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SYNTHESIS AND SCREENING OF SOME NEWER 6, 8-DICHLORO-2-METHYL-3-(SUBSTITUTED)-4(3H)-QUINAZOLINONES AS ANTIMICROBIAL AGENTS

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6,8-Dichloro-2-methyl-3(4′-N-substituted sulphonamidophenyl)-4(3H)-quinazolinones (IIa-g) were prepared through interaction of the benzoxazin-4-one (I) with some sulpha. Also, 6,8-dichloro-3(N-chloroacetylamino)-4(3H)-quinazolinone (IV) was prepared and condensed with amino compound, to give (V*a-d*). Condensation of the 3-amino derivative (IIIa) with aldehydes under different conditions gave (VI) and (VII). The acid chloride (X) underwent condensation with amino compounds to give (XII*a*-c) and (XIII*a-d*). Cyclization of (XIII*d*) with acetic anhydride gave the benzoxazinone derivative (XIV). Some of these compounds have antimicrobial activity.

Key Words : Synthesis; Screening ; 6,8-Dichloro-2-methyl-3-(substituted)-4 (3H)-quinazolinones; Antimicrobial Agents; Heraus Instrument

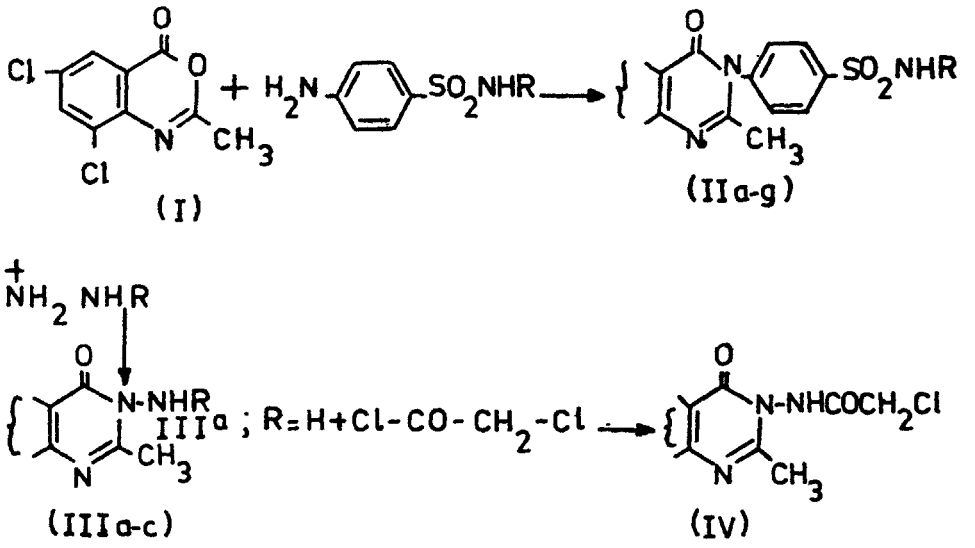
VARIOUS 4(3H)-quinazolinones have been reported to be associated with diverse biological[1,2] and pharmacological properties.[3,4] Again sulphonamides are drugs of proven therapeutic importance and are used against a wide spectrum of bacterial ailments. Therefore, it was considered of interest to incorporate them in one nucleus on the hope of improving their activities.

Thus, 6,8-dichloro-2-methyl-3(4′-N-substituted sulphonamidophenyl)-4(3H)-quinazolinones (II*a-g*) were prepared through interaction of 6,8-dichloro-2-methyl-3,1-benzoxazin-4-one (I)[5] with some sulpha derivatives.

