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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1-(4-METHYL-2-OXO-2H-1-BENZOPYRAN-7-YLOXOACETYL)-4-ALKYLTHIOSEMICARBAZIDES; 1,3,4-THIADIAZOLES AND 1,2,4- TRIAZOLES.

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A series of 1-(4-methyl-2-oxo-2H-1-benzopyran-7-yloxoacetyl)-4-alkylthiosemicarbazides, S-triazoles and their methyl derivatives has been synthesized by condensation of 4-methyl-2-oxo-2H-1-benzopyran-7-yloxo-acetyl hydrazine with alkyl isothiocyanates. Subequent ring closure of the substituted thiosemicarbazides yielded the S-triazoles, and reaction with methyl iodide gave the corresponding methyl derivatives. The substituted 1,3,4-thiadiazoles have been synthesized by cyclodehydration of the substituted thiosemicarbazides with phosphoric acid. The biological activity of some new compounds is reported.

Key words: Substituted 1,3,4-Thiadiazoles, 1,2,4-Triazoles, Biological activity.

Introduction

Thiosemicarbazides are convenient intermediates for the synthesis of 1,3,4-thiadiazoles and 1,2,4-triazoles. They are also known for their antitubercular [1], antifungal [2], and hypoglycemic [3] properties. In view of these, and in continuation of our work [4-6] in this area, the synthesis of some new heterocyclic compounds containing the thiadiazole or triazole, and benzopyranone nucleus are reported here.

Experimental

All compounds were analyzed for their carbon, hydrogen, nitrogen and sulphur contents. The melting points of these compounds were determined using Fisher-John's melting point apparatus and are uncorrected. Infrared (ir) spectra of all the compounds were recorded in nujol as a mull using a beckman Model-33 double beam infrared spectrophotometer. The nmr spectra were recorded using either a Varian T 60 instrument at 60 MHz or on a Varian EM-390 instruments at 90 MHz using TMS as internal reference. Mass spectra were recorded using either an AEIMS-30 instrument or on a Varian MAT III instrument at 70 ev.

4-Methyl-2-oxo-2H-1-benzopyran-7-yloxoacetamide (2). A mixture of 1 (0.01 mol), chloroacetamide (0.01 mol) and anhydrous potassium carbonate (10 g) in dry acetone (100 ml) was refluxed on a water-bath for 15 hr. The reaction mixture was cooled and poured into water. The resultings solid was filtered off, and recrystallized from an appropriate solvent to give 2 (Table 2). Ir: 3390, 3210 (NH_2), 1715 (CO of pyrone), 1695 (CO of amide) and 1605 cm^{-1} (cm^{-1} (C=C).

4-Methyl-2-oxo-2H-1-benzopyran-7-yloxoacetic acid (3). A mxiture of 2 (0.01 mol) and 5 ml of 1N NaOH was heated under reflux for 2 hr. The hot reaction mixture was acidified to pH 1 with concentrated HCl. The resulting solid was filtered off, and recrystallized from an apprpriate solvent to give 3 (Table 2). Ir: 3470-2870 (br., OH), 1730-1705 (CO of α-pyrone and carboxylic acid), 1610 (C=C) and 1405 and cm^{-1} (C-OH).

Methyl-4-methyl-2-oxo-2H-1-benzopyran-7-yloxoacetate (4): A mixture of 3 (0.01 mol), absolute methanol (3 ml) and dry benzene (6 ml) was refluxed on a water-bath, whilst sulphuric acid (0.5 ml) was added dropwise, and refluxing was continued for 12-14 hr. The mixture was cooled and extracted with ehter, and the ether layer dried, then distilled under reduced pressure to yield pure 4 (Table 2). Ir: 1745 (CO of ester), 1715 (CO of x-pyrone), 1605 (C=C) and 1220, 1210 cm^{-1} (ether linkage). ^{1}H-nmr ($CDCl_3$),δ2.1 (s, 3H, CH_3), 3.1 (S,3H,OCH_3), 3.5 (br., s, 2H, OCH_2) and 6.5-7.5 ppm (m,4h, Ar-H).

4-Methyl-2-oxo-2H-1-benzopyran-7-yloxoacetyl hydrazine (5). A solution of ester 4 (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (30 ml) was heated under reflux for 4 hr. The product obtained after cooling was filtered off, dried, and recrystallized from an appropriate solvent to give 5 (Table 2). Ir: 3420, 3210 (NH_2), 3280 (NH), 1715 (CO of α-pyrone), 1690 (CO of acid hydrazide) and 1605 cm^{-1} (C=C). ^{1}H-nmr (CF_3 COOD) : δ 2.0 (s,3H, CH_3), 3.3 (br., s, 2H, OCH_2), 5.1 (br.,s, 2H,NH_2), 6.5-7.4 (m,4H,Ar-H) and 10.3 ppm (br,s,1H,CONH).

