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SYNTHESIS AND REACTIONS OF 2-AMINO-4 (SUBSTITUTED PHENYL)-5, 6, 7, 8-TETRABROMO-1 (2H)-PHTHALAZINONE DERIVATIVES

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2-Amino-4 (substituted phenyl)-5, 6, 7, 8-tetrabromo-1 (2H)-phthalazinones 3 a-c have been prepared via the interaction of the benzoxazones 2 a-c with hydrazine hydrate in boiling pyridine. The reaction of 3 a with carbon disulphide and hydrazine hydrate in the presence of liquid ammonia gave 2-thiosemicarbazide phthalazinone derivative 4. Also the reaction of 3 a with each of phenylisothiocyanate, chloroacetyl chloride and α-chloroacetanilide gave the corresponding N-Phenyl aminocarbothiamido, α-chloroacetamido and N-phenyl carbonylmethylamino phthalazinones 6, 9, 11, respectively. The biological activity of some compounds has been described.

Key words: 2-Amino-4 (substituted phenyl)-5, 6,7,8-tetrabromo-1(2H)-Phthalazinones 3a-c.

Introduction

As a continuation of the recent studies [1-2] directed towards the synthesis of new biologically active phthalazinone derivatives, considerable attention has been drawn to the synthesis of aminophthalazinones as intermediates for obtaining of diverse pharmaceutically active compounds.

Experimental

Melting points are uncorrected. IR spectra (KBr) were recorded on Pye. Unicam spectrophotometer. ^{1}H-nmr spectra were recorded at 90MHz on a Varian EM-360-L spectrometer using TMS as internal reference and $CDCl_3$ as solvent.

Tetrabromo-o-aroylbenzoic acid derivatives 1a-c. A mixture of (0.01 mole) of tetrabromophthalic anhydride and each of toluene, o-chlorotoluene and 1,2-dichlorobenzene (0.01 mole) was stirred on water bath, then (0.8 mole) of anhydrous $AlCl_3$ was added under Friedel-Craft reaction conditions. The reaction mixture was refluxed for 2 hr, left overnight, then poured over ice/HCl. The excess solvents distilled off by steam distillation and the solid separated was crystallized from the proper solvent to give 1a-c. The mother liquor contains the undesired o-alkylated products with yield range 15-20%.

3-(Substituted phenyl)-4, 5-benzo-1, 2-oxazin-6-ones 2a-c. A mixture of tetrabromo-o-aroylbenzoic acid derivatives 1a-c (0.01 mole) and hydroxylamine hydrochloride (0.01 mole) was refluxed in 40 ml pyridine for 3 hr. The reaction mixture was cooled, then poured over ice-HCl. The solid separated were filtered, dried and cyrstallized from the proper solvents to give 2a-c.

2-Amino-4-(substituted phenyl)-5, 6, 7, 8-tetrabromo-1 (2H)-phthalazinone 3a-c. A mixture of the benzoxazinones 2a-c (0.1 mole) and hydrazine hydrate (0.01 mole) was refluxed in boiling n-butanol for 6 hr. The reaction mixture was filtered off on hot, concentrated and cooled in ice bath. The solid separated was filtered, dried and recrystallized from toluene.

2-Thiosemicarbazide-1(2H)-phthalazinone-4. A mixture of 2-amino-o-tolyl-5,6,7,8,-tetrabromo-1 (2H)-phthalazinone 3a (0.01 mole), ethanol (30 ml) CS_2 (50 ml) and NH_4OH (20 ml) was mixed slowly during 15 min. with stirring and then allowed to stand for 1 hr. Sodium monochloroacetate (0.02 mole) was added to it, followed by addition of 50% hydrazine hydrate (14 ml). The reaction was concentrated to half of its volume and allowed to stand overnight, resulting the thiosemicarbazide derivative 4.

Formation of thiosemicarbazones 5a-c. A mixture of the thiosemicarbazide 3a (0.01 mole) and each of benzaldehyde, anisaldehyde and p-chlorobenzaldehyde (0.01 mole) was refluxed in 40 ml ethanol for 2 hr. The reaction mixture was allowed to stand overnight at room temperature. The solid product was dried and recrystallized from the proper solvents.

Formation of aminocarbothiamide 6: To a solution of 2-aminophthalazinone 3a (0.01 mole) in 40 ml ethanol was added to (0.01 mole) of phenylisothiocyanate. The mixture was refluxed for 6 hr. The resulting solid was washed with cold ethanol and recrystallized from ethanol.

Formation of thiobarbituric acid derivative 7. A mixture of the aminocarbothiamide 6 (0.01 mole) and malonic acid (0.15 mole) in acetyl chloride (10 ml) was condensed on a water bath. The solution was then poured over crushed ice with stirring. The resulting solid was filtered, washed with cold water and recrystallized from ethanol and chloroform to give 7 as yellow solid.