II*a* ; R = H
b ; R = guanidinyl
c ; R = 2-pyridinyl
d ; R = 2-pyrimidinyl
II*e* ; R = 2-pyrimidinyl-4′,6′-dimethyl
f ; R = 2-pyrimidinyl-4′-methyl
g ; R = thiazolyl

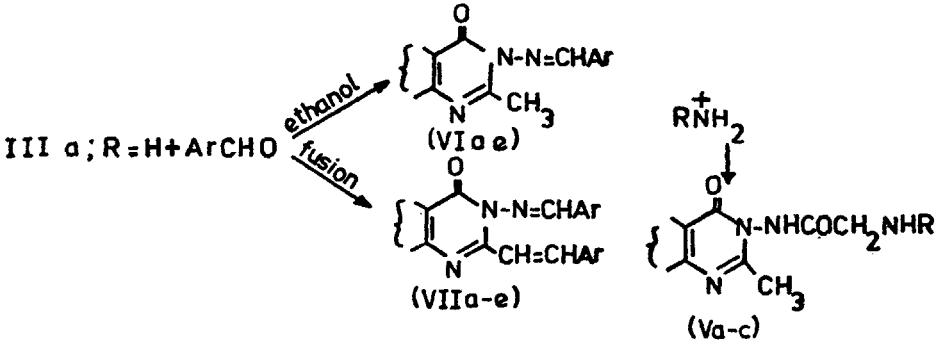
Condensation of (I) with hydrazine hydrate in boiling ethanol gave 3-amino-6, 8-dichloro-2-methyl-4(3H)-quinazolinone (III*a*; R = H). Similarly, (I) underwent condensation with phenylhydrazine or 4-nitrophenylhydrazine to give 3-phenyl-amino or (4′-nitrophenylamino)-6,8-dichloro-2-methyl-4(3H)-quinazolinone (III*b, c*) respectively.

III *b* ; $R = C_6H_5$
c ; $R = C_6H_4\text{-}NO_2\text{-}p$



Interaction of (III*a*) with chloroacetyl chloride in dioxane yielded 6,8-dichloro-3-(N-chloroacetylamino)-4(3H)-quinazolinone (IV). The reactivity of the chlorine atom in (IV) was demonstrated by its reaction with aliphatic and aromatic amines as well as some sulpha drugs to give (V).

V *a* ; R = C_4H_9-iso
b ; R = CH_2-C_6H_5
c ; R = C_6H_4-OCH_3-*p*
V *d* ; R = sulphathiazolyl
e ; R = sulphapyridinyl



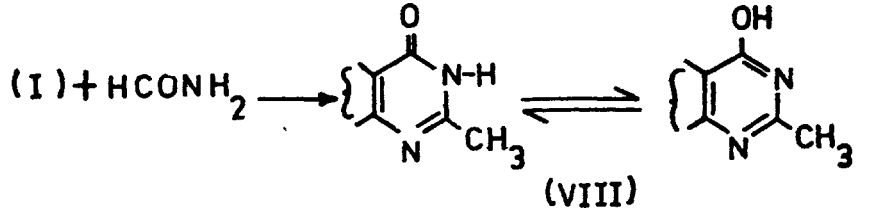
Dhar,[6] reported the anticonvulsant activity of a number of 2-styryl-4(3H)-quinazolinones, thus when (III*a*) was allowed to react with aromatic aldehydes in ethanol under reflux, it gave 3-(arylidenemino)-6,8-dichloro-2-methyl-4(3H)-quinazolinones (VI*a-e*). On the other hand condensation of (III*a*) with the same aromatic aldehydes under the conditions of fusion in presence of anhydrous zinc chloride yielded 3-arylideneamino-2-(substituted styryl)-6,8-dichloro-4(3H)-quinazolinones (VII*a-e*).

