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Synthesis and Biological Activity of New Pyrazoline and Pyrazole Derivatives

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ABSTRACT. Condensation of p-sulfamylphenylhydrazine with chalcones, leads either to hydrazones **2** or to pyrazolines **3**. Oxidation of **3** afforded pyrazole derivatives **4**. Benzenesulfonylureas **5** and thioureas **6** were also prepared. Cyclization of the thioureido group of compounds **6** by treating with ethyl bromoacetate, ethyl β-bromopropionate and α-bromoacetophenone afforded the corresponding thiazolidinone, thiazinone and thiazoline derivatives **7, 8, 9** respectively. The biological activity of the prepared compounds were also studied and they were found inactive.

KEY WORDS: Pyrazolines; Benzenesulfonylureas; Benzenesulfonylthioureas.

Introduction

A wide variety of pharmacological properties have been encountered with di-and trisubstituted pyrazoles. This include antiflammatory[1-4], antibacterial[5-7], antineoplastic[8,9], antiallergitic[10,11] and hypoglycemic activities[12,16]. In this report some new trisubstituted pyrazolines and pyrazoles were prepared with the hope that they may be have some potential antibacterial value properties.

Results and Discussion

Condensation of the key intermediate, p-sulfamylphenylhydrazine hydrochloride with substituted chalcones **1** afforded 3,5-diaryl-l-(p-sulfamylphenyl)-Δ^2-pyrazolines (3; Table 1). However, reaction of p-sulfamylphenylhydrazine hydrochloride with chalcones **1** in the presence of sodium acetate and few drops of acetic acid yielded the corresponding arylhydrazones (2; Table 1) which were easily cyclized to pyrazolines **3** when boiled with few drops of HCl. The IR spectra of **2** showed two strong absorption bands at 1600-1608 and 1625-1643cm^{-1} for ν C = C and ν C = N respectively, as well as two bands at 1335-1350 and 1170-1185cm^{-1} due to the $SO_2N<$ function. The NH appeared in the 3150-3265cm^{-1} region. On the other hand, the IR spectra of the pyrazoline

derivatives **3** displayed two absorption bands at 3250-3264 and 3365-3382 cm^{-1} indicative of the NH_2 group, in addition to two strong bands at 1333-1365 and 1164-1175 cm^{-1} for the SO_2N group. The structure of pyrazolines **3** was further confirmed by their ^1H NMR spectra which exhibited besides the aromatic signals, two multiplets at δ 5.5-5.8 and 2.7-4.0. The low field multiplet is assigned to H-5 of the pyrazoline while the other multiplet to H-4 (Table 2).

TABLE 1. Physical and analytical data of compounds 2-6.

