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Synthesis and Antimicrobial Activity of some New Thiazolo-, Quinoxalino-, Piperidino- and Naphthatriazino- coumarins

S. S. EL-MORSY*, A. A. FADDA and M. S. EL-HOSSINI

Department of Chemistry, Faculty of Science, Mansoura University, Mansoura, Egypt

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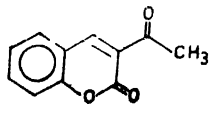
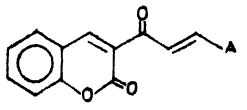
Various derivatives from 3-acetylcoumarin are prepared : aminothiazole (9), coumarilic acid ( ), piperidone (12), quinoxaline (14) and naphthatriazine (15). Active methylene compounds react with the arylidene (2a, b) to give the cyclohexanone derivatives (4a, b, respectively). SeO_2 on reaction with 1 gives the α,β-diketon (13) which reacts with hydrazine to give 18. The antimicrobial activities of the products against different organisms are discussed.

SEVERAL pharmacologically active compounds contain quinoline, thiazole, pyridine and quinoxaline moieties[1-3]. In continuation of our earlier work on heterocyclic systems, we describe here the synthesis and antibacterial activity of the title compounds.

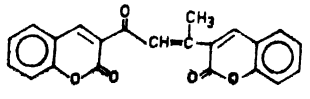
Interaction of 1 with the aldehydes gave the corresponding chalcones (2a, b). From the reaction of 1 with 3-pyridinealdehyde, two products could be isolated, one of them was analysed for the expected chalcone (2a) while the other was analysed for 3.



1



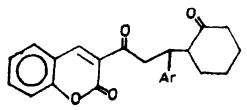
2a ; Ar = 3-pyridyl
2b ; Ar = 2-furfuryl



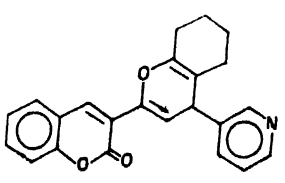
3

The structure 3 was further confirmed when the experiment was repeated under identical condition without using 3-pyridinealdehyde. The product may be a result of aldol condensation.

Interaction of 2a, b with cyclohexanone furnished an addition product which gave analytical results compatible with 4a, b. Cyclisation of 4a may be effected either by heating with acetic acid – hydrochloric acid mixture or by polyphosphoric acid to give 5. Compound 4b when treated with ammonium acetate, afforded the quinolino compound 6, the structure being confirmed by elemental analyses and ir spectral data, ν_{max} 3 310 cm^{-1} (NH).



4a ; Ar = 3-pyridyl
4b ; Ar = 2-furfuryl



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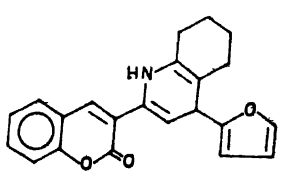
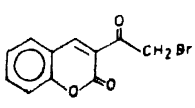


6

Bromination of 1 with bromine (1 : 1) in acetic acid gave the ω-bromo derivative (7) whose structure was confirmed based on elemental analyses, ir spectra, 1 730 (CO) and 695 cm^{-1} (CBr), and previous work[4,5]. On the other hand, bromination of 1 in aqueous sodium hydroxide solution to give coumarilic acid (8), was in agreement with the reported work[6]. Interaction of 7 with excess thiourea in alcohol afforded 2-aminothiazole (9) whose structure was based on elemental analyses, ir spectra, 3 480 and 3 420 cm^{-1} (NH_2) and previous work[4].