VI or VII *a* ; $R = C_6H_5$ VI or VII *d* ; $R = C_6H_4.OCH_3$-*p*

b ; $R = C_6H_4.CH_3$-*o* *e* ; $R = C_6H_4.NO_2$-*p*

c ; $R = C_6H_4.Cl$-*p*

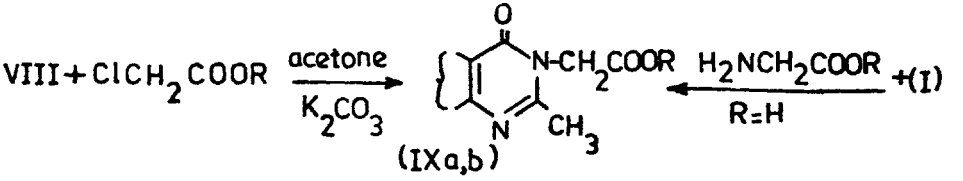
Treatment of (I) with formamide gave 6, 8-dichloro-2-methyl-4 (3H)-quinazolinone (VIII).[7]



(VIII)

Compound (VIII) was allowed to react with chloroacetic acid in dry acetone and in presence of anhydrous K_2CO_3. The obtained product gave analytical data compatible with the isomeric products (IX*a*) or the oxoalkylated (X) as would be expected from the two tautomeric forms of (VIII).

An authentic sample of (IX*a*) was obtained through the interaction of (I) with glycine in acetic acid (m.p. & mixture m.p.).

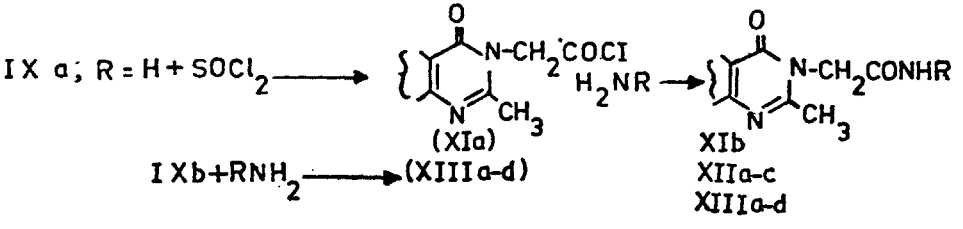


(IXa,b)

The reaction of (VIII) was repeated with ethyl chloroacetate to give (IX*b* ; $R : C_2H_5$),[8] which on alklaline hydrolysis with alcoholic sodium hydroxide gave (IX*a*).

The acid chloride (XI*a*) which obtained through interaction of (IX*a*) with thionyl chloride was confirmed by its reaction with hydrazine hydrate to give the corresponding hydrazide derivative (*b* ; $R = NH_2$).[8]

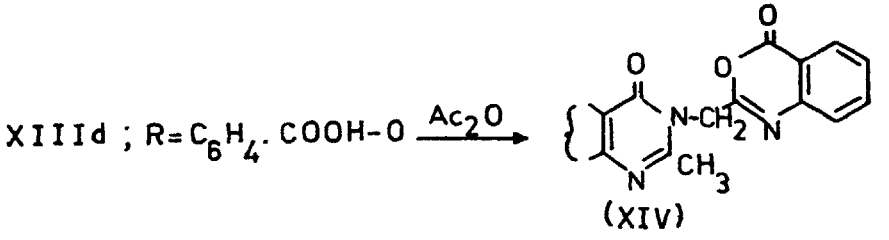
Interaction of the acid chloride (XI*a*) with some sulpha drugs furnished the corresponding sulphonamide derivatives (XII *a–c*).



XII *a* ; *R* = sulphathiazolyl
b ; *R* = sulphapyridinyl
c ; *R* = sulphapyrimidinyl

Interaction of the ester derivative (IX*b*) with some amines under the condition of fusion gave the corresponding carboxamide derivative of type (XIII *a-d*).

XIII *a* ; *R* = $CH_2C_6H_5$
b ; *R* = C_6H_5
XIII *c* ; *R* = $C_6H_4.OCH_3$-*p*
d ; *R* = $C_6H_4.COOH$-*o*



(XIV)

The carboxamide derivatives (XIII *a-d*) were also obtained through interaction of (XI*a*) with the requisite amine. Cyclization of (XIII*d*) with acetic anhydride afforded the corresponding benzoxazone derivative (XIV).