Compound	R	R`	Yield %	mp °C	Molecular formula	Elemental analysis Calcd / % C	H	N	S	Found / % C	H	N	S
2A	C_6H_5		78	146	$C_{29}H_{23}N_3O_2S$	72.96	4.82	8.80	6.70	73.12	5.00	8.91	6.78
2B	p-$CH_3C_6H_4$		74	154	$C_{30}H_{25}N_3O_2S$	73.31	5.09	8.55	6.51	73.51	5.21	8.65	6.71
2C	p-Br C_6H_4		76	178	$C_{29}H_{22}BrN_3O_2S$	62.58	3.95	7.55	5.75	62.67	4.11	7.70	5.80
3A	C_6H_5		88	262	$C_{29}H_{23}N_3O_2S$	72.96	4.82	8.80	6.70	73.12	5.00	9.12	6.85
3B	p-$CH_3C_6H_4$		82	282	$C_{30}H_{25}N_3O_2S$	73.31	5.09	8.55	6.51	73.09	5.21	8.72	6.61
3C	p-Br C_6H_4		85	284	$C_{29}H_{22}BrN_3O_2S$	62.58	3.95	7.55	5.75	62.68	4.02	7.56	5.89
4A	C_6H_5		75	208	$C_{29}H_{21}N_3O_2S$	73.26	4.42	8.84	6.73	73.34	4.20	8.61	6.83
4B	p-$CH_3C_6H_4$		72	212	$C_{30}H_{23}N_3O_2S$	73.62	4.70	8.58	6.54	73.75	4.62	8.70	6.50
4C	p-Br C_6H_4		68	215	$C_{29}H_{20}BrN_3O_2S$	62.81	3.61	7.58	5.78	63.00	3.71	7.82	5.91
5Aa	C_6H_5	C_6H_5	82	170	$C_{36}H_{28}N_4O_3S$	72.48	4.69	9.39	5.36	72.51	4.50	9.52	5.45
5Ab	C_6H_5	Cyclohexyl	80	173	$C_{36}H_{34}N_4O_3S$	71.76	5.64	9.30	5.31	71.86	5.74	9.51	5.32
5Ac	C_6H_5	α-Naphthyl	62	186	$C_{40}H_{30}N_4O_3S$	74.30	4.64	8.67	4.95	74.56	4.75	8.76	5.01
5Ba	p-$CH_3C_6H_4$	C_6H_5	78	183	$C_{37}H_{30}N_4O_3S$	72.78	4.92	9.18	5.24	73.00	5.11	9.08	5.26
5Bb	p-Ch_3Ch_4	Cyclohexyl	79	238	$C_{37}H_{36}N_4O_3S$	72.08	5.84	9.09	5.19	72.11	5.80	9.00	5.31
5Ca	p-Br C_6H_4	C_6H_5	75	188	$C_{36}H_{27}BrN_4O_3S$	64.00	4.03	8.29	4.74	64.20	4.12	8.31	4.82
5Cb	p-Br C_6H_4	Cyclohexyl	78	192	$C_{36}H_{33}BrN_4O_3S$	63.43	4.84	8.22	4.69	63.31	4.92	8.00	4.82
6Aa	C_6H_5	C_6H_5	70	152	$C_{36}H_{28}N_4O_2S_2$	70.58	4.57	9.15	10.45	70.70	4.70	9.21	10.62
6Ad	C_6H_5	Benzyl	72	190	$C_{37}H_{30}N_4O_2S_2$	70.92	4.79	8.94	10.22	71.01	5.00	8.71	10.12
6Ba	p-$CH_3C_6H_4$	C_6H_5	69	148	$C_{37}H_{30}N_4O_2S_2$	70.92	4.79	8.94	10.22	70.72	4.80	9.02	10.41
6Bd	p-$CH_3C_6H_4$	Benzyl	71	175	$C_{38}H_{32}N_4O_2S_2$	71.25	5.00	8.75	10.00	71.31	4.89	8.90	9.89
6Ca	p-Br C_6H_4	C_6H_5	68	176	$C_{36}H_{27}BrN_4O_2S_2$	62.51	3.90	8.10	9.26	62.30	4.10	8.05	9.52
6Cd	p-Br C_6H_4	Benzyl	65	142	$C_{37}H_{29}BrN_4O_2S_2$	62.97	4.11	7.94	9.08	63.08	3.99	8.00	9.12

TABLE 2. Physical and analytical data of compounds 7-9.

