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Search for physiologically active compounds: Part XXVIII. Synthesis of 7-chloro-2-methyl and 2-(2-furyl), 3-aryl-4-quinazolones

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ABSTRACT

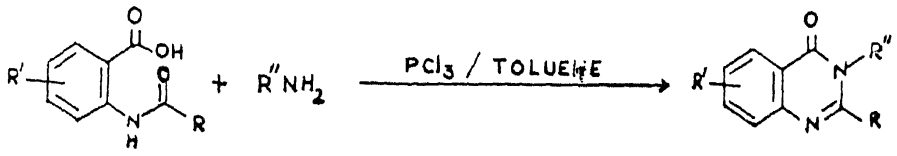
A number of 2-methyl-3-aryl-7-chloro and 2-(2-furyl)-3-aryl-4-quinazolones have been synthesised by condensing N-acyl anthranilic acids with primary aromatic amines using phosphorus trichloride in dry toluene. All these quinazolone derivatives have been screened for their antibacterial, antifungal and fishtoxic properties.

1. INTRODUCTION

A NUMBER of alkaloids having quinazolone moiety in their structure were isolated from different plants.[1–8] These compounds were known to possess useful physiological properties like antimalarial,[4, 5, 9–14] bronchodialatory[15] and hypotensive[7] action. A large number of substituted 4-quinazolones were synthesised and screened for different physiological properties.[16] Some of these with hypnotic, sedative, anticonvulsant and diuretic properties have been marketed as drugs. 2-phenyl-3-benzoyl-4-quinazolone[17] was found to exhibit fungistatic and pesticidal properties. Brooker and Newbold[18] reported strong fungicidal activity and low phytotoxicity by 6-iodo-2-ter-butyl-3-hydroxy-4-quinazolone. Klosa[19] noticed that 3-(5-nitro-2-furfurylidine amino)-4-quinazolones with methyl, ethyl, propyl, butyl and isobutyl groups as 2-substituents were useful as bactericides. 2-β-(5-Nitro-2-furyl) vinyl-3-phenyl-4-quinazolone,[20] its 3-*o*-tolyl analogue[20] and 2-*p*-chloro-styryl-3-phenyl-4-quinazolone,[20] were found to act as bactericides. A number of 7-nitro-2-methyl-3-aryl-4-quinazolones[21] synthesised in these laboratories were found to possess antimicrobial properties and fish toxicity.

* Deceased

A careful survey of the literature revealed that while a number of variously substituted 4-quinazolones have been screened for different physiological properties, no systematic investigation has been carried out to evaluate their antibacterial, antifungal and fish toxic properties. Taking into consideration the useful physiological properties associated with furyl moiety and halo group, the synthesis of 2-methyl-3-aryl-4-quinazolones as reference compounds and of 2-methyl-3-aryl-7-chloro and 2-(2-furyl)-3-aryl-4-quinazolones has been undertaken. For the synthesis of these compounds the method of condensing N-acyl anthranilic acids with aromatic primary amines in dry toluene using phosphorus trichloride as the condensing agent has been adopted.[22]



SYNTHESIS

Equimolecular quantities of N-acetylanthranilic acid and twenty aromatic primary amines have been condensed in dry toluene using phosphorus trichloride to give the corresponding 2-methyl-3-aryl-4-quinazolones (table 1). Of these, 2-methyl-3-(2-nitro-4-chlorophenyl) derivative has been prepared for the first time.

2-(2-furyl)-3-aryl-4-quinazolones are likewise prepared by the condensation of N-furoylanthranilic acid and aromatic primary amines and their analytical data is given in table 2.

4-chloro-N-acetylanthranilic acid under similar conditions yielded 7-chloro-2-methyl-3-aryl-4-quinazolones whose properties are included in table 3.

SPECTRAL DATA

The ir spectra were recorded on Perkin-Elmer Infracord 137 and the uv spectra on Beckman DB spectrophotometer.

