

SYNTHESIS OF SOME 3-SUBSTITUTED 4(3H)-QUINAZOLINONE AND 4(3H)-QUINAZOLINETHIONE DERIVATIVES AND RELATED FUSED BIHETEROCYCLIC RING SYSTEMS

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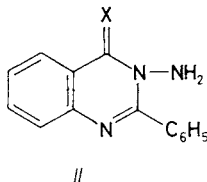
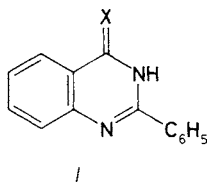
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The reactions of 2-phenyl-4(3H)-quinazolinone, 2-phenyl-3-amino-4(3H)-quinazolinone, and corresponding thiones with phenyl isocyanate or phenyl isothiocyanate were investigated. The resulting urea and thiourea quinazolinone or quinazolinethione derivatives reacted with hydrazine hydrate, phenylhydrazine, and urea or thiourea to form fused biheterocyclic ring systems with potential biological activities. The products were identified by IR, ^1H NMR, and mass spectroscopy.

4(3H)-Quinazolinone derivatives have been reported to possess central nervous system (CNS) depressant¹⁻⁴, anticonvulsant^{5,6}, antimalarial^{7,8}, antibacterial^{9,10}, and antimicrobial activities¹¹.

Our interest is oriented to the synthesis of some new 3-substituted 4(3H)-quinazolinones and their thiono analogues. Synthesis of fused biheterocyclic ring related systems has been one of our tasks. The cyclocondensation of the carbonyl and/or the thiocarbonyl group of the quinazolinone and/or quinazolinethione nucleus and the carbonyl and/or the thiocarbonyl group in the position 3 of the side chain gives various fused biheterocyclic ring systems, depending on the reagent and the cyclisation conditions.

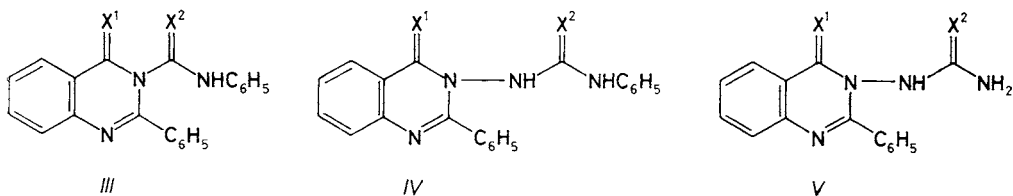
The present work deals with the reaction of 2-phenyl-4(3H)quinazolinone (*Ia*), 3-amino-2-phenyl-4(3H)-quinazolinone (*Iia*) as well as thiones *Ib* and *Iib* with phenyl isocyanate or phenyl isothiocyanate.



In formulae I and II: a, X = O b, X = S

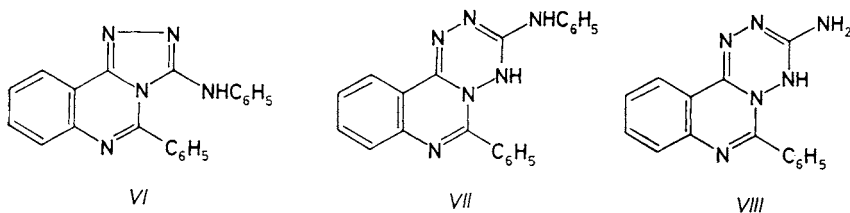
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The starting 2-phenyl-4(3*H*)-quinazolinone (*Ia*) is obtained from the reaction of 2-phenyl-4*H*-3,1-benzoxazin-4-one¹² with formamide¹³. The corresponding thione *Ib* is prepared by the reaction of *Ia* with triethylamine solubilised phosphorus pentasulfide¹⁴. 3-Amino-2-phenyl-4(3*H*)-quinazolinone (*IIa*) is produced in the reaction of 2-phenyl-4*H*-3,1-benzoxazin-4-one with hydrazine hydrate. The corresponding thione *IIb* is formed by the reaction of 2-phenyl-4*H*-3,1-benzothiazin-4-thione with hydrazine hydrate.