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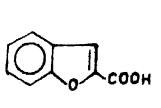

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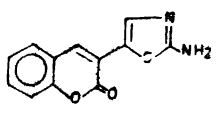
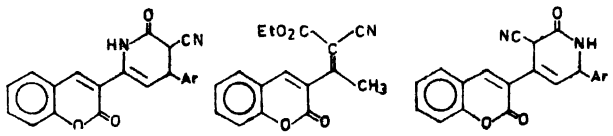


9

Interaction of 2a with ethylcyanoacetate and ammonium acetate furnished the corresponding car-

bonitrile derivative (10). Compound 10 was also obtained by heating 2a with cyanoacetamide. On the other hand, on heating ethyl α-cyano-1-acetylcoumarinoacetate (11) with 3-pyridinealdehyde in ammonium acetate, 1,2,5,6-tetrahydro-6-oxo-4-(2-oxo-2*H*-1 benzopyran-3-yl) [2, 3'-bispyridine]-5-carbonitrile (12) was obtained The structures 10 – 12 were supported by elemental analyses and ir specrta, 2 240 (CN), 1 720 (CO) and 1 540 cm^{-1} (highly ionic CO).

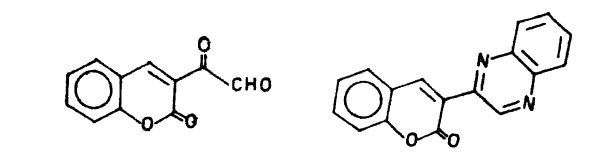


10 11 12

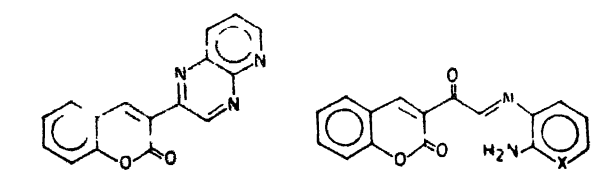
10, 12 ; Ar = 3-pyridyl

Treatment of 1 with selenium dioxide gave α,2-dioxo-2*H*-1-benzopyran-3-acetaldehyde (13), the structure of which was based on elemental analyses, ir spectr aand analogous work[7,8]. The authors interest was focussed on the behaviour of 13 to wards the reaction with diamines to obtain naphthatriazine or quinoxaline derivatives. Compound 13 was treated with *o*-phenylenediamine and 2,3-diaminopyridine in alcohol to give 3-(2-quinoxalinyl)-2*H*-1-benzopyran-2-one (14) and 3-pyrido[2,3-*b*]-pyrazin-2-yl-2*H*-1-benzopyran-2-one (15), respectively. However, an attempt to isolate the intermediate 16 and 17 was unsuccessful.

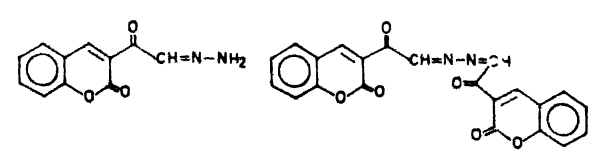
Condensation of 13 with hydrazine hydrate was successful and the hydrazone derivative of type 18 was obtained and not 19. The structure of 18 was established by elemental analyses and ir spectral data.



13 14



15 16 ; X = CH, 17 ; X = N



18 19

All these compounds have been characterised by their analytical and spectral data, and screened against bacteria by cup-plate agar diffusion method against *E coli, Staphylococcus aureus, Str. viridanes. Ps. aeruginosa* and *Candida albicans* at the concentrations, 50 and 100 μg cm^{-3}. The results with 50 μg cm^{-3} are presented in Table 2.

Experimental

The purity of the compounds was checked by tlc. Melting points were determined in open capillary method and are uncorrected. Ir spectra (KBr) were obtained on a Pye-Unicam 2000 spectrophotometer, and ^1H nmr spectra ($CDCl_3$) at 60 MHz on a Varian A-60 spectrometer using TMS as internal standard.

Condensation of **1** *with aldehydes :* A mixture of 1 (0 02 mol), the requisite aldehyde (0 02 mol) and piperidine (0.1 ml) in n-butanol (50 ml) was refluxed for 6 h. The product (2a, b) was recrystallised from ethanol. In case of 2a, the insoluble part was recrystallised from acetic acid to give 3.