Screening For Antimicrobial Activity

The antimicrobial activities of the synthesized compounds were tested using the hole plate and paper disc methods.[9-11]

The results indicate that the activity of the compounds is of a high order against all the species in the compounds containing both the quinazoline and the sulpha moieties. The results recorded in Table I.

Compound 6,8-dichloro-2-methyl-3(4'-N-pyridylsulphonamidophenyl)-4-(3H)-quinazolinone (II*c*) was found to be active against all the tested organisms (25μg/ml). While compounds (II*a*, II*d* and XII*b*) were be active against only *Bacillus mycoides*, *Bacillus megaterium* and *Saccharomyces*.

Experimental

Melting points were determined on an electrothermal melting point apparatus and are uncorrected. Mycroanalyses were carried out at microanalytical unit of the Cairo University on 'Heraeus instrument' by using rate of oxygen method and benzoic acid as standard. IR spectra were recorded on a Pye-Unicum Sp-1200 and Sp-1000 using KBr technique (ν_{max} in cm^{-1}), and ^{1}HNMR spectra were recorded on a varian EM — 360L. 60 MHz spectrophotometer using TMS as internal standard chemical shift (δ) in ppm.

TABLE I

Antimicrobial screening results of 6,8-dichloro-2,3-(disubstituted)-4(3H)-quinazolinones

Compd. (No.)	*Escherichia coli B* PP01	*Psedomonas aeruginosa*	*Bacillus mycoides*	*Bacillus negaterium*	*Saccharomyces cervicia*
	Activity (MIC)	Activity (MIC)	Activity (MIC)	Activity (MIC)	Activity (MIC)
II*a*	(−)	(−)	++ (50)	++ (50)	++ (50)
b	(−)	(−)	(−)	(−)	(−)
c	+++ (30)	++++ (25)	++++ (25)	++++ (25)	++++ (25)
d	(−)	(−)	+++ (30)	+++++ (20)	++ (50)
e	(−)	(−)	(−)	(−)	(−)
f	(−)	(−)	(−)	(−)	(−)
g	(−)	(−)	(−)	(−)	(−)
III*b*	(−)	(−)	(−)	(−)	(−)
c	(−)	(−)	(−)	(−)	(−)
IV	(−)	(−)	(−)	(−)	(−)
V*a*	(−)	(−)	(−)	(−)	(−)
b	(−)	(−)	(−)	(−)	(−)
c	(−)	(−)	(−)	(−)	(−)
d	(−)	(−)	(−)	(−)	(−)
e	(−)	(−)	(−)	(−)	++ (50)
VI*a*	(−)	(−)	(−)	(−)	(−)
b	(−)	(−)	(−)	(−)	(−)
c	(−)	(−)	(−)	(−)	(−)
d	(−)	(−)	(−)	(−)	++ (50)
e	(−)	(−)	(−)	(−)	(−)
VII*a*	(−)	(−)	(−)	(−)	(−)
b	(−)	(−)	(−)	(−)	(−)
IX*a*	(−)	(−)	(−)	(−)	(−)
XII*a*	(−)	(−)	(−)	(−)	(−)
b	(−)	(−)	+++ (30)	+++ (30)	+++ (30)
c	(−)	(−)	(−)	(−)	+++ (30)

(M.I.C.) Minimum Inhibitory Concentration calculated as (ug/ml).
(−) = No activity
Number of (+) are proportional with activity.

6,8-Dichloro-2-methyl-3(4'-N-Substituted Sulphonamidophenyl)-4(3H)-quinazolinones (IIa-g)

A mixture of (I; 0.01 mol) and the appropriate sulpha drug ((0.012 mol) in pyridine (50 ml) was heated under reflux for 8 hrs. Cooled and then poured into cold dilute HCl to give (II*a-g*; Table I) : IR showed bands at 3310 (SO_2NH) and 1680 (C = O) ^{1}HNMR spectrum of (II*b* in $DMSOD_6$) showed at 2.2 3H, *s*, CH_3, 6.8 4H, hump, $C(=NH)(NH_2)$, SO_2NH disappeared on deuteration and 7.5–8.3 6H, *m*, Ar − H.

