

ARTICLES

SYNTHESIS AND EFFECT OF GAMMA IRRADIATION ON SOME NEW 6,8-DICHLORO-4-(3H)-QUINAZOLINONES OF BIOLOGICAL INTEREST

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ABSTRACT

Condensation of 2-phenyl-6,8-dichloro-3,1-benzoxazin-4-one (I) with hydrazine hydrate and some sulpha drugs gave IIa and IXa-d respectively. The 3-amino derivative (IIa) was allowed to react with acid anhydrides, phenyl isocyanate or isothiocyanate and aromatic aldehydes as well as arylsulphonyl chloride to give IVa, b, Va, b, VIa-d and VIIa, b respectively. Thiazolidinones (VIIa, b) were obtained by the reaction of VIa, c with mercaptoacetic acid. The effect of gamma irradiation on and antibacterial activity of some of the synthesized compounds are described here.

INTRODUCTION

VARIOUS 4(3H)-quinazolinones have been investigated for biological and pharmacological activities¹⁻⁴. The halogenated derivatives are reported to possess tranquilizer and hypnotic activity⁵. In view of these findings, we undertook the synthesis and evaluation of antimicrobial activity of some novel 6,8-dichloro-2-phenyl-4(3H)-quinazolinones. The effect of gamma irradiation on some of these compounds was also studied.

RESULTS AND DISCUSSION

Reaction of 6,8-dichloro-2-phenyl-3,1-benzoxazin-4-one (I)⁶ with hydrazine hydrate gave 3-amino-6,8-dichloro-2-phenyl-4(3H)-quinazolinone (IIa) as a main product, with the formation of III. Compound III was confirmed through its synthesis by fusion of I with the 3-amino derivative.

The structure of II was confirmed on the basis of analytical data and IR spectrum which showed NH₂ bands as double peaks at 3300 and 3320 cm⁻¹. IR spectrum of III showed disappearance of NH₂ bands. Similarly I underwent condensation with benzoylhydrazine to give IIb. Its IR spectrum showed bands at 3250 (NH), and 1720 and 1680 cm⁻¹ (CO). On the other hand IIb can also be synthesized

by the reaction of IIa with benzoyl chloride in dry pyridine.

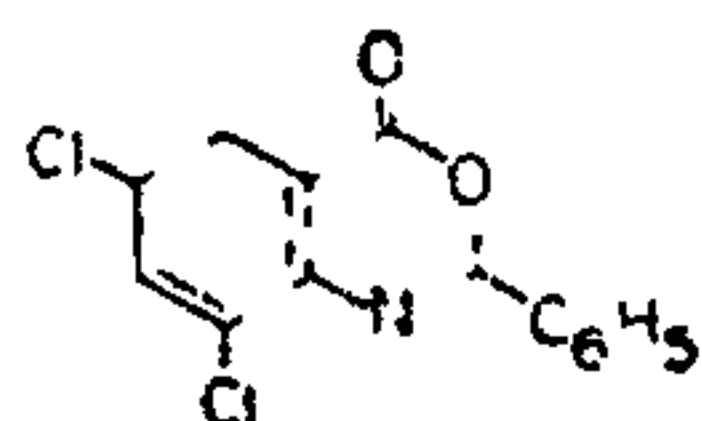
Compound IIa was found to react with phthalic anhydride or tetrabromophthalic anhydride to give the phthalimido derivatives (IVa, b). The structure of IV was established from elemental analyses and IR measurements which revealed the presence of CO (1760, 1740 and 1700 cm⁻¹).

The hypoglycaemic activity⁷ of urea and thiourea derivatives led us to react IIa with phenyl isocyanate or isothiocyanate to obtain the corresponding urea and thiourea derivatives (Va, b). Structure elucidation of V was based on IR spectra, which exhibited bands at 3400, 3350 (NH), 1720, 1680 cm⁻¹ (C=O) for Va, while for Vb the C=S band appeared at 1340 cm⁻¹. The UV spectrum of Vb in DMF showed two sets of bands at λ_{max} 270, 315 nm (log ϵ at 4.11, 4.19).