Compound	R	R`	Yield %	mp °C	Molecular formula	Elemental analysis Calcd / % C	H	N	S	Found / % C	H	N	S
7Aa	C_6H_5	C_6H_5		257	$C_{38}H_{28}N_4O_3S_2$	69.93	4.29	8.58	9.81	70.10	4.30	8.70	10.00
7Ad	C_6H_5	Benzyl		248	$C_{39}H_{30}N_4O_3S_2$	70.27	4.50	8.40	9.60	70.45	8.51	8.62	9.62
7Ba	p-CH_3 C_6H_4	C_6H_5		284	$C_{39}H_{30}N_4O_3S_2$	70.27	4.50	8.40	9.60	70.35	4.62	8.42	9.85
7Ca	p-Br C_6H_4	C_6H_5		296	$C_{38}H_{27}BrN_4O_3S_2$	63.38	3.69	7.66	8.75	63.50	3.90	7.75	8.92
8Ba	p-$CH_3C_6H_4$	C_6H_5		182	$C_{40}H_{32}N_4O_3S_2$	70.58	4.70	8.23	9.41	70.54	4.92	8.51	9.61
8Bd	p-CH_3 C_6H_4	Benzyl		194	$C_{41}H_{34}N_4O_3S_2$	70.89	4.84	8.06	9.22	71.02	5.00	8.31	9.35
8Cd	p-Br C_6H_4	Benzyl		188	$C_{40}H_{31}BrN_4O_3S_2$	63.24	4.08	7.37	8.43	63.42	4.12	7.47	8.51
9Ad	C_6H_5	Benzyl		180	$C_{45}H_{34}N_4O_2S_2$	74.38	4.68	7.71	8.81	74.45	4.60	7.90	8.62
9Bd	p-CH_3 C_6H_4	Benzyl		208	$C_{46}H_{36}N_4O_2S_2$	74.59	4.86	7.56	8.64	74.51	5.01	7.90	8.42
9Ca	p-Br C_6H_4	C_6H_5		154	$C_{44}H_{31}BrN_4O_2S_2$	66.75	3.91	7.08	8.09	66.81	4.11	7.21	8.15
9Cd	p-Br C_6H_4	Benzyl		188	$C_{45}H_{33}BrN_4O_2S_2$	67.08	4.09	6.96	7.95	67.30	4.30	7.11	8.00

Mild oxidation of the pyrazoline derivatives **3** with bromine water led to the formation of the corresponding pyrazoles (**4**; Table 1). In consistent with the proposed structures the ^{1}H NMR spectra of these pyrazoles showed the aromatic protons as multiplets in the δ 7.0-8.4 and lacked the two multiplets existing in the corresponding pyrazolines (Table 3).

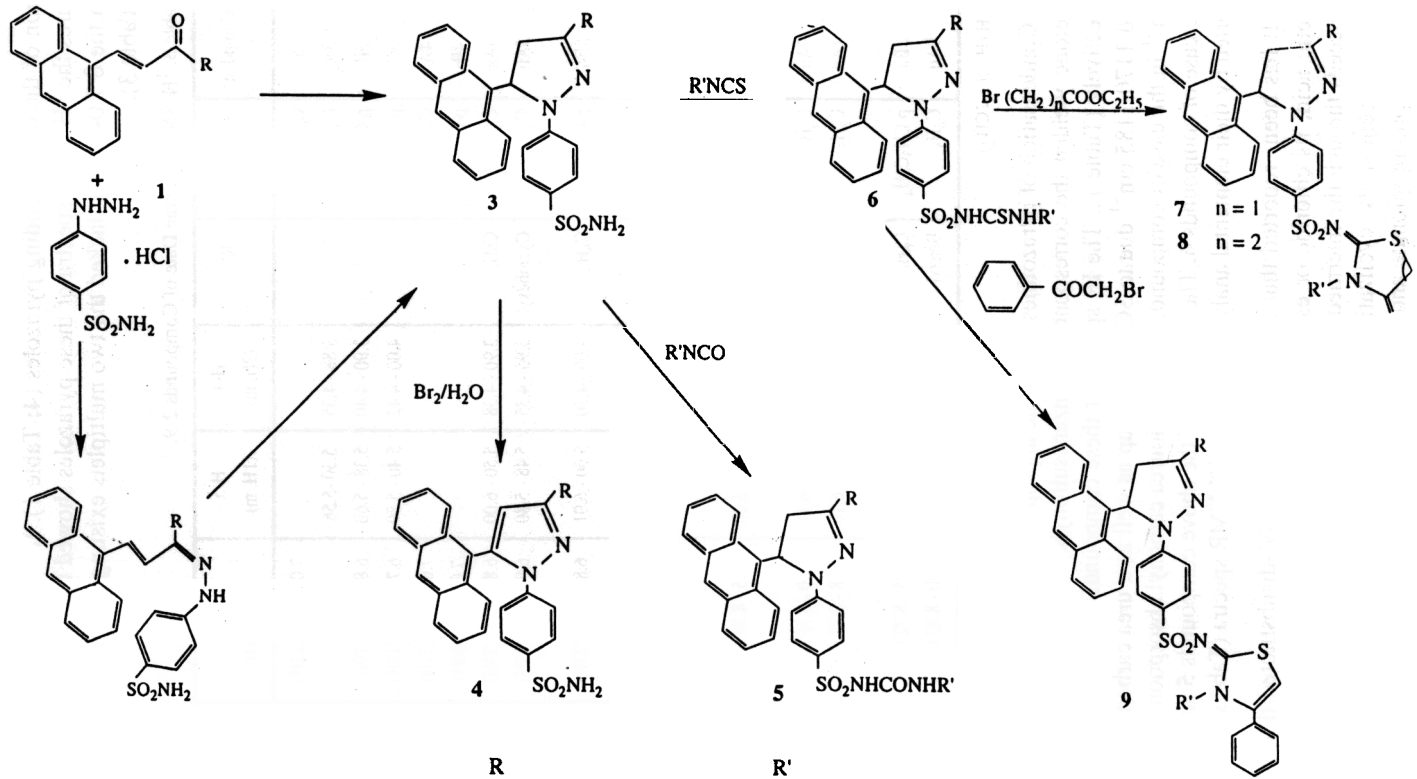
Table 3. ^{1}H NMR Spectrae Date of Compounds 2-9.