Condensation of (I) with Hydrazines

A solution of (I; 0.01 mol) in ethanol (50 ml) was treated with the requisite hydrazine derivative (0.02 mol). The reaction mixture was refluxed for 1 hr to give (III*a*, *c*; Table I) : IR measurements showed bands at 3250 (NH) and 1700 (C = O).

3-(N-Chloroacetylamino)-6,8-dichloro-2-methyl-4(3H)-quinazolinone (IV)

To a solution of (III*a* ; 0.01 mol) in dry dioxane (50 ml), chloroacetyl chloride (0.01 mol) and triethylamine (2 ml) were added. The reaction mixture was refluxed for ½ hr. to give (IV; Table I) : IR spectrum showed bands at 3200 (NH), 1720, 1700 (C = 0) : ^{1}HNMR spectrum of (IV in CD_3COOD) showed signals at 2.6 (3H, *s*, CH_3, 3.4 1H, *s*, NH disappeared on deuteration, 4.3 2H, *s*, CH_2 and 7.8 — 8.2 2H, *m*, Ar — H.

Condensation of (IV) with Amino Compounds

A mixture of (IV; 0.01 mol), the appropriate amino compound (0.012 mol) and triethylamine (2 ml) in dry benzene was refluxed for 2 hrs. to give (V*a-c*; Table I) : IR spectra showed bands at 3300 (NH secondary amine as broad band) and for compounds (V*d* & *e*) showed bond at 3150 ($-SO_2NH$).

3-(Arylideneamino)-6,8-dichloro-2-methyl-4(3H)-quinazolinones (VIa-e)

A solution of (III*a*; 0.01 mol) in ethanol (50 ml) was treated with the requisite aldehyde (0.01 mol) and piperidine (2 ml). The reaction mixture was refluxed for one hr. to give (VI*a-e*; Table I) : IR spectra showed the disappearance of NH_2 bands which present in the parent compound.

3-(Arylideneamino)-2 (Substituted Styryl)-6,8-dichloro-4(3H)-quinazolinones (VIIa-f) A mixture of (III*a*; 0.01 mol), the requisite aldehyde and anhydrous zinc chloride (0.5g.) was fused at 190° for an hour to give (VII*a-f*; Table I) : IR spectra showed the disappearance of NH_2 bands which present in the parent compound.

6,8-Dichloro-2-methyl-4(3H)-quinazolinonylsacetic Acid (IXa)

Method (a)—A mixture of (VIII; 0.01 mol), chloroacetic acid (0.015 mol) and anhydrous K_2CO_3 in dry acetone (50 ml) was refluxed for hrs to give (IX*a*; Table I) : IR spectrum showed the presence of carboxylic group as broad and at 2950-3320.

Method (b)—A mixture of (I; 0.01 mol) and glycine (0.012 mol) in acetic acid (50 ml) was refluxed for 3 hrs to give (IX*a*; m.p. and m.m.p.).

Interaction of (IXa) with Ethyl Chloroacetate

To a solution of (VIII; 0.01 mol) in dry acetone, ethyl chloroacetate of (0.015 mol) and anhydrous K_2CO_3 (0.5g.) were added. The reaction mixture was refluxed for 20 hrs to give (IX*b*; Table II).