In the ir region, while 2-methyl-3-aryl-4-quinazolones exhibit a strong absorption band around 1681–1689 cm^{-1}, the 2-(2-furyl) and 7-chloro-2-

Table 1. 2-Methyl-3-aryl-4-quinazolones

Sl. No.	Aryl group		m.p. in °C	Solvent of crystallisation
1.	Phenyl	..	147[29]	Methanol
2.	*o*-Tolyl	..	115[30]	,,
3.	*m*-Tolyl	..	126[29]	,,
4.	*p*-Tolyl	..	149–50[29]	,,
5.	*o*-Anisyl	..	132[29]	,,
6.	*p*-Anisyl	..	168[29]	,,
7.	*p*-Phenetyl	..	156[29]	,,
8.	*o*-Chlorophenyl	..	127[29]	,,
9.	*m*-Chlorophenyl	..	129[29]	Ethanol
10.	*p*-Chlorophenyl	..	156[29]	Methanol
11.	2, 4-Dichlorophenyl	..	146[30]	Ethanol
12.	3, 4-Dichlorophenyl	..	165[30]	,,
13.	2, 5-Dichlorophenyl	..	160[31]	Methanol
14.	2, 4, 6-Trichlorophenyl	..	143[29]	,,
15.	*p*-Bromophenyl	..	169[30]	,,
16.	*o*-Nitrophenyl	..	168[30]	Ethanol
17.	*m*-Nitrophenyl	..	100[30]	,,
18.	*p*-Nitrophenyl	..	154[30]	Methanol
19.	2-Nitro-4-methylphenyl	..	179[30]	,,
20.	2-Nitro-4-chlorophenyl*	..	192	,,

* $C_{15}H_{10}ClN_3O_3$ required 7·5% N and found to have 7·4% N.

methyl analogues absorb around 1655–1690 cm^{-1} and 1670–1695 cm^{-1} respectively, all assignable to the carbonyl function.

The uv spectra for most of the compounds showed three strong bands around 218–236 nm, 262–277 nm and 302–308 nm. For some compounds a shoulder at 315 nm has been recorded. These values are in general agreement with those obtained earlier for similar compounds.[23,24]

Forty-seven compounds prepared in the present investigation have been screened for their fish toxicity using *Barbus ticto*, fungistatic activity using

Table 2. 2-(2-Furyl)-3-aryl-4-quinazolones. (All compounds are crystallised from methanol.)

Sl. No.	Aryl Group	m.p. in °C	Molecular formula	% Nitrogen	
				Found	Calculated
1.	Phenyl	215[32]	..	..	..
2.	*o*-Tolyl	159	$C_{19}H_{14}N_2O_2$	8·94	9·27
3.	*m*-Tolyl	208	$C_{19}H_{14}N_2O_2$	9·40	9·27
4.	*p*-Tolyl	228[32]	..	..	..
5.	*o*-Anisyl	137	$C_{19}H_{14}N_2O_3$	9·00	8·78
6.	*p*-Anisyl	204[32]	..	..	..
7.	*p*-Phenetyl	216[32]	..	..	..
8.	*o*-Chlorophenyl	192	$C_{18}H_{11}ClN_2O_2$	8·86	8·68
9.	*p*-Chlorophenyl	205[32]	..	..	..
10.	2, 4-Dichlorophenyl	182	$C_{18}H_{11}Cl_2N_2O_2$	8·00	7·82
11.	3, 4-Dichlorophenyl	174	$C_{18}H_{11}Cl_2N_2O_2$	7·92	7·82
12.	2, 5-Dichlorophenyl	190	$C_{18}H_{19}Cl_2N_2O_2$	7·90	7·82
13.	2, 4, 6-Tribromophenyl	120	$C_{18}H_9Br_3N_2O_2$	5·12	5·33
14.	*o*-Nitrophenyl	207	$C_{18}H_{11}N_3O_4$	13·00	13·25
15.	*m*-Nitrophenyl	201	$C_{18}H_{11}N_3O_4$	13·16	13·25
16.	*p*-Nitrophenyl	206	$C_{18}H_{11}N_3O_4$	13·14	13·25
17.	2-Nitro-4-methylphenyl	218	$C_{19}H_{13}N_3O_4$	12·12	12·24

Table 3. 7-Chloro-2-methyl-3-aryl-4-quinazolones. (All compounds are crystallised from methanol.)