1-(phthalazinon-2-yl)-3-phenyl-5-arylazothiobarbituric acid 8a-c. Aromatic amines namely, aniline, p-chloroaniline (0.01 mole) were taken in HCl-acetic acid (4:3) and cooled

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below -5°C in freezing mixture. Cold aqueous $NaNO_2$ solution (0.15 mole) was added to the cold solution to undergo diazotisation. The diazonium salt was added to the cold solution 7 in pyridine with stirring. The resulting solution was left in freezing mixture for 1hr and then left overnight at room temperature. It was then poured over crushed ice, the solid separated was filtered, washed with water and recrystallised for the proper solvent to give 8a-c.

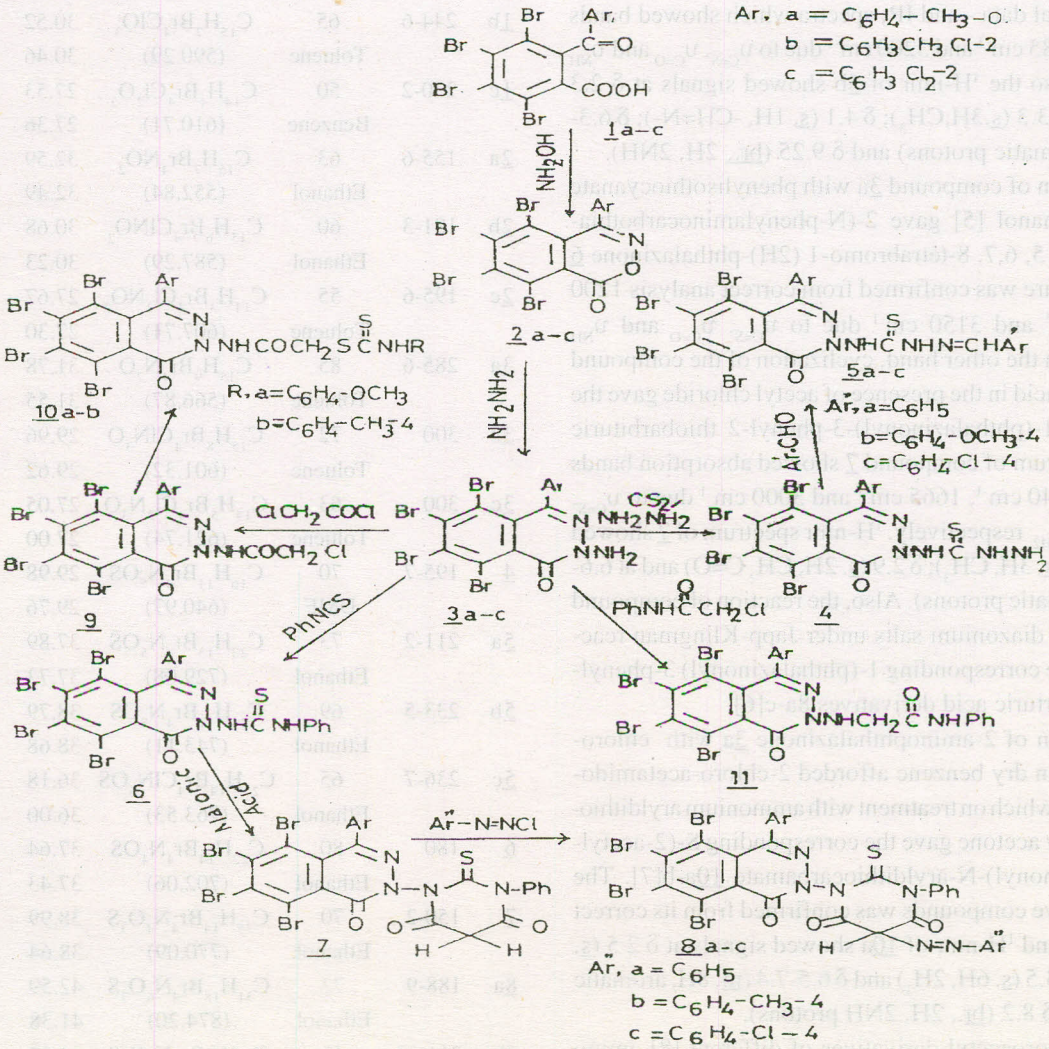
2-Chloroacetamido-4-o-tolyl-5,6,7,8-tetrabromo-1(2H)-phthalazinone 9. A mixture of 2-aminophthalazinone 3a (0.01 mole) and chloroacetyl chloride (0.01 mole) in dry benzene (40 ml) was refluxed for 5 hr, the excess solvent was evaporated under reduced pressure. The solid separated was crystallized from benzene.

S-(2-Acetylaminophthalazinonyl)-N-aryldithiocarbamates 10a-b. A mixture of 9(0.01 mole) and ammonium aryldithiocarbamate (0.01 mole) in dry acetone was stirred for 2 hr at room temp. and then refluxed for 2 hr. Excess solvent was distilled, the solid product washed with water and recrystallised from ethanol.

2-(N-phenylcarbamoylmethylamino)-4-tolyl-5,6,7,8-tetrabromo-1-(2H phthalazinone (11). A mixture of 2-aminophthalazinone 3a (0.01 mole) and α-chloroacetanilide (0.01 mole) in ethanol (40 ml) was refluxed for 4 hr. The excess solvent was then distilled off and solid separated was dried and recrystallized from ethanol.