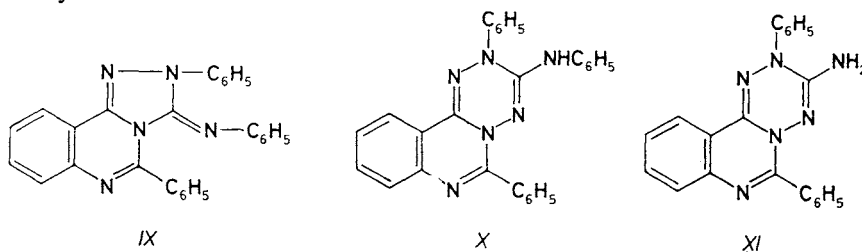
In formulae III-V: a, $X^1 = O$; $X^2 = O$ b, $X^1 = O$; $X^2 = S$ c, $X^1 = S$; $X^2 = O$
 d, $X^1 = S$; $X^2 = S$

3-(*N'*-Phenylamido)-2-phenyl-4(3*H*)-quinazolinone (*IIIa*), 3-(*N'*-phenylthioamido)-2-phenyl-4(3*H*)-quinazolinone (*IIIb*), 3-(*N'*-phenylamido)-2-phenyl-4(3*H*)-quinazolinethione (*IIIc*), and 3-(*N'*-phenylthioamido)-2-phenyl-4(3*H*)-quinazolinethione (*IIId*) are obtained from reaction of *Ia* and *Ib* with phenyl isocyanate or phenyl isothiocyanate, respectively. The *N*-phenyl-*N'*-[2-phenyl-4(3*H*)-quinazolinon-3-yl]urea (*IVa*), *N*-phenyl-*N'*-[2-phenyl-4(3*H*)-quinazolinon-3-yl]thiourea (*IVb*), *N*-phenyl-*N'*-[2-phenyl-4(3*H*)-quinazolinethion-3-yl]urea (*IVc*) and *N*-phenyl-*N'*-[2-phenyl-4(3*H*)-quinazolinethion-3-yl]thiourea (*IVd*) are obtained by the reaction of *IIa* or *IIb* with phenyl isocyanate or phenyl isothiocyanate, respectively. 2-Phenyl-3-carbamidoamino-4(3*H*)-quinazolinone (*Va*), 2-phenyl-3-thiocarbamidoamino-4(3*H*)-quinazolinone (*Vb*), 2-phenyl-3-carbamidoamino-4(3*H*)-quinazolinethione (*Vc*), and 2-phenyl-3-thiocarbamidoamino-4(3*H*)-quinazolinethione (*Vd*) are formed by the reaction of 2-phenyl-3,1-benzoxazin-4-one or 2-phenyl-3,1-benzothiazin-4-thione with semicarbazide or thiosemicarbazide, respectively.

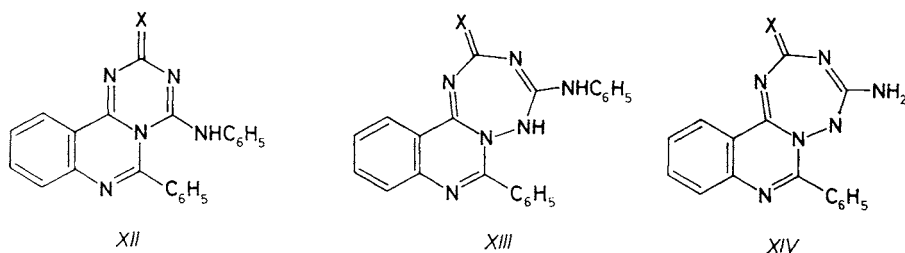


Compounds *IIIa-d*, *IVa-d*, and *Va-d* are characterised by carbonyl and/or thiocarbonyl groups activated by the neighbouring nitrogen atoms. They react readily with hydrazine hydrate, yielding respectively the cyclocondensation products, 3-anilino-5-phenyl-*s*-triazolo[4,3-*c*]quinazoline (*VI*), 3-anilino-6-phenyl-4*H-s*-tetrazino[1,6-*c*]quinazoline (*VII*), and 3-amino-6-phenyl-4*H-s*-tetrazino[1,6-*c*]quinazoline (*VIII*).

Similarly, the reaction of *IIIa-d*, *IVa-d*, and *Va-d* with phenylhydrazine affords the fused biheterocyclic ring systems, 2,3-dihydro-2,5-diphenyl-3-(phenylimino)-*s*-triazolo[4,3-*c*]quinazoline (*IX*), 3-anilino-2,6-diphenyl-2*H-s*-tetrazino[1,6-*c*]quinazoline (*X*), and 3-amino-2,6-diphenyl-2*H-s*-tetrazino[1,6-*c*]quinazoline (*XI*), respectively.