Compd. no.	R	R`	H-4 (2H, m)	H-5 (1H, m)	Ar H / NH_2 or NH	Others
5	C_6H_5				7.00 - 8.85 (22H)	9.30 (s, 1H, NH)
3A	C_6H_5		3.88 - 4.35	5.30 -5.56		
3B	p-$CH_3C_6H_4$		3.90 - 4.40	5.38 - 5.60	6.85 - 8.90 (19H)	2.45 (s, 3H, CH_3)
3C	p-BrC_6H_4		4.00 - 4.42	5.40 - 5.80	6.79 - 8.95 (19H)	
4A	C_6H_5				7.00 - 8.92 (21H)	
4B	p-$CH_3C_6H_4$				7.05 - 8.86(20H)	2.38 (s, 3H, CH_3)
5Aa	C_6H_5	C6H5	3.90 - 4.38	5.50 - 6.00	6.80 - 8.90 (24H)	9.9 (s, 1H, NH)
5Ab	C_6H_5	Cyclohexyl	3.95 - 4.35	5.48 - 5.80	6.90 - 8.92 (19H)	1.3 - 1.8 (m, 1 1H, cyclohexyl),9.70 (s, 1H, NH)
5Ba	p-$CH_3C_6H_4$	C_6H_5	4.00 - 4.30	5.60 - 6.01	6.87 - 8.75 (23H)	9.85 (s, 1H, NH), 2.38 (s, 3H, CH_3)
6Aa	C_6H_5	C_6H_5	4.05 - 4.40	5.45 - 5.90	6.95 - 8.90 (24H)	9.65 (s, 1H, NH)
6Ad	C_6H_5	Benzyl	3.95 - 4.40	5.52 - 5.88	7.00 - 8.88 (24H)	4.85 (d, 2H, CH_2), 9.70(s, 1H, NH)
6Ba	p-$CH_3C_6H_4$	C_6H_5	3.85 - 4.30	5.58 - 6.00	6.85 - 8.80 (23H)	2.40 (s, 3H, CH_3), 9.90 (s, 1H, NH)
7Aa	C_6H_5	C_6H_5	3.80 - 4.30	5.70 - 6.11	6.80 - 8.75 (23H)	4.40 (s, 2H, CH_2)
7Ad	C_6H_5	Benzyl	3.78 - 4.28	5.65 - 6.10	6.78 - 8.88 (23H)	4.35 (s, 2H, CH_2), 4.8 (s, 2H, CH_2)
8Ba	p-$CH_3C_6H_4$	C_6H_5	3.90 - 4.35	5.70 - 6.12[a]	6.95 - 8.72 (22H)	2.38 (s, 3H, CH_3)
9Ad	C_6H_5	Benzyl	3.85 - 4.41	5.50 - 6.21	7.00 - 8.85 (28H)	4.82 (s, 2H, CH_2)