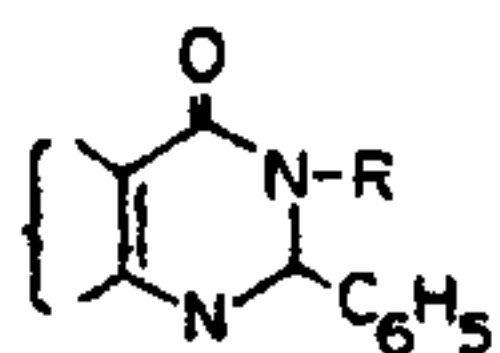
The hydrazone derivatives (VIa-d) were formed through condensation of IIa with aromatic aldehydes. IR spectra of VI revealed the disappearance of NH₂ bands characteristic for the parent compound (IIa). Cyclization of VIa, c with mercaptoacetic acid gave the thiazolidinones (VIIa, b). IR spectra exhibited bands at 1710 and 1680 cm⁻¹ (C=O).

Sulphonamides are drugs of proven therapeutic importance⁹. Therefore it was considered of interest to incorporate the sulphonamido moiety in the quinazolinone nucleus by two methods. Condensation of the 3-amino derivative (IIa) with arylsulphonyl chloride gave the sulphonamido derivatives (VIIIa, b). IR spectra displayed characteristic absorption bands

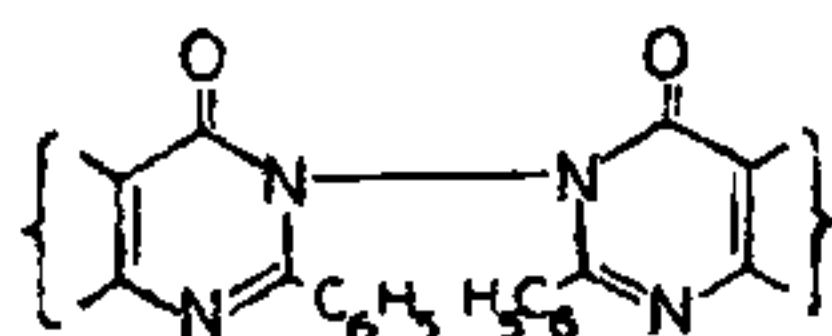
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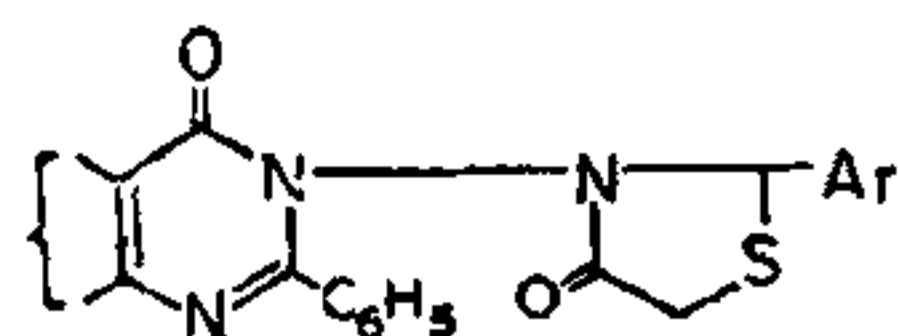
I



- IIa: R = NH₂
 IIb: R = NHCOC₆H₅
 IVa: R = Phthalimido
 IVb: R = Tetrabromophthalimido
 Va: R = NHCONHC₆H₅
 Vb: R = NHCSNHC₆H₅
 VIa: R = C₆H₅
 VIb: R = C₆H₄ · CH₃-*p*
 VIc: R = C₆H₄ · OCH₃-*p*
 VI d: R = C₆H₄ · NO₂-*p*
 VIIIa: R = NHO₂SC₆H₄ · Cl-*p*
 VIIIb: R = NHO₂SC₆H₄ · CH₃-*p*
 IXa: R = Sulphaguanidinyl
 IXb: R = Sulphapyridinyl
 IXc: R = Sulphadimidinyl
 IXd: R = Sulphathiazolyl



III



VII

- VIIa: Ar = C₆H₅
 VIIb: Ar = C₆H₄ · OCH₃-*p*.

at 3200 (NHSO₂) and 1710 cm⁻¹ (C=O). The PMR spectrum of VIIIb in DMSO-d₆ exhibited signals at 2.3 (3H, s, CH₃), 4.3 (1H, hump NH; D₂O exchangeable) and 7.1–8.2 ppm (11H, m, Ar-H). Another type of sulphonamido derivatives (IXa–d) were obtained through condensation of I with sulpha drugs. IR spectra showed bands at 3150 (NHSO₂) and 1700 cm⁻¹ (C=O).