TABLE II

The physical data of the newer synthesized compounds

Compd. (No.)	M.P. (°C)	Solvent Cryst.	Yield (%)	Mol. Formula	Analyses %			
					Required		Found	
					C	H	N	S
IIa	280	E	85	$C_{15}H_{11}Cl_2N_3O_3S$	46.87	2.86	10.93	8.33
					46.81	2.91	10.80	8.42
b	280	B	87	$C_{16}H_{13}Cl_2N_5O_3S$	45.07	3.05	16.43	7.51
					45.12	3.02	16.61	7.42
c	280	B	86	$C_{20}H_{14}Cl_2N_4O_3S$	52.06	3.03	12.14	6.94
					52.17	3.08	12.17	6.95
d	280	A	74	$C_{19}H_{13}Cl_2N_5O_3S$	49.35	2.81	15.15	6.92
					49.21	2.71	15.16	6.99
e	280	A	62	$C_{20}H_{15}Cl_2N_5O_3S$	50.42	3.15	14.70	6.51
					50,71	3.18	14.90	6.81
f	280	E	65	$C_{21}H_{17}Cl_2N_5O_3S$	51.42	3.46	14.28	6.53
					51.32	3.47	14.31	6.44
g	280	A	75	$C_{18}H_{12}Cl_2N_4O_3S_2$	46.25	2.56	11.99	13.70
					46.90	2.51	11.90	13.82
IIIa	236	B	78	$C_9H_7Cl_2N_3O$	44.26	2.86	17.21	—
					44.30	2.82	17.30	—
b	210	B	78	$C_{15}H_{11}Cl_2N_3O$	56.25	3.43	13.12	—
					56.50	3.40	13.20	—
c	280	B	80	$C_{15}H_{10}Cl_2N_4O_3$	49.31	2.73	15.34	—
					49.30	2.43	15.51	—
IV	186	B	70	$C_{11}H_8Cl_2N_3O_2$	41.18	2.49	13.10	—
					40.22	2.53	13.20	—
Va	158	E	62	$C_{15}H_{18}Cl_2N_4O_2$	50.42	5.04	15.68	—
					50.31	5.16	15.49	—
b	280	E	67	$C_{18}H_{16}Cl_2N_4O_2$	55.24	4.09	14.32	—
					55.31	4.10	14.41	—
c	280	E	65	$C_{18}H_{16}Cl_2N_4O_3$	53.07	3.93	13.75	—
					53.12	3.99	13.88	—
d	195	A	70	$C_{20}H_{16}Cl_2N_6O_4S_2$	44.52	2.96	15.58	11.87
					44.63	2.85	15.61	11.91
e	175	A	69	$C_{22}H_{15}Cl_3N_6O_4S$	49.53	3.37	15.75	6.00
					49.70	3.40	15.90	6.02
VIa	205	A	80	$C_{16}H_{11}Cl_2N_3O$	57.83	3.31	12.65	—
					57.63	3.43	12.69	—
b	209	A	77	$C_{17}H_{13}Cl_2N_3O$	58.95	3.75	12.13	—
					58.86	3.62	12.30	—
c	212	A	89	$C_{16}H_{10}Cl_3N_3O$	52.45	2.73	11.47	—
					52.31	2.81	11.42	—
d	242	E	85	$C_{17}H_{13}Cl_2N_3O_2$	54.83	3.49	11.29	—
					54.71	3.33	11.51	—
e	228	A	79	$C_{16}H_{10}Cl_2N_4O_4$	48 85	2.54	14.24	—
					48.69	2.61	14.41	—

Contd.

Table II : (*Contd.*)