[a] 6H (H - 5 + 2CH_2)

Condensation of pyrazolines **3** with the appropriate isocyanate and isothiocyanate in dry acetone yielded the corresponding benzenesulfonylurea **5** and thiourea **6** derivatives respectively (Table 1). The IR spectra of these compounds exhibited two bands 1325-1368 and 1170-1185 cm^{-1} due to $SO_2N <$ group as well as a urea carbonyl band at 1655-1662 cm^{-1} in the case of compounds **5** and a thiourea carbonyl absorption at 1130-1145c m^{-1} in the case of compounds **6.** The structure of the above compounds **5** and **6** were further supported by their elemental analysis as well as ^{1}H NMR spectra (Tables 2 and 3).

It has been reported that condensation of N, N`-disubstituted thiourea with chloroacetic acid, its chloride or ester afforded 2-imino-4-oxothiazolidines, and the reaction proceeds through the intermediate formation of the cyclic pseudothiohydantoic acid[16-19]. In the present study, cyclization of the thiourea derivatives **6,** with ethyl bromoacetate, ethyl β-bromopropionate and α-bromoacetophenone afforded the corresponding 4-oxo-



R

A C_6H_5
B p - $CH_3C_6H_4$
C p - BrC_6H_4

R'

C_6H_5
Cyclohexyl
α - Naphthyl
$C_6H_5CH_2$

thiazolidin, 4-oxo-5,6-dihydrothiazine and thiazoline derivatives **7-9** respectively. IR spectra of **7** and **8** showed a cyclic carbonyl absorption at 1722-1730 cm^{-1} and two bands at 1335-1365 cm^{-1} and 1170-1182 cm^{-1} for the SO_2N group. The structures of the latter compounds **7-9** were further supported by their ^1H NMR data (Table 3).

Biological Testing

Compounds 3-9 were screened for their antibacterial and antifungal activity following agar-diffusion-method[16], using gram-positive bacteria *Staphylococcus aureus* and gram-negative bacteria *Escherichia coli.* The antifungal testing was carried out against *Candida albicans.* A standard sterilised filter paper disc (5 mm dia) impregnated with the solution of compound in ethanol (1 mg/ml^{-1}) was placed on an agar plate seeded with the test organism. The plates were incubated for 24 hr at 37°C and the zones of inhibition of bacterial growth round the disc was observed.

From the screening results, it was evident that all the compounds were not significantly active towards the organisms used. Hence, no specific structure activity relationship could be established.

Experimental

Melting points were determined on a Kofler hot stage apparatus and were uncorrected. ^1H NMR Spectra were recorded on a Varian EM 390-90 MHz spectrometer using TMS as internal standard. IR spectra were recorded on unicam SP 1025 infrared spectrometer.

Arylhydrazone derivatives (2; Table 1)

A solution of the appropriate chalcone (1; 10 mmol) in ethanol (30 ml) was refluxed with a mixture of p-sulfamylphenylhydrazine hydrochloride (11mmol), few drops of acetic acid and sodium acetate (20 mmol) in water (5 ml) for 1 hr and poured into water. The precipitated product was then filtered and recrystallized from methanol to give the hdyrazone derivative as orange needles.

5-Anthracen-9-yl-3-aryl-1-(p-sulfamylphenyl-Δ^2-pyrazolines (3; Table 1)

A solution of the appropriate chalcone (1; 10 mmol) in ethanol (50 ml) was refluxed with p-sulfamylphenylhydrazine hydrochloride (11 mmol) for 4hr, cooled and diluted with water. The precipitated crude product was filtered and recrystrallized from ethanol as yellow needles.

The pyrazoline **3A** was also prepared in 65% yields when a solution of **2A** (10 mmol) in ethanol (30 ml) was refluxed with HCl (0.5 ml) for 2hr.

5-Anthracen-9-yl-3-aryl-1-(p-sulfamylphenyl) pyrazoles (4; Table 1)

A suspension of **3** (10 mmol) in water (10 ml) was treated with 5% bromine water until a faint yellow colour developed with stirring. The stirring was continued for 2 hr and the crude pyrazole collected and recrystallized from methanol as needles.