Sl. No.	Aryl Group	m.p. in °C	Molecular formula	% Nitrogen	
				Found	Calculated
1.	Phenyl ..	173	$C_{15}H_{11}ClN_2O$	10·18	10·35
2.	*o*-Tolyl ..	115	$C_{16}H_{13}ClN_2O$	9·80	9·84
3.	*m*-Tolyl ..	138	$C_{16}H_{13}ClN_2O$	9·78	9·84
4.	*p*-Tolyl ..	170	$C_{16}H_{13}ClN_2O$	9·80	9·84
5.	*p*-Anisyl ..	146	$C_{16}H_{13}ClN_2O_2$	9·10	9·17
6.	*p*-Phenetyl ..	152	$C_{17}H_{15}ClN_2O_2$	9·14	9·06
7.	*p*-Chlorophenyl ..	198	$C_{15}H_{10}Cl_2N_2O$	9·00	9·18
8.	2, 4-Dichlorophenyl ..	173	$C_{15}H_9Cl_3N_2O$	8·00	8·15
9.	3, 4-Dichlorophenyl ..	178	$C_{15}H_9Cl_3N_2O$	7·96	8·15
10.	2, 5-Dichlorophenyl ..	140	$C_{15}H_9Cl_3N_2O$	7·98	8·15

Aspergillus niger and bacteriostatic activity using *Bacillus coli, B. subtilis* and *Staphylococcus aureus* as test organisms.

FISH TOXICITY

The method of Krishnaswamy and Seshadri[25] has been adopted for evaluating the fish toxicity. All the compounds have been screened at 20 ppm concentration and those compounds which showed toxicity in ten minutes or less were further tested at 10 ppm and 5 ppm (table 4). The results given in table 4 demonstrate that the nature and number of the substituents in the 3-aryl group have a significant role in determining the extent of fish toxicity. The disubstituted phenyl groups seem to be more effective than the monosubstituted. Of these, the 2, 5-dichlorophenyl and 2-nitro-4-methylphenyl and 2-nitro-4-chlorophenyl moieties are the most promising. Among the compounds having a monosubstituted phenyl group in 3-position, 2-(2-furyl)-3-*p*-anisyl-4-quinazolone is considerably toxic.

FUNGISTATIC ACTIVITY

The fungistatic activity has been determined using *Aspergillus niger* as the test organism adopting the radial growth technique[26] at 100 ppm concentration. Those compounds which exhibited 75% or more inhibition of growth have been further screened at 10 ppm and the results presented in table 5. The results show that halo and nitro groups present in the

Table 4. Fish-toxicity at 20, 10 and 5 ppm concentration.

Sl. No.	–4–quinazolone	Concentration and turning time in minutes		
		20 ppm	10 ppm	5 ppm
1.	2-Methyl-3-(2, 5-dichlorophenyl) ..	10	18	22
2.	2-Methyl-3-(2, 4, 6-trichlorophenyl) ..	8	15	25
3.	2-Methyl-3-(2-nitro-4-methylphenyl) ..	5	8	12
4.	2-Methyl-3-(2-nitro-4-chlorophenyl) ..	8	14	16
5.	7-Chloro-2-methyl-3-(2, 5-dichlorophenyl) ..	8	18	20
6.	2-(2-Furyl)-3-*p*-anisyl ..	7	9	21
7.	2-(2-Furyl)-3-(2-nitro-4-methylphenyl) ..	6	12	14

3-aryl moiety enhance the activity while the introduction of chloro group in 7-position does not confer any additional activity. The replacement of 2-methyl by 2-(2-furyl) group is observed to increase the activity.

