb*, respectively.

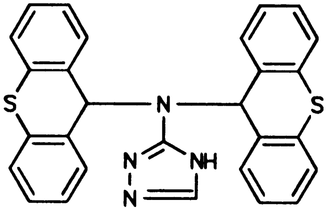
The compounds prepared in this work were tested for their molluscicidal activity towards *Biomphalaria alexandrina* snails, the intermediate host of *Shistosoma mansoni*, the main cause of bilharziasis in Egypt. Different concentrations of the compounds in aqueous solutions (100, 50, 25 and 12.5 ppm) were used for an exposure period of three days.

TABLE I
Synthesized thioxanthen-9-yl substituted heterocycles

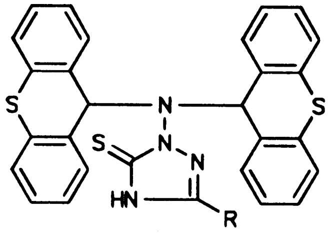
Compound	Reaction time, h	M. p., °C (Solvent[a])	Yield %	Formula (M. w.)	Calculated/Found % C	% H	% S
II	0.5	191	56	$C_{22}H_{17}N_3S$	74.3	4.8	9.0
		(B)		(355.4)	74.2	4.7	8.4
III	6	247	81	$C_{17}H_{14}N_2OS$	69.3	4.8	10.9
		(A)		(294.4)	69.2	4.8	10.8
IV	168	176	25	$C_{17}H_{13}NO_2S$	69.1	4.4	10.8
		(E)		(295.3)	68.5	5.0	11.0
V	168	196	23	$C_{21}H_{13}NO_2S$	73.4	3.8	9.3
		(A/E)		(343.3)	73.4	3.6	8.8
VI	0.5	217	70	$C_{28}H_{20}N_4S_2$	70.5	4.2	13.4
		(C)		(476.6)	70.3	4.2	13.8
VIIa	0.5	222	78	$C_{34}H_{24}N_4S_3$	69.8	4.1	16.4[b]
		(C)		(584.7)	69.3	4.2	16.9
VIIb	24	202	67	$C_{34}H_{23}ClN_4S_3$	65.9	3.7	15.5
		(C)		(619.2)	66.0	4.0	15.5

[a] Crystallization solvents: A acetone, B benzene, E ethanol, C acetic acid; [b] calculated: 9.6% N; found: 9.5% N.

It has been found that compounds *III* and *VI* exhibit distinct activity and bleeding was noticed in snails immersed in test solutions at all the concentrations. The nematocidal activity of the compounds was evaluated against the root-knot nematode *Meloidogyne javanica* which is the most prevalent and destructive phytoparasitic nematode in Egypt. This was carried out with aqueous solution of different concentrations (100, 50 and 25 ppm) using the systemic granular nematocide Nemacur as a standard. Compounds *VIIa* and *VIIb* showed a satisfactory effect only at the 100 ppm concentration.



VI



VIIa, R = C_6H_5

VIIb, R = 4-ClC_6H_4

TABLE II

IR, ^{1}H NMR and mass spectral data of thioxanthen-9-yl substituted heterocycles

Compound	IR, cm^{-1}	^{1}H NMR (δ, ppm)
II	3 460 (NH_2), 3 370 (NH), 3 070 (arom. CH), 1 615 (NH_2), 1 500 (arom. ring)	4.9 s, 1 H (H-9); 7.1 – 7.5 m, 16 H (arom. H, NH and NH_2)
III	3 410, 3 320 (NH), 1 710 (amide)	
IV^a	3 840 (OH), 3 070 (arom. CH), 2 995, 2 940 and 2 860 (CH_2), 1 750 (imide), 1 720 (C=O)	
V	3 085 (arom. CH), 1 760 (imide), 1 700 (C=O), 1 460, 1 445 (arom. ring)	
VI	3 220 (NH), 3 070 (CH), 1 570 (arom. ring)	
VIIa	3 230 (S=C–N), 1 580 (arom. ring), 1 565, 1 550 (NH), 1 200 (C=S)	5.4 s, 2 H (H-9); 6.9 – 7.6 m, 21 H (arom. H); 7.8 s, 1 H (NH)
VIIb	3 220 (S=C–N), 1 590 (arom. ring), 1 200 (C=S), 740 (C–Cl)	

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[a] MS (*m*/*z*): 295 (M^+, 4%), 197 (M^+ – succinimidyl, 7.7%).

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