4-Alkyl-1-(4-methyl-2-oxo-2H-1-benzopyran-7-yloxoacetyl)-thiosemicarbazides (6a-c). Equimolar quantities of 5 (0.01 mol) and alkylisothiocyanate namely methyl isothiocyanate, ethyl isothiocyanate and phenyl isothiocyanate (0.01 mol) were refluxed in butanol (50 ml) for 4 hr. The product obtained after cooling was filtered, dried, and

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recyrstallized from an appropriate solvent to give 6a-c (Table 2) Ir: 3240 (NH), 1720-1710 (CO of α-pyrone), 1680-1665 (CO of acid hydrazide), 1350-1367 (C=S) and 1605 cm^{-1} (C=C). ^{1}H-nmr of 6b (DMSO-d_6) : δ 1.1 (t, 3H, CH_2 CH_3), 2.0 (s, 3H,CH_3), 3.0 (q, 2H, NCH_2), 3.4 (br., s, 2H, OCH_2), 6.5-7.3 (m, 4H,Ar-H), 9.6 (br.,s,2H, NHCSNH) and 10.2 ppm (br., s, 1H, CONH). ^{1}H-nmr of 6c (DMSO-d_6: δ 2.1 (s, 3H,CH_3), 3.3 (br.,s,2H,OCH_2), 6.5-7.4 (m,9H,Ar-H), 9.7 (br.,s,2H), NHCSNH) and 10.3 ppm (br.,s,1H,CONH). Mass of 6c:m/z 383 (M^+), 248, 233, 217, 189, 177, 176, 159, 135, 103, 93, 77, 51.

TABLE 1. INSECTICIDAL ACTIVITY OF SOME SYNTHESIZED COMPOUNDS AGAINST MOSQUITO LARVAE

Concentration	5ppm		10ppm		15ppm	
Compd	dead	mortality	dead	mortality	dead	mortality
No	No	%	No	%	No	%
6b	7	35	11	55	14	70
6c	3	15	5	25	9	45
7a	6	30	13	65	14	70
7b	6	30	10	50	19	95
8a	3	15	4	20	6	30
8b	3	15	7	35	11	55

7-(5-Alkylamino-1,3,4-thiadiazol-2-ylmethoxy)-4-methyl-2-oxo-2H-1-benzopyrans (7a,b). Thiosemicarbazides (6a,c) (0.01 mol) were added with stirring to anhydrous phosphoric acid (20 ml) during 20 min. The flask was heated on an oil bath at 120°C for 0.5 hr, and the slurry was poured over ice-water. The solid which separated was filtered off, and recrystallized from an appropriate solvent to give 7a,b. Ir:3215-3200 (NH), 1715 (CO) of α-pyrone), 1630 (C=N) and 1605 cm^{-1} (C=C). ^{1}H-nmr of 7b (CF_3 COOD): δ 2.0 (s,3H,CH_3), 3.4 (br., s, 2H, OCH_2), 6.5-7.5 (m,9H,Ar-H) and 10.4 ppm (br.,s,1H,NH).

Reaction of 5 with alkyl isothiocyanate: Formation of 7a,b. A solution of 5 (0.01 mol) and alkyl isothiocyanate namely methyl isothiocyanate and phenyl isothiocyanate (0.01 mol) in acetic acid (20 ml) was heated under reflux for 2 hr. The reaction mixture was cooled and poured onto water. The