Interaction of **2a, b** *with cyclohexanone .* A mixture of 2a, b (0.01 mol), cyclohexanone (0.01 mol) and piperidine (0.5 ml) in n-butanol (50 ml) was refluxed for 8 h. Dilute HCl was then added to give 4a, b.

Cyclisation of **4a** *:* A solution of 4a (0.01 mol) in acetic acid – hydrochloric acid mixture (1 : 1, 50 ml) was refluxed for 4 h. The product on concentration gave 5.

Cyclisation of **4b** *:* A mixture of 4b (0.01 mol) and ammonium acetate (0.03 mol) in glacial acetic acid was refluxed for 20 h. The product on concentration gave 6.

Bromination of **1** *:* (i) A solution of 1 (0.01 mol) in acetic acid (20 ml) was treated with bromine (0.01 mol) in acetic acid (20 ml) and then concentrated to give 7. (ii) A mixture of 1 (0.01 mol) and bromine (0.01 mol) were dissolved in alcoholic potassium hydroxide (10%, 50 ml) and left to stand at room temperature for 1 day. Dilute HCl was then added to give 7.

Thiazole formation from ω-haloketone : To a solution of 7 (0.01 mol) in ethanol (50 ml), was added thiourea (0.02 mol). The reaction mixture was then refluxed for 4 h and worked up to give 9.

Carbonitrile formation : (i) A mixture of 2a (0.01 mol), ethyl cyanoacetate (0.013 mol) and ammonium acetate (0.08 mol) was heated in an oil-bath at 150° for 2 h. The product on recrystallisation from dilute ethanol gave 10. (ii) To a solution of 1 (0.01 mol) in dry xylene (50 ml), was added ethyl cyanoacetate (0.013 mol) and ammonium acetate (0.08 mol). The reaction mixture was refluxed for ~10 h using Dean-Stark water separator. The product on concentration and cooling gave 11. A mixture of 11 (0.01 mol) and 3-pyridinealdehyde

TABLE 1—PHYSICAL AND NMR SPECTRAL DATA OF COMPOUNDS 2 – 18

Compd. no.	Yield %	M.p. °	Mol. formula	N % : Found/ (Calcd.)	δ
2a	75	75	$C_{17}H_{11}NO_3$	5.1 (5.0)	5.2 (s, 1H), 5.6 (d, 1H), 6.0 (d, 1H), 7.2 – 8.0 (m, 8H)
3	30	182	$C_{23}H_{14}O_5$	–	2.3 (s 3H), 6.3 (s, 1H), 5.0 (s, 1H), 5.3 (s, 1H), 7.2 – 7.9 (m, 8H)
4a	62	135	$C_{23}H_{20}NO_4$	3.5 (3.7)	0.8 (m, 1H), 1.2 (d, 2H), 1.5 (m, 1H), 1.8 – 2.8 (m, 8H), 5.2 (s, 1H), 7.2 – 8.0 (m, 8H)
5	56	160	$C_{23}H_{19}NO_3$	3.6 (3.9)	1.8 – 2.9 (m, 8H), 5.2 (s, 1H), 7.1 – 7.8 (m, 9H)
6	70	212	$C_{22}H_{18}NO_3$	4.2 (4.0)	1.9 – 2.8 (m, 8H), 5.07 (s. 1H), 8 8 (s, NH), 7.2 – 8.0) (m, 8H)
7	75	120	$C_{11}H_7O_3Br$	–	2.3 (s, 2H), 5.3 (s, 1H), 7.2 – 8.0 (m, 4H)
8	46	190	$C_9H_6O_3$	–	–
9	66	193	$C_{12}H_{11}N_3O_3S$	11.5 (11.3)	6.1 (s, 1H), 5.2 (s, 1H), 7.1 – 8.0 (m, 4H), 10 0 (d, 2H)
10	73	182	$C_{20}H_{12}N_2O_3$	12.3 (12.3)	2.3 (d, 1H), 2.5 (d, 1H), 5.1 (s, 1H), 7.2 – 8.0 (m, 8H)
11	69	121	$C_{16}H_{13}NO_4$	5.1 (4.9)	1.0 (t, 3H), 1.8 (s, 3H), 5.0 (s, 1H), 7.1 – 7.8 m, 4H)
12	77	190	$C_{20}H_{13}N_3O_3$	12.3 (12.3)	2.2 (d, 1H), 2.5 (d, 1H), 5.1 (s, 1H), 7.2 – 8 0 (m, 8H)
13	50	104	$C_{11}H_8O_4$	–	5.0 (s, 1H), 7.1 – 7.9 (m, 4H)
14	80	155	$C_{17}H_{10}N_2O_3$	10.1 (10.2)	5,1 (s, 1H), 7.1 – 8.0 (m, 9H)
15	72	190	$C_{16}H_9N_3O_3$	15.2 (15.3)	5.2 (s, 1H), 7.2 – 8.1 (m, 8H)
18	65	135	$C_{11}H_9N_3O_3$	13.9 (13.6)	4.0 (d, 2H), 5 1 (s, 1H), 7.1 – 8.0 (m, 4H)