Effect of gamma irradiation on some of the synthesized compounds

Nine compounds (IIa, III, IVa, IVb, Va, Vb, VIIIa, IXb and IXd) were irradiated in dimethylformamide (III, IXb and IXd at 5 × 10⁻⁵ M; the rest at 1 × 10⁻⁴ M) using the well-known chemical method with ferrous sulphate as dosimeter⁹. Irradiation was carried out at room temperature in the presence of atmospheric oxygen. Several doses between 5 and 200 Gy were used.

Ultraviolet spectra of all the irradiated compounds except IVb did not reveal major changes. Compound IVb gave a greatly altered UV absorption profile after irradiation with 200 Gy.

Antibacterial activity

Most of the synthesized compounds were screened for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Streptococcus*. The procedure was according to Ammar *et al.*¹⁰ Minimum inhibitory concentration (MIC) was determined by the dilution assay technique of Lechevalier *et al.*¹¹ Assay plates were incubated at 37°C for one day.

Only two compounds (VIIIa, b) showed activity against all three tested organisms while the other tested compounds showed activity against one or two of the tested organisms. This indicates that incorporation of the sulphonamido moiety with the quinazolinone nucleus confers higher activity against the tested organisms. The results are given in table 1.

EXPERIMENTAL

Melting points were determined on electrothermal melting point apparatus and are uncorrected. Microanalyses were carried out at the Microanalytical Data Unit, Cairo University, on a Heraeus instrument. IR spectra were recorded on a Pye-Unicam Sp-1200 and Sp-1000 using KBr technique. UV and visible absorption spectra were recorded using a Beckman

Table 1 Antimicrobial activity of some 6,8-dichloro-2-phenyl-3-substituted-4(3H)-quinazolinones

Compound	Minimum inhibitory concentration (µg/ml)		
	<i>E. coli</i>	<i>Staph. aureus</i>	<i>Streptococcus</i>
IIa	+(100)	—	—
IIb	—	—	—
III	—	—	+(100)
IVa	—	—	+(100)
IVb	—	—	+(100)
Va	—	+(100)	—
Vb	—	—	+(100)
VIa	—	—	+(100)
VIb	+(100)	—	—
VIc	+(100)	+(100)	—
VI d	++(50)	—	—
VIIIa	+++ (30)	++(50)	+(100)
VIIIb	+(100)	+(100)	+(100)
IXa	++(50)	—	—
IXb	—	—	+(100)
IXc	—	+(100)	++(50)

The number of '+' is proportional with activity; '—' indicates no activity.

double beam spectrophotometer model 24 in the range 190 to 700 nm. PMR spectra were recorded on a Varian EM-360 L 60 MHz spectrometer using TMS as internal standard. Gamma irradiation source was a Gamma Cell 40, which is caesium-137.

Condensation of I with hydrazines was carried out according to the reported method¹¹. Physicochemical data for the synthesized compounds are given in table 2.

3-Benzoylamino-2-phenyl-6,8-dichloro-4(3H)-quinazolinone (IIb)

To a solution of IIa (0.01 mol) in pyridine (30 ml),

benzoyl chloride (0.01 mol) was added and the reaction mixture was refluxed for 15 min to give IIb.

Preparation III

A mixture of I (0.01 mol), the 3-amino derivative (IIa; 0.01 mol) and anhydrous $ZnCl_2$ (0.5 g) was fused at 160°C for half an hour to give III.

Reaction of IIa with phthalic anhydride or tetrabromophthalic anhydride

A mixture of IIa (0.01 mol) and phthalic anhydride or tetrabromophthalic anhydride (0.01 mol) in acetic acid (50 ml) was refluxed for 5 h to give IVa, b.