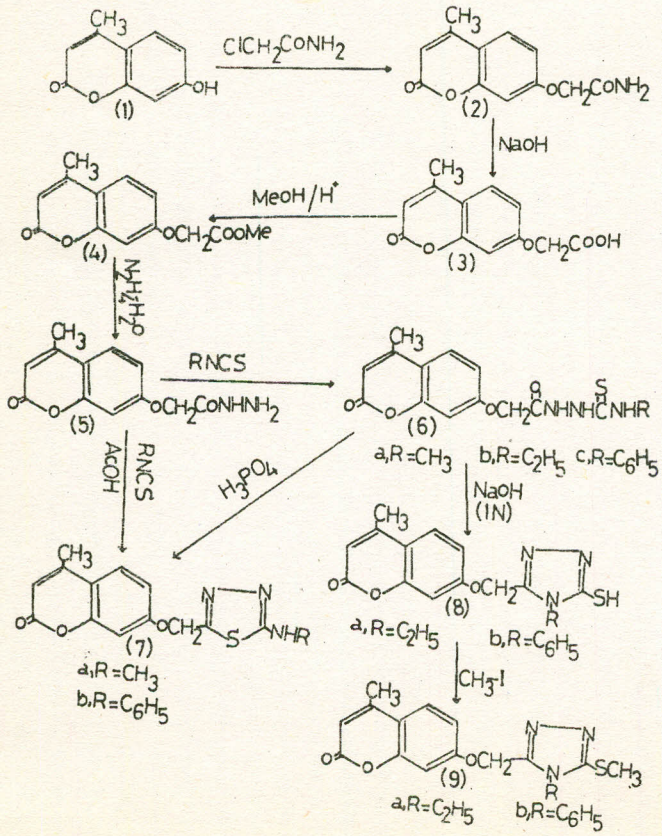
TABLE 2. CHARACTERIZATION DATA OF THE COMPOUNDS 2-9

Compd No.	m.p.,°C (Colour)	Crystallized from (Yield %)	Mol. formula	Analysis Found (%) C	H	(Calcd) N	S
2	235 (Paleyellow)	Ethanol 78	$C_{12}H_{11}NO_4$	61.41 (61.80	4.36 4.72	5.58 6.00	- -)
3	207 (Colourless)	Methanol (68)	$C_{12}H_{10}O_5$	61.33 (61.53	4.01 4.27	- -	- -)
4	123 (Colourless)	Ethanol (75)	$C_{13}H_{12}O_5$	63.10 (62.90	4.62 4.83	- -	- -)
5	205 (Colourless)	Butanol (63)	$C_{12}H_{12}N_2O_4$	57.81 (58.06	4.50 4.83	10.98 11.29	- -)
6a	190 (Colourless)	Butanol (80)	$C_{14}H_{15}N_3O_4S$	52.07 (52.33	4.51 4.67	12.85 13.08	9.69 9.93)
6b	195 (Colourless)	Butanol (83)	$C_{15}H_{17}N_3O_4S$	53.46 (53.73	4.83 5.07	12.26 12.53	9.37 9.55)
6c	180 (Colourless)	Butanol (85)	$C_{19}H_{17}N_3O_4S$	59.21 (59.53	4.05 4.43	10.67 10.96	8.10 8.35)
7a	295 (Paleyellow)	Ethanol (75)	$C_{14}H_{13}N_3O_3S$	55.05 (55.44	3.96 4.29	13.52 13.86	10.21 10.56)
7b	240 (Paleyellow)	Ethanol (78)	$C_{19}H_{15}N_3O_3S$	62.25 (62.46	3.84 4.10	11.30 11.50	8.47 8.76)
8a	240 (Paleyellow)	Ethanol (70)	$C_{15}H_{15}N_3O_3S$	56.62 (56.78	4.47 4.73	12.93 13.24	9.76 10.09)
8b	260 (Paleyellow)	Ethanol (73)	$C_{19}H_{15}N_3O_3S$	62.17 (62.46	3.75 4.10	11.28 11.50	8.49 8.76)
9a	160 (Colourless)	Methanol (65)	$C_{16}H_{17}N_3O_3S$	57.81 (58.00	4.82 5.13	12.39 12.68	9.25 9.66)
9b	140 (Colourless)	Methanol (63)	$C_{20}H_{17}N_3O_3S$	63.06 (63.32	4.07 4.48	10.79 11.08	8.10 8.44)

solid obtained was filtered off, and recrystallized from an appropriate solvent to give 7a,b (Table 2).

7-(5-merapto-4-alkyl-1,2,4-triazol-3-ylmethoxy)-4-methyl-2-oxo-2H-l-benzopyrans (8a, b). Thiosemicarbazides (6b,c) (0.01 mol) were hydroxide solution (4%, 25 ml) for 3 hr. The resulting solution was treated with charcoal, filtered, and cooled. The filtrate was acidified with hydrochloric acid to pH 5-6. The solid which appeared was filtered off, and recyrstallized from an appropriate solvent to give 8a, b (Table 2. Ir: 3230 (NH), 2580 (weak,SH), 1720 (CO of α-pyrone), 1625 (C=N), 1605 (C=C) and 1325 cm^{-1} (C=S). 1H-nmr of 8a (CF_3COOD): δ 1.2 (t, 3H, CH_2CH_3), 2.0 (s,3H,CH_3), 3.4 (br., s, 2H, OCH_2), 3.8 (q 2H,NCH_2), 4.6 (br.,s,1H,SH), 6.5-7.3 (m,4H,Ar-H) and 9.8 ppm (br.,s,1H,NHCS). ^{1}H-nmr of 8b (DMSO-d_6): δ 2.1 (s, 3H,CH_3), 3.5 (br.,s,2H,OCH_2), 4.7 (br.,s,1H,SH), 6.4-7.4 (m,9H,Ar-H) and 9.9 ppm (br.,s,1H,NHCS). Mass of 8b: m/z 365 (M^+), 190, 176, 148, 147, 131,117, 91, 77, 51.

