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Synthesis of Newer Antipyrinyl-phenothiazine, Antipyrinyl-acridine and Sulpha Derivatives of Expected Biological Activity

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Abstract ☐ As potential antibacterial agents, several antipyrine derivatives were synthesized from 4-formylantipyrine and antibacterial activities of the synthesized compounds were also examined.

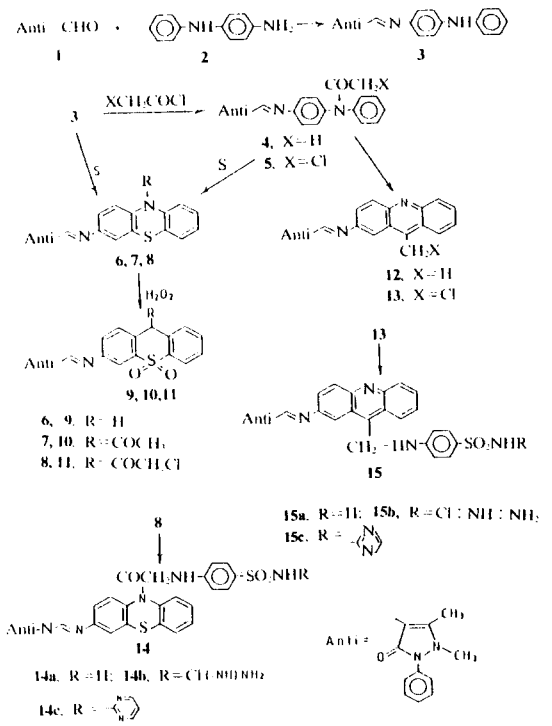
Keywords ☐ Antipyrine, phenothiazine, acridine, sulphas, antibacterial activity.

Since antipyrine is biologically active[1,2], the pharmacological and biological activities[3,4] of the N-substituted phenothiazenes as well as the antitumour[5,6], antimicrobial[7] activities of acridine derivatives are also expected. Therefore, with the aim of producing biologically active drugs, it was our target to combine the antipyrine nucleus with the phenothiazine and the acridine ring system. Thus, 4-formylantipyrine **1** was reacted with *p*-aminodiphenylamine **2** in ethanol in the presence of acetic acid to give the Schiff's base **3**. Also, the N-acetyl and N-chloroacetyl drivatives **4** and **5** were formed *via* reaction of **3** with acetyl and chloroacetyl chloride in toluene in presence of triethylamine. Structures **3**, **4** and **5** were established based on the elemental and spectral analyses which are in good agreement with these structures. Reaction of **3**, **4** and **5** with sulphur powder in *O*-dichlorobenzene gave the corresponding phenothiazone derivatives **6**, **7** and **8**, respectively. Structures **6**, **7** and **8** were established based not only on the microanalytical data of the isolated products, but also on their IR and ^{1}H-NMR spectra which showed in addition to the expected signals in each structure, the presence of 15 proton (aromatic and ethylenic protons) in compound **6**. However, in **7** and **8** there is **13** proton (aromatic and ethylenic protons) in each one.

The corresponding sulphones **9**, **10** and **11** were obtained *via* oxidation of the phenothizenes **6**, **7** and **8** by H_2O_2 in acetic acid medium. Structures **9**, **10** and **11** were established on the bases of the elemental analyses and IR spectra which exhibiting bands at 1350 and 1160 cm^{-1} due to assym and sym. ν ($-SO_2$), respectively. Also, (NH) in compound **6** failed to appear in its usual form as a sharp band and was replaced by a broad one at 3250-3100 cm^{-1}.

Unsuccessful attempt to obtain the acridine derivatives **12** and **13** *via* heating of compounds **4** and **5** in refluxing xylene in the presence of anhydrous $ZnCl_2$ for 10 hours. However, compounds **12** and **13** were obtained *via* fusion of compounds **4** and **5** with anhydrous $ZnCl_2$ at 170°C for 1 h. Structures **12** and **13** were confirmed based on the elemental and spectral analyses. The IR spectral data showed absence of the absorption band at 1690 cm^{-1} characteristic to N-CO·CH_3 and N-CO·CH_2Cl groups. Also, the ^{1}H-NMR spectra of the isolated products revealed in addition to the expected signals in each structure, the presence of 13 proton (aromatic and ethylenic protons) in each one.