BACTERIOSTATIC ACTIVITY

All the compounds have been screened for their bacteriostatic activity by the tube dilution method[27] at 100 ppm using *Bacillus coli*, *B. subtilis* and *Staphylococcus aureus* as the test organisms. Compounds which completely inhibited the growth of all the three organism have been further screened at 10 ppm (table 6). It is interesting to note that 7-chloro-2-methyl-3-aryl-4-quinazolones and 2-(2-furyl)-3-aryl-4-quinazolones are more active than 2-methyl-3-aryl-4-quinazolones. Also, the superior bacteriostatic activity of 2-(2-furyl) compounds, compared to the 7-chloro-2-methyl derivatives is worth noting.

Table 5. Fungistatic activity at 100 and 10 ppm concentrations (Fungi used : *Aspergillus niger*)

Sl. No.	-4-quinazolone		% inhibition of growth at	
			100 ppm	10 ppm
1.	2-Methyl-3-*o*-chlorophenyl	..	80	36
2.	2-Methyl-3-*p*-chlorophenyl	..	80	49
3.	2-Methyl-3-(2, 4-dichlorophenyl)	..	90	63
4.	2-Methyl-3-(2, 5-dichlorophenyl)	..	78	30
5.	2-Methyl-3-(3, 4-dichlorophenyl)	..	76	42
6.	2-Methyl-3-(2, 4, 6-trichlorophenyl)	..	90	68
7.	2-Methyl-3-(2-nitro-4-methylphenyl)	..	75	62
8.	2-Methyl-3-(2-nitro-4-chlorophenyl)	..	75	53
9.	7-Chloro-2-methyl-3-(2, 4-dichlorophenyl)	..	78	48
10.	7-Chloro-2-methyl-3-(2, 5-dichlorophenyl)	..	78	36
11.	7-Chloro-2-methyl-3-(3, 4-dichlorophenyl)	..	76	23
12.	2-(2-Furyl)-3-*o*-nitrophenyl	..	90	61
13.	2-(2-Furyl)-3-*p*-nitrophenyl	..	90	67
14.	2-(2-Furyl)-3-(2, 4, 6-tribromophenyl)	..	90	64

Table 6. Bacteriostatic activity at 10 ppm

Sl. No.	4-quinazolone		*B. coli*	*B. subtilis*	*S. aureus*
1.	7-Chloro-2-methyl-3-(2,4-dichlorophenyl)	..	±	±	±
2.	7-Chloro-2-methyl-3-(2, 5-dichlorophenyl)	..	±	±	±
3.	7-Chloro-2-methyl-3-(3, 4-dichlorophenyl)	..	±	±	±
4.	2-(2-Furyl)-3-(2, 4-dichlorophenyl)	..	—	—	—
5.	2-(2-Furyl)-3-(2, 5-dichlorophenyl)	..	—	±	±
6.	2-(2-Furyl)-3-(3, 4-dichlorophenyl)	..	±	±	±
7.	2-(2-Furyl)-3-(3, 4, 6-tribromophenyl)	..	—	—	—
8.	2-(2-Furyl)-3-(2-nitro-4-methylphenyl)	..	±	±	±

± : Partial growth — : No growth + : Full growth

B. coli: *Bacillus coli*
B. subtilis: *Bacillus subtilis*
S. aureus: *Staphylococcus aureus*

2. EXPERIMENTAL

I. N-ACYL ANTHRANILIC ACIDS

N-acetyl anthranilic acid, N-acetyl-4-chloroanthranilic acid[28] were prepared by the acetylation of the respective amino acids with acetic anhydrite in glacial acetic acid. N-furoyl anthranilic acid was obtained by the action of furoyl chloride on anthranilic acid in dry benzene in the presence of anhydrous sodium carbonate and subsequent acidification.

II. 2-METHYL, 7-CHLORO-2-METHYL and 2-(2-FURYL), 3-ARYL-4-QUINAZOLONES

A well stirred mixture of N-acyl anthranilic acid (0·005 mole), primary amine (0·005 mole) in dry toluene (20 ml) was treated with phosphorus trichloride (0·0016 mole) in toluene (5 ml). The reaction mixture was refluxed for two hrs, cooled, made alkaline with aqueous sodium carbonate solution and steam distilled. The residue was recrystallised from a suitable solvent.

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