Table 2 Physicochemical data for 6,8-dichloro-2-phenyl-3-substituted-4-(3H)-quinazolinones

Compound	M.P. (°C)	Cryst. solvent	Yield (%)	Mol. formula	Analysis (%)		
					Required	Found	
IIa	200	E	79	$C_{14}H_9N_3OCl_2$	54.90	2.94	13.72
					54.95	2.90	13.80
IIb	219	E	80	$C_{21}H_{13}N_3O_2Cl_2$	61.46	3.17	10.24
					61.50	3.25	10.35
III	180	E/W	35	$C_{28}H_{14}N_4O_2Cl_4$	57.93	2.41	9.65
					57.98	2.56	9.75
IVa	232	A	72	$C_{22}H_{11}N_3O_3Cl_2$	60.55	2.52	9.63
					60.67	2.71	9.70
IVb	250	A	75	$C_{22}H_7N_3O_3Br_4Cl_2$	35.10	0.93	5.59
					35.15	1.00	5.62
Va	235	E	59	$C_{21}H_{14}N_4O_2Cl_2$	59.29	3.29	13.12
					59.32	3.35	13.25
Vb	228	E	54	$C_{21}H_{14}N_4OSCl_2$	57.14	3.17	12.69
					57.10	3.15	12.75
VIa	158	E	81	$C_{21}H_{13}N_3OCl_2$	63.95	3.29	10.65
					63.87	3.25	10.60
VIb	218	E	86	$C_{22}H_{15}N_3OCl_2$	64.70	3.67	10.29
					64.75	3.62	10.35
VIc	228	E	80	$C_{22}H_{15}N_3O_2Cl_2$	62.26	3.53	9.90
					62.30	3.60	9.85
VIId	234	E	79	$C_{21}H_{12}N_4O_3Cl_2$	57.40	2.73	12.75
					57.45	2.80	12.80
VIIa	230	E	42	$C_{23}H_{15}N_3O_2SCl_2$	58.97	3.21	8.97
					58.90	3.25	8.85
VIIb	250	E	46	$C_{24}H_{17}N_3O_3SCl_2$	57.83	3.41	8.34
					57.92	3.54	8.42
VIIIa	142	E	63	$C_{20}H_{12}N_3O_3SCl_3$	49.94	2.49	8.74
					49.87	2.52	8.81
VIIIb	194	E	66	$C_{21}H_{15}N_3O_3SCl_2$	54.78	3.26	9.13
					54.68	3.30	9.12
IXa	136	A	72	$C_{25}H_{16}N_4O_3SCl_2$	57.36	3.06	10.70
					57.40	3.10	10.63
IXb	238	A	78	$C_{21}H_{15}N_3O_3SCl_2$	51.64	3.07	14.34
					51.70	3.12	14.42
IXc	202	A	69	$C_{26}H_{19}N_5O_3SCl_2$	56.52	3.44	12.68
					56.64	3.52	12.60
IXd	260	A	71	$C_{23}H_{14}N_4O_3S_2Cl_2$	52.17	2.64	10.58
					52.25	2.70	10.65

E, Ethanol; W, water; A, acetic acid.

Reaction of IIa with phenyl isocyanate or isothiocyanate

To a solution of IIa (0.01 mol) in benzene (50 ml) phenyl isocyanate or isothiocyanate (0.01 mol) was added. The reaction mixture was refluxed for 3 h to give VIa, b.

Condensation of IIa with aromatic aldehydes

This was done according to the reported method¹¹.

Cyclization of IVa, c with mercaptoacetic acid

A solution of IVa, c (0.01 mol) in benzene (50 ml) was treated with mercaptoacetic acid (0.01 mol). The mixture was refluxed for 12 h to give VIIa, b.

Condensation of IIa with arylsulphonyl chlorides

A mixture of IIa (0.01 mol), the requisite arylsulphonyl chloride (0.01 mol) and triethylamine (0.5 ml) in benzene (50 ml) was refluxed for 3 h to give VIIIa, b.

3-(4-N-substituted sulphonamido)-phenyl-6, 8-dichloro-2-phenyl-4(3H)-quinazolinones (IXa-d)

These were prepared according to the reported method¹².

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