The remarkable biological activities of sulphonamides[8] directed us to synthesize some of these compounds. Thus, interaction of compounds **8** and **13** with the corresponding sulphur derivatives in dioxane/pip. medium afforded the corresponding **14a-c** and **15a-c**, respectively. Structures **14** and **15**, were established based on the elemental and spectral analyses which are in good agreement with these structures.



BACTERIOLOGICAL TESTING AND RESULTS

The newly synthesized compounds were tested for their antimicrobial activity *in vitro* against the gram positive bacteria (*Staphylococcus aureus* and *Bacillus cereus*) and gram negative bacteria (*Eascherichia coli* and *Serralia* sp.). The compounds were dissolved in dimethylsulphoxide and used at 10 mg/ml concentration on the nutrient broth and nutrient agar media following the filter paper disc method[9]. The inhibition zones caused by various compounds on the tested microorganisms were measured to the nearest millimeter (see Table I).

The antimicrobial investigation revealed that most of the compounds under test were effective against gram positive and gram negative bacteria. Thus, it has been noted first that compounds **3-8** showed only slight activity against bacteria strains. However, compounds **14a-c** and **15a-c** show the greatest antimicrobial activity. This may be due to the presence of the sulpha moiety in these compounds. Also, it has been found that most of listed compounds have the greatest activity against *Bacillus cereus*.

Table I. Antimicrobial activity of the newly synthesized compounds against bacteria strains

Compd.	Gram positive		Gram negative	
	Staphyloco-acus aureus	*Bacillus cereus*	*Eascherichia coli*	*Serralia* sp.
3	+*	+	−	−
4	−	+	+	−
5	−	++	+	+
6	+	+	+	+
7	+	+	+	++
8	+	+	+	−
9	−	++	−	+
10	+	++	+	++
11	+	++	+	+
12	++	++	++	+
14a	+	+++	++	++
14b	++	+++	+	++
14c	++	+++	++	++
15a	+++	+++	++	+
15b	+++	+++	+	++
15c	++	+++	++	+

*The inhibition zones caused by the compounds were measured as follows:
up to 1 cm − negative; up to 1 cm + slight activity. up to 2 cm ++ medium activity; up to 3 cm +++ the greatest activity.

EXPERIMENTAL METHODS

All melting points are uncorrected. IR spectra were recorded KBr discs on a shimadzu 408 spectrophotometer. ^{1}H-NMR spectra were obtained on an EM-390 90 MHz spectrometer using TMS as internal standard, and chemical shifts are expressed in δ ppm. Microanalyses were performed by the microanalytical unit at Cairo University.

Reaction of 4-formylantipyrine 1 with p-aminodiphenylamine 2: Formation of 3

Equimolar amounts of 4-formylantipyrine **1** and *p*-aminodiphenylamine **2** (0.01 mole) in ethanol (50 ml) was treated with few drops of acetic acid. The reaction mixture was refluxed for 1/2 h. The solid product was collected, crystallized from ethanol to give the Schiff's base **3**, (Table II).