TABLE 2—RESULTS OF ANTIMICROBIAL ACTIVITY* OF COMPOUNDS 2 – 18

Compd. no.	*E. c*	*S. a*	*S. v*	*P. a*	*C. a*
2a	20	15	0.0	0.0	0.0
2b					
4a	23	15	0.0	26	0.0
5	25	15	0.0	19	0.0
6	29	18	15	23	0.0
7	30	22	0 0	21	0.0
8	20	0.0	0.0	15	0.0
9	27	15	20	27	0 0
10	29	0.0	0.0	25	0.0
11	28	0.0	17	0.0	0.0
12	30	0.0	0 0	27	0.0
13	20	0.0	0.0	15	0 0
14	27	20	17	22	0.0
15	29	21	15	27	0.0
18	22	0.0	0.0	19	0.0

**E. c* = *E. coli*; *S. a* = *S. aureus*, *S. v* = *S. viridane*, *P. a* = *P. aeruginosa*, *C. a* = *C. albicans*; Diameter of inhibition zone in mm.

(0.01 mol) was heated in an oil-bath at 150° for 2 h. The product on cooling and recrystallisation from dilute alcohol gave 1,2,5,6-tetrahydro-6-oxo-4-(2-oxo-2*H*-1-1-benzopyran 3-yl)[2,3'-dipyridine]-5-carbonitrile.

α,2-Dioxo-2H-1-benzopyran-3-acetaldehyde (**13**): It was prepared following the reported methods[7,8].

3-(2-Quinoxalinyl-2H-1-benzopyran-2-one (**14**) *and 3-pyridol[2,3-b]pyrazin-2-yl-2H-1-benzopyran-2-one* (**15**): A mixture of **13** (0.01 mol), *o*-phenylenediamine and/or 2,3-diaminopyridine (0.01 mol) in ethanol (50 ml) was refluxed for 6 h. The product on concentration and cooling gave **14** and **15**, respectively.

Formation of the hydrazone derivative of **13**: To a solution of **13** (0.01 mol) in ethanol (50 ml) was added hydrazine hydrate (0.01 mol). The reaction mixture was refluxed for 2 h. The product on concentration and cooling gave **18**.

Antibacterial activity: The results of screening at 50 $\mu g\ cm^{-3}$ indicate that aminothiazolo-, quinolino-, glyoxalo-, carbonitrilo-, quinoxalino- and naphthatriazino- coumarins are quite active against all the microorganisms and had no anti-candidiasis activity. All the compounds are highly significant from chemotherapeutic point of view, since many of them exhibiting activities against gram-negative bacteria are recorded to have antitumour activity[9].

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