7-(5-methylthio-4-alkyl-1,2,4-triazol-3-ylmethoxy)-4-methyl-2-oxo-2H-l-benzopyrans (9a, b):. To a suspension of 8a, b (0.01 mol), fused sodium acetate (2 g) and methyl iodide (0.01 mol) were added. The mixture was refluxed for 6 hr, cooled to room temperature, and poured on ice-water. The white solid which appeared was filtered off, and recrystallized from an appropriate solvent to give 9a, b (Table 2). Ir: 1715(C) of α-pyrone), 1630 (C=N) and 1605 cm^{-1} (C=C). ^{1}H-nmr of 9a ($CDCl_3$): δ 1.2(t,3H,CH_2CH_3), 2.1 (s,3H,CH_3), 2.6(s,3H,SCH_3), 3.3 (br,s,2H,OCH_3), 3.9(q,2H,NCH_2) and 6.4-7.3 ppm (m,4H,Ar-H). ^{1}H-nmr of 9b ($CDCl_3$): δ 2.1 (s,3H, CH_3), 2.67(s,3H,SCH_3), 3.4 (br,2H,OCH_2) and 6.5-7.4 ppm (m, 9H, Ar-H). Mass of 9a : m/z 331 (M^+), 317, 176, 156, 128, 115,77,69,51.



Scheme 1.

Results and Discussion

The 4-methyl-2-oxo-2Hl-benzopyran-7-yloxoacetamide (2), prepared via alkylation of 7-hydroxyl-4-methylcoumarin with chloroacetamide according to the literatue method [6], was hydrolysed to give 4-methyl-2-oxo-2H-l-benzopyran-7-yloxoacetic acid (3).

Esterification [7,8] of compound 3 with methyl alcohol in acid medium gave the corresponding methyl-(4-methyl-2-oxo-2H-l- benzopyran-7-yloxoacetate (4). Ester (4), on condensation with hydrazine hydrate in absolute ethanol gave the corresponding 4-methyl-2-oxo-2H-l-benzopyran-7-yloxoacetyl hydrazine (5), which was allowed to react with alkyl isothiocyanates to give the corresponding 4-alkyl-l-(4-methyl-2-oxo-2H-l-benzopyran-7-yloxoacetyl) thiosemicarbazides (6a-c) in good yields.

7-(5-Alkylamino-1,3,4-thiadiazol-2-ylmethoxy)-4-methyl-2- oxo-2H-l-benzopyrans (7a, b) could be obtained by the cyclodehydration of thiosemicarbazides (6) with phosphoric acid. The structure (7) were confirmed by reacting of 4-methyl-2-oxo-2H-l-benzopyran-7-yloxoacetyl hydrazine (5) with alkyl isothiocyanates in boiling acetic acid under reflux, when the same products were formed.

The 7-(5-mercapto-4-alkyl-l-2,4-triazol-3-ylmethoxy)-4-methyl-2-oxo-2H-l-benzopyrans (8a,b) were obtained by refluxing thiosemicarbazides (6) with 2N sodium hydroxide. These thiols (8), when treated with methyl iodide in presence of sodium actate [9] in acetone, formed the 7-(5-methylthio-4-alkyl-1,2,4-triazol-3-ylmethoxy)-4-methyl-2-oxo-2H-l-benzopyrans (9a, b).

Biological Activity Culex pipiens mosquitoes are the main vector of some parasitic diseases (filarieasis), viral diseases (rift vally fever) and encephilitis, in most of localities in the world, especially in Egypt [10]. Using ethanolic solutions, with different concentration, all of the newly synthesized compounds were tested of their insecticide effect against mosquito larvae. Twenty larva of mosquito were used for each compound at different concentrations (5,10,15 ppm) in every experiment. The results indicated that the compounds 6b, 7a, b and 8b have a insecticidal role in mosquito control (larval stage). The screening results for the compounds 6a, c; 7a,b; 8a,b are shown in Table 1.

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