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
VII*a*	196	A	76	$C_{20}H_{15}Cl_2N_3O$	65.79	3.57	10.00	—
					65.81	3.59	10.10	—
b	239	A	79	$C_{25}H_{19}Cl_2N_3O$	66.96	4.24	9.39	—
					66.82	4.29	9.32	—
c	280	A	68	$C_{23}H_{13}Cl_4N_3O$	56.44	2.65	8.58	—
					56.41	2.71	8.81	—
d	248	A	73	$C_{25}H_{19}Cl_2N_3O_2$	62.50	3.95	8.75	—
					62.42	3.91	8.82	—
e	280	A	70	$C_{23}H_{13}Cl_2N_5O_5$	54.11	2.54	13.72	—
					54.20	2.62	13.80	—
IX*a*	270	A	71	$C_{11}H_8Cl_2N_2O_3$	45.99	2,78	9.75	—
					45.90	2.75	9.63	—
XI*a*	280	D	58	$C_{11}H_7Cl_3N_2O_2$	43.27	2.29	9.18	—
					43.25	2.31	9.20	—
XII*a*	183	A	73	$C_{20}H_{15}Cl_2N_3O_4S_2$	45.80	2.86	13.35	12.21
					45.73	2.65	13.21	12.41
b	232	A	72	$C_{22}H_{17}Cl_2N_5O_4S$	50.96	3.28	13.51	6.17
					50.99	3.31	13.71	6.22
c	183	A	69	$C_{21}H_{16}Cl_2N_6O_4S$	48.55	3.08	16.18	6.16
					48.62	3.10	16.03	6.21
XIII*a*	280	E	62	$C_{18}H_{15}Cl_2N_3O_2$	57.44	3.98	11.17	—
					57.66	3.91	11.10	—
b	280	A	65	$C_{17}H_{13}Cl_2N_3O_2$	56.35	3.59	11.60	—
					56.00	3.60	11.72	—
c	280	A	70	$C_{18}H_{15}Cl_2N_3O_3$	55.10	3.82	10.71	—
					55.15	3.99	10.78	—
d	280	E	60	$C_{18}H_{13}Cl_2N_3O_4$	53.20	2.70	10.34	—
					53.30	2.86	10.13	—
XIV	280	E	70	$C_{18}H_{11}Cl_2N_3O_3$	55.67	2.83	10.82	—
					55.41	2.90	10.73	—

A = Acetic acid B = Benzene D = Dioxane E = Ethanol

Hydrolysis of (Xb)

A solution of (IX*b*; 0.01 mol) in 10 per cent alcoholic sodium hydroxide (50 ml) was heated under reflux for an hour, cooled and neutralized with dilute HCl to give (IX*a*; m.p. and m.m.p.).

Preparation of (XIa)

A solution of (IX*a*; 0.01 mol) in dry dioxane (50 ml) was stirred at room temperature while thionyl chloride (0.015 mol) was added over a period of 45 minutes. The reaction mixture was refluxed for 2 hrs. to give (XI*a*; Table II).

Interaction of the Acid Chloride (X) with some Sulpha Derivatives

A mixture of (XI*a*; 0.01 mol), the requisite sulpha (0.01 mol) and triethylamine (2 ml) in dry dioxane was stirred for 2 hrs to give (XII*a-c*) : IR spectra showed bands at 3300 and (NH amide), 3150 (NH sulphonamide).

6,8-Dichloro-2-methyl-4(3H)-quinazolinonylacetamides (XIIIa-d)

Method (a)—A solution of (IX*a*; 0.01 mol) in benzene (50 ml) was treated with the requisite amine (0.012 mol) and triethylamine (2 ml). The mixture was stirred for 2 hrs to give the corresponding carboxamide derivative of type (XIII*a-d*: Table II) : IR showed bands at 3280 (NH amide) : ^{1}HNMR spectrum of (XIII*a* in CD_3COCD_3) showed signals at 2-1 3H, *s*, CH_3, 4.7 1H, *s*, NH; which disappeared on deuteration, 4.9 2H, *s*, CH_2 and 7.4 — 8.3 7H, *m*, Ar — H.

Method (b)—A mixture of (X*b*; 0.01 mol) and the requisite amine (0.012 mol) was fused at 160° for one hr. to give (XIII*a*-d; m.p. and m.m.p.).

Cyclization of (XIIId)—A solution of (XIII*d*; 0.01 mol) in acetic anhydride (20 ml) was refluxed for one hr to give (XIV; Table I) : IR spectrum showed the disappearance of (NH amide) which present in the parent compound.

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