Fusion of *IIIa-d*, *IVa-d*, and *Va-d* with urea or thiourea at elevated temperature gives the cyclocondensation biheterocyclic fused ring systems, 6-phenyl-4-anilino-2*H-s*-triazino[1,2-*c*]quinazolin-2-one (*XIIa*), 6-phenyl-4-anilino-2*H-s*-triazino[1,2-*c*]quinazolin-2-thione (*XIIb*), 4-anilino-7-phenyl[1,2,4,6]tetrazepino[1,7-*c*]quinazolin-2(5*H*)-one (*XIIIa*) or 4-anilino-7-phenyl[1,2,4,6]tetrazepino[1,7-*c*]quinazolin-2(5*H*)-thione (*XIIIb*), and 4-amino-7-phenyl[1,2,4,6]tetrazepino[1,7-*c*]quinazolin-2(5*H*)-one (*XIVa*) or 4-amino-7-phenyl[1,2,4,6]tetrazepino[1,7-*c*]quinazolin-2(5*H*)-thione (*XIVb*), respectively.



In formulae *XII-XIV*: a, X = O b, X = S

The preliminary screening data of compounds *VI-XI*, *XIIa, b*, *XIIIa, b*, and *XIVa, b* show antibacterial and antifungicidal activities. The biological data will be published separately.

TABLE I
Physical and analytical data

Compound	M.p., °C (yield, %)	Formula (M ⁺) ^a	Calculated/found			
			% C	% H	% N	% S
<i>IIIa</i>	201—202 (75)	C ₂₁ H ₁₅ N ₃ O ₂ (341)	73·89	4·43	12·31	—
			73·68	4·26	12·10	—
<i>IIIb</i>	177—178 (72)	C ₂₁ H ₁₅ N ₃ OS (357)	70·57	4·23	11·76	8·97
			70·28	4·16	11·52	8·83
<i>IIIc</i>	182—183 (65)	C ₂₁ H ₁₅ N ₃ OS (357)	70·57	4·23	11·76	8·97
			70·32	4·10	11·54	8·78
<i>III d</i>	162—163 (68)	C ₂₁ H ₁₅ N ₃ S ₂ (373)	67·53	4·05	11·25	17·17
			67·43	4·00	11·05	17·00
<i>IVa</i>	207—208 (88)	C ₂₁ H ₁₆ N ₄ O ₂ (356)	70·77	4·53	15·72	—
			70·88	4·42	15·50	—
<i>IVb</i>	193—194 (80)	C ₂₁ H ₁₆ N ₄ OS (372)	67·72	4·33	15·04	8·61
			67·78	4·22	15·20	8·50
<i>IVc</i>	236—237 (76)	C ₂₁ H ₁₆ N ₄ OS (372)	67·72	4·33	15·04	8·61
			67·85	4·28	15·10	8·40
<i>IVd</i>	168—169 (86)	C ₂₁ H ₁₆ N ₄ S ₂ (388)	64·92	4·15	14·42	16·51
			64·76	4·10	14·30	16·38
<i>Va</i>	298—299 (70)	C ₁₅ H ₁₂ N ₄ O ₂ (280)	64·28	4·32	19·99	—
			64·32	4·30	19·82	—
<i>Vb</i>	178—179 (78)	C ₁₅ H ₁₂ N ₄ OS (296)	60·79	4·08	18·90	10·81
			60·75	4·00	18·74	10·62
<i>Vc</i>	224—225 (68)	C ₁₅ H ₁₂ N ₄ OS (296)	60·79	4·08	18·90	10·81
			60·68	3·98	18·76	10·80
<i>Vd</i>	156—157 (62)	C ₁₅ H ₁₂ N ₄ S ₂ (312)	57·67	3·87	17·94	20·52
			57·78	3·66	17·72	20·44
<i>VI</i>	192—193 (65)	C ₂₁ H ₁₅ N ₅ (337)	74·74	4·48	20·78	—
			74·66	4·23	20·56	—
<i>VII</i>	203—204 (58)	C ₂₁ H ₁₆ N ₆ (352)	71·57	4·58	23·85	—
			71·72	4·42	23·80	—
<i>VIII</i>	222—223 (68)	C ₁₅ H ₁₂ N ₆ (276)	65·20	4·38	30·42	—
			65·40	4·40	30·50	—
<i>IX</i>	216—217 (72)	C ₂₇ H ₁₉ N ₅ (413)	78·43	4·63	16·94	—
			78·63	4·53	16·82	—
<i>X</i>	232—233 (52)	C ₂₇ H ₂₀ N ₆ (428)	75·68	4·71	19·61	—
			75·87	4·65	19·48	—

TABLE I
(Continued)