Table II. Analytical data of the synthesized compounds

Compound	m.p℃	C.S.	Formula	Calc./found				
			(mol.wt)	C %	H %	N %	S %	Cl %
3	192	E	$C_{24}H_{22}N_4O$	75.39	5.76	14.66		
	93		(382)	75.80	5.90	14.30		
4	180	E	$C_{26}H_{24}N_4O_2$	73.58	5.66	13.21		
	85		(424)	73.30	5.40	13.00		
5	160	E	$C_{26}H_{23}N_4O_2Cl$	68.05	5.02	12.21		7.74
	80		(458.5)	68.20	5.30	12.00		8.10
6	257	T	$C_{24}H_{20}N_4SO$	69.90	4.85	13.59	7.77	
	72		(412)	70.20	5.20	13.80	7.50	
7	210	T	$C_{26}H_{22}N_4SO_2$	68.72	4.85	12.33	7.05	
	73		(454)	68.50	5.10	12.10	6.80	
8	223	T	$C_{26}H_{21}N_4O_2SCl$	63.87	4.30	11.46	6.55	7.27
	75		(488.5)	63.80	4.40	11.60	6.40	7.40
9	130	E	$C_{24}H_{20}N_4O_3S$	64.87	4.50	12.61	7.21	
	50		(444) 0	65.10	4.30	12.80	7.10	
10	171	E	$C_{26}H_{22}N_4SO_4$	64.19	4.53	11.52	6.58	
	52		(486) 0	64.50	4.10	11.70	6.30	
11	178	E	$C_{26}H_{21}N_4O_4SCl$	59.94	4.03	10.76	6.15	6.82
	51		(520.5)	60.10	4.30	10.90	6.40	6.50
12	281	D	$C_{26}H_{22}N_4O$	76.85	5.42	13.79		
	63		(406) 0	77.00	5.40	14.10		
13	250	D	$C_{26}H_{21}N_4OCl$	70.83	4.77	12.71		8.06
	56		(440.5)	71.20	5.10	12.50		7.90
14a	282	D	$C_{32}H_{28}N_6S_2O_4$	61.54	4.49	13.46	10.26	
	70		(624)	61.30	4.30	13.50	10.40	
14b	296	D	$C_{33}H_{30}N_8S_2O_4$	59.46	4.50	16.82	9.61	
	58		(666)	59.20	4.40	16.80	9.30	
14c	273	M	$C_{36}H_{30}N_8S_2O_4$	61.54	4.27	15.95	9.12	
	61		(702)	61.80	4.70	16.30	8.90	
15a	360	M	$C_{32}H_{28}N_6S_1O_3$	66.65	4.86	14.58	5.56	
	62		(576)	66.40	4.90	14.70	5.40	
15b	315	M	$C_{33}H_{30}N_8SO$	64.08	4.85	18.13	5.18	
	50		(618)	64.30	4.90	18.30	5.30	
15c	327	D	$C_{36}H_{30}N_8SO_3$	66.06	4.59	17.12	4.89	
	45		(654)	66.40	4.30	16.90	5.10	

E=Ethanol; T=Toluene D=Dixane; M=D.M.F

Acetylation and chloroacetylation of 3: Formation of 4 and 5

To a solution of **3** (0.01 mol) and few drops of triethylamine in dry toluene (50 m*l*), acetyl chloride or chloroacetyl chloride (0.012 mol) were added dropwise at room temperature followed by refluxing for 1 h. Removal to toluene under reduced pressure followed by trituration of the residue with light petrol (40-60℃) furnished products which on crystallization from the proper solvent gave the N-acetyl and N-chloroacetyl derivatives **4** and **5** (cf. Table II).

Reaction of 3, 4 and 5 with sulphur: Formation of phenothiazine derivatives 6, 7, and 8: General procedure

A mixture of **3**, **4** and **5** (0.01 mol), sulphur powder (0.02 mol) and iodine (0.1 g) in *O*-dichlorobenzene (20 m*l*) was heated under reflux at 200-210℃ for 2 h. Trituration with light petrol (40-60℃) furnished products which on crystallization from the proper solvent gave the corresponding phenothia-

zines **6**, **7** and **8**, respectively (cf. Table II).

Oxidation of phenothiazines 6, 7 and 8: Formation of sulphones 9, 10 and 11: General procedure

A suspension of **9**, **10** and **11** (0.01 mol) and H_2O_2 (30%, 20 ml) in acetic acid (20 ml) was heated under reflux for 10 h, the solvent was then removed *in vacuo* and the remaining products were triturated with ice-cold water. The remaining solids were collected by filtration and crystallized from the proper solvent to give the corresponding sulphones **9**, **10** and **11** (cf. Table II).

Formation of acridine derivatives 12 and 13: General procedure

A mixture of **4** or **5** (0.01 mol) and anhydrous $ZnCl_2$ (0.01 mol) was fused in an oil-bath at 170-190C for 2 h. The products obtained were washed with water and recrystallized from the proper solvent to give the corresponding acridine derivatives **12** and **13** respectively (cf. Table II).

Reaction of 8 and 13 with sulpha derivatives: Formation of 14a-c and 15a-c: General procedure

Equimolar amounts of **8** or **13** and the corresponding sulpha (0.01 mol) in dioxane containing catalytic amount of piperidine was heated under reflux for 3 h. The solvent was then evaporated under reduced pressure. The remaining solids were collected by filtration and recrystallised from the proper solvent to give the corresponding **14a-c** and **15a-c** respectively, (cf. Table II).

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