Substituted p-(5-Anthracen-9-yl-3-aryl-Δ^2-pyrazolin-1-yl) benzenesulfonylureas (5; Table 1)

A mixture of **3** (10 mmol) and anhydrous potassium carbonate (20 mmol) in dry acetone (25 ml) was stirred and refluxed for 1 hr. At this temperature, a solution of the appropriate isocynate (15 mmol) in dry acetone (5 ml) was added dropwise. After the mixture was stirred and refluxed 18 hr, acetone was removed under reduced pressure, and the solid residue was dissolved in water. The crude product was isolated by acidification with 2N HCl and purified by recrystallization from ethanol as needles.

Substituted p-(5-Anthracen-9-yl-3-aryl-Δ^2-pyrazolin-1-yl) benzenesulfonylthioureas (6; Table 1)

A mixture of **3** (10 mmol) and anhydrous potassium carbonate (20 mmol) in dry acetone (25 ml) was stirred and treated with the appropriate isothiocyanate (12 mmol). After the mixture was stirred and refluxed for 10hr, acetone was removed under reduced pressure, and the solid mass dissolved in water and acidified with 2N HCl. The crude product was purified by recrystalllization from ethanol as yellowish needles.

3-Substituted 2-[p-(5-Anthracen-9-yl-3-aryl-Δ^2-pyrazolin-1-yl) benzenesulfonylimino] -4-oxothiazolidines (7; Table 2)

A mixture of **6** (10 mmol) ethyl bromoacetate (10 mmol) and sodium acetate (20mmol) in absolute ethanol (10 ml) was refluxed for 2 hr. The reaction mixture was then filtered while hot, concentrated and allowed to cool. The product obtained was recrystallized from ethanol as needles.

3-Substituted 2-[p-(5-Anthracen-9-yl-3aryl-Δ^2-pyrazolin-1-yl) benzenesulfonylimino] -4-oxo-5,6-dihydro-1,3-thiazines (8; Table 2)

A solution of **6** (10 mmol) in absolute ethanol (10 ml) was refluxed with ethyl β-bromopropionate (10 mmol) and sodium acetate (20 mmol) for 2hr. The reaction mixture was then cooled and poured into water; the precipitated thiazine was recrystallized from ethanol as needles.

3-Substituted 2-[p-(5-Anthracen-9-yl-3-aryl-Δ^2-pyrazolin-1-yl) benzenesulfonylimino] -1,3,-thiazines (9; Table 2)

A solution of the corresponding thiourea derivative **6** (10 mmol) in absolute ethanol (10 ml) was refluxed with α–bromoacetophenone (10 mmol) and sodium acetate (20 mmol) for 2 hr. The reaction mixture was then cooled, poured into water and the precipitated thiazine was recrystallized from ethanol as needles.

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تحضير ودراسة التأثير الحيوي لمشتقات جديدة من البايرازولين والبايرازول

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جدة - المملكة العربية السعودية

و** قسم الكيمياء ، كلية العلوم ، جامعة الاسكندرية - مصر

المستخلص . يؤدي تكاثف مركب سلفاميل فينايل هيدرازين مع الشالكونات إما إلى تكوين الهيدرازونات (2) أو إلى تكوين البايرازولينات (3) . أكسدة المركبات (3) يؤدي إلى تكوين مشتقات بايرازول (4) . مركبات بنزين سلفونيل يوريا (5) والثيويوريا (6) تم تحضيرها أيضًا . تحلق مجموعة الثيويوريدو للمركبات (6) بمعالجتها بواسطة أثيايل بروموستات وإيثايل - بيتا - بروموبربيونات وألفا - بروموسيتوفينون يعطي مشتقات الثيازوليدينون وثيازينون وثيازولين 7 ، 8 ، 9 على التوالي . وقد تم أيضًا دراسة التأثير الحيوي لهذه المركبات المحضرة ووجد أنه ليس لها تأثير .