Compound	M.p., °C (yield, %)	Formula (M ⁺) ^a	Calculated/found			
			% C	% H	% N	% S
<i>XI</i>	245–246 (73)	C ₂₁ H ₁₆ N ₅ (338)	74.53	4.77	20.70	—
			74.62	4.71	20.50	—
<i>XIIa</i>	219–220 (66)	C ₂₂ H ₁₅ N ₅ O (365)	72.32	4.14	19.17	—
			72.38	4.02	19.20	—
<i>XIIb</i>	230–231 (57)	C ₂₂ H ₁₅ N ₅ S (381)	69.27	3.96	18.36	8.41
			69.10	3.81	18.21	8.20
<i>XIIIa</i>	233–234 (63)	C ₂₂ H ₁₆ N ₆ O (380)	69.46	4.24	22.09	—
			69.48	3.92	22.00	—
<i>XIIIb</i>	226–227 (52)	C ₂₂ H ₁₆ N ₆ S (396)	66.65	4.07	21.20	8.08
			66.48	3.90	21.30	8.00
<i>XIVa</i>	238–239 (67)	C ₁₆ H ₁₁ N ₆ O (303)	63.15	3.98	27.62	—
			63.23	3.88	27.38	—
<i>XIVb</i>	226–227 (58)	C ₁₆ H ₁₁ N ₆ S (319)	59.98	3.78	26.23	10.01
			59.77	3.80	26.20	10.00

^a From molecular weight determinations.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were measured with a Unicam-1 200 spectrometer. Potassium bromide technique was used. The ¹H NMR spectra were recorded with a Varian A-60 MHz spectrometer using (C²H₃)₂SO (40 mg/0.4 ml as a solvent. The chemical shift values were expressed in ppm using tetramethylsilane as an internal standard. The mass spectra were recorded with a Nermeg R10-10C spectrometer with a direct inlet source temperature of 110°C and a beam energy of 70 eV.

Compounds *IIIa–d* and *IVa–d*

An equimolar mixture of phenyl isocyanate or phenyl isothiocyanate (0.01 mol) and the appropriate 4(3*H*)-quinazolinone¹³ *Ia* or *Ia* or 4(3*H*)-quinazolinethione¹⁴ *Ib* or *Ib* (0.01 mol) in benzene (25 ml) was refluxed for 3 h. The mixture was concentrated under reduced pressure. On cooling the solid was filtered off, washed repeatedly with dilute HCl followed by ether and recrystallised from ethanol to give compounds *IIIa–d* and *IVa–d*, respectively. The physical, analytical, and spectroscopic data are given in Tables I and II.

TABLE II
IR and ^1H NMR spectroscopic data

Compound	IR spectra ($\bar{\nu}$, cm^{-1})	^1H NMR spectra (δ , ppm)
<i>IIIa</i>	1 695 (C=O); 1 660 (C=O); 3 350 (NH)	6.7–8.3 (14 H, m, ArH); 10.3 (1 H, s, NH)
<i>IIIb</i>	1 690 (C=O); 1 240 (C=S); 3 345 (NH)	6.8–8.2 (14 H, m, ArH); 10.7 (1 H, s, NH)
<i>IIIc</i>	1 680 (C=O); 1 260 (C=S); 3 360 (NH)	6.6–8.2 (14 H, m, ArH); 10.5 (1 H, s, NH)
<i>IIId</i>	1 245 (C=S); 1 250 (C=S); 3 330 (NH)	6.8–8.4 (14 H, m, ArH); 10.8 (1 H, s, NH)
<i>IVa</i>	1 690 (C=O); 1 665 (C=O); 3 360–3 340 (NH)	6.6–8.3 (14 H, m, ArH); 10.5 (1 H, s, NH); 11.6 (1 H, s, NH)
<i>IVb</i>	1 690 (C=O); 1 250 (C=S); 3 360–3 320 (NH)	6.7–8.3 (14 H, m, ArH); 10.8 (1 H, s, NH); 11.8 (1 H, s, NH)
<i>IVc</i>	1 695 (C=O); 1 245 (C=S); 3 350–3 330 (NH)	6.6–8.4 (14 H, m, ArH); 10.8 (1 H, s, NH); 11.8 (1 H, s, NH)
<i>IVd</i>	1 240 (C=S); 1 250 (C=S); 3 350–3 330 (NH)	6.8–8.5 (14 H, m, ArH); 10.8 (1 H, s, NH); 11.8 (1 H, s, NH)
<i>Va</i>	1 690 (C=O); 1 645 (C=O); 3 460, 3 380 (NH, NH ₂)	7.3–8.5 (9 H, m, ArH); 9.6 (2 H, bs, NH ₂); 11.6 (1 H, s, NH)
<i>Vb</i>	1 690 (C=O); 1 240 (C=S); 3 450, 3 380 (NH, NH ₂)	7.3–8.4 (9 H, m, ArH); 9.8 (2 H, bs, NH ₂); 11.6 (1 H, s, NH)
<i>Vc</i>	1 660 (C=O); 1 245 (C=S); 3 450, 3 370 (NH, NH ₂)	7.3–8.5 (9 H, m, ArH); 9.6 (2 H, bs, NH ₂); 11.7 (1 H, s, NH)
<i>Vd</i>	1 240 (C=S); 1 245 (C=S); 3 450, 3 365 (NH, NH ₂)	7.3–8.5 (9 H, m, ArH); 9.8 (2 H, bs, NH ₂); 11.8 (1 H, s, NH)
<i>VI</i>	1 645 (C=N); 3 340 (NH)	6.5–8.5 (14 H, m, ArH); 9.9 (1 H, s, NH)
<i>VII</i>	1 635 (C=N); 3 330 (NH)	6.6–8.4 (14 H, m, ArH); 10.5 (1 H, bs, NH); 10.8 (1 H, bs, NH)
<i>VIII</i>	1 640 (C=N); 3 345 (NH)	7.3–8.4 (9 H, m, ArH); 9.6 (2 H, bs, NH ₂); 10.8 (1 H, s, NH)
<i>IX</i>	1 640 (C=N)	6.6–8.5 (19 H, m, ArH)
<i>X</i>	1 645 (C=N); 3 340 (NH)	6.6–8.4 (19 H, m, ArH); 9.8 (1 H, s, NH)
<i>XI</i>	1 640 (C=N); 3 450–3 350 (NH ₂)	6.6–8.5 (14 H, m, ArH); 9.6 (2 H, s, NH ₂)
<i>XIIa</i>	1 660 (C=O); 3 340 (NH)	6.6–8.4 (14 H, m, ArH); 9.9 (1 H, s, NH)
<i>XIIb</i>	1 240 (C=S); 3 350 (NH)	6.7–8.5 (14 H, m, ArH); 10.0 (1 H, s, NH)
<i>XIIIa</i>	1 665 (C=O); 3 330 (NH)	6.6–8.4 (14 H, m, ArH); 9.8 (1 H, s, NH); 10.8 (1 H, s, NH)
<i>XIIIb</i>	1 240 (C=S); 3 335 (NH)	6.7–8.5 (14 H, m, ArH); 9.9 (1 H, s, NH); 10.8 (1 H, s, NH)
<i>XIVa</i>	1 665 (C=O); 3 450–3 360 (NH ₂)	7.3–8.4 (9 H, m, ArH); 9.6 (2 H, s, NH ₂)
<i>XIVb</i>	1 245 (C=S); 3 460–3 360 (NH ₂)	7.4–8.5 (9 H, m, ArH); 9.8 (2 H, s, NH ₂)

Compound *Va-d*

To a solution of 2-phenyl-3,1-benzoxazin-4-one or 2-phenyl-3,1-benzothiazin-4-thione (0.01 mol) in ethanol (30 ml) semicarbazide hydrochloride or thiosemicarbazide hydrochloride (0.012 mol) and sodium acetate (0.5 g) were added. The mixture was heated under reflux for 5 h, concentrated and cooled. The product was filtered off, washed repeatedly with ethanol and crystallized from ethanol. The physical, analytical, and spectroscopic results are reported in Tables I and II.

Compounds *VI-VIII* and *IX-XI*

A mixture of *IIIa-d*, *IVa-d* or *Va-d* (0.01 mol) and hydrazine hydrate or phenylhydrazine (15 ml) was heated at 150–160°C for 3 h and then poured into ice cold water (100 ml). The solid products were filtered, washed several times with ethanol and crystallized from ethanol to give *VI* and *VII*, *VIII* and *IX*, or *X* and *XI*, respectively. The obtained physical, analytical, and spectroscopic results are collected in Tables I and II.

Compounds *XIIa,b*, *XIIIa,b*, and *XIVa,b*

A mixture of urea or thiourea (0.15 mol) with appropriate 3-substituted quinazolinone or 3-substituted quinazolinone *IIIa-d*, *IVa-d* or *Va-d* (0.01 mol) and anhydrous ZnCl₂ (0.5 g) was heated at 140–150°C for 3 h, cooled, washed with water and then with HCl (5% solution) and filtered. The product was washed with water to remove any trace of ZnCl₂ and crystallized from ethanol to give *XIIa,b*, *XIIIa,b*, and *XIVa,b*. The obtained physical, analytical, and spectroscopic data are listed in Tables I and II.

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