Results and Discussion

This paper deals with synthesis and reaction of 2-amino-4 (substituted phenyl)-5,6,7, 8-tetrabromo-1 (2H) - phthalazinone derivatives. The compounds 2-amino-4-o-tolyl, 3'-chlorotolyl, 3', 4'-dichlorophenyl 5,6,7, 8-tetrabromo-1 (2H)-phthalazinones 3a-c were prepared via the reaction of 3-(substituted) phenyl) 4,5-benzo-l, 2-oxazin-6-ones 2a-c with hydra-



Scheme 1

zine hydrate in boiling pyridine [3]. The structure of the aminophthalazinones 3a-c was established from its correct analytical data and IR spectra which showed absorption bands at 1640 cm^{-1}, 1685^{-1} and 3400 cm^{-1} attributable to $\upsilon_{C=N}$, $\upsilon_{C=O}$ and υ_{NH2} respectively.

The reaction of 3a with carbon disulphide in liquid ammonia below 5°C in the presence of sodium monochloroacetate followed by treatment with hydrazine hydrate [4] afforded 2-thiosemicarbazide phthalazinone 4. The structure of 4 was confirmed form IR spectrum which showed bands at 1300 cm^{-1}, 1680 cm^{-1} and 3300 cm^{-1} due to $\upsilon_{C=S}$, $\upsilon_{C=O}$ and υ_{NHNH2} respectively. Also ^{1}H-nmr spectrum of 4 showed signal at δ 2.4 (s, 3H, CH_3); δ 5.3 (br. 2H, $2NH_2$); δ 7.3-7.9 (m, m 3H, aromatic protons) and δ 8.0 (br 2H, 2NH). Also condensation of the compound 4 with different aromatic aldehydes namely, benzaldehyde, anisaldehyde and p-chlorobenzaldehyde in boiling ethanol yielded the corresponding thiosemicarbazones 5a-c. The structure of compounds 5a-c was confirmed from it correct analytical data - and IR, spectra which showed bands at 1200 cm^{-1}, 1685 cm^{-1} and 3200 cm^{-1} due to $\upsilon_{C=S}$, $\upsilon_{C=O}$ and υ_{NH} respectively, also the ^{1}H-nmr of 5b showed signals at δ 2.3 (S. 3H, CH_3); δ 3.3 (s.3H,CH_3); δ 4.1 (s, 1H, -CH=N-); δ 6.3-7.1 (m, 8H, aromatic protons) and δ 9.25 (br., 2H, 2NH).

The reaction of compound 3a with phenylisothiocyanate in refluxing ethanol [5] gave 2-(N-phenylaminocarbothiamido)-4-o-tolyl 5, 6,7, 8-tetrabromo-1 (2H)-phthalazinone 6 which its structure was confirmed from correct analysis 1200 cm^{-1}, 1680 cm^{-1} and 3150 cm^{-1} due to $\upsilon_{C=S}$, $\upsilon_{C=O}$ and υ_{NH} respectively. On the other hand, cyclization of the compound 6 with malonic acid in the presence of acetyl chloride gave the corresponding 1-(phthalazinonyl)-3-phenyl-2 thiobarbituric acid 7. IR spectrum of compound 7 showed absorption bands at 1230cm^{-1}, 1640 cm^{-1}, 1665 cm^{-1} and 3000 cm^{-1} due to $\upsilon_{C=S}$, $\upsilon_{C=N}$ $\upsilon_{C=0}$ and υ_{CH2} respectively. ^{1}H-nmr spectrum of 7 showed signals at δ 2.3 (s, 3H, CH_3); δ 2.9 (s. 2H, CH_2 C=O) and at 6.6-7.2 (m 9H, aromatic protons). Also, the reaction of compound 7 with different diazonium salts under Japp-Klingman reaction afforded the corresponding 1-(phthalazinonyl) 3-phenyl-5-arylazothiobarturic acid derivatives 8a-c[6].

The reaction of 2-aminophthalazinone 3a with chloroacetyl chloride in dry benzene afforded 2-chloro-acetamidophthalazinone 9 which on treatment with ammonium aryldithiocarbamate in dry acetone gave the corresponding S-(2-acetyl-aminophthalazinonyl)-N-aryldithiocarbamate 10a-b[7]. The structure of above compounds was confirmed from its correct analytical data and ^{1}H-nmr of 10a showed signals at δ 2.5 (s, 2H, CH_2CO); δ 3.5 (s. 6H, $2H_3$) and δ 6.5-7.4 (m, 8H, aromatic protons) and at δ 8.2 (br., 2H, 2NH protons).

Also, N-chloroacetyl derivatives of different [8] amino heterocyclic compounds have been reported to exhibit wide spectrum biological activities. With this view it was though of interest to synthesis of 2 (N-phenylcarbamoymethylamino) 1 (2H)-phthalazinone 11 through the reaction of 3a with α-chloroacetanilide in refluxing ethanol. Characterisation and physical data are listed in Table 1.

Antimicrobial activity. The purified compounds were screened for antimicrobial activity using cup-plate [9] method. The testing was carried out at concentration of 100 $\mu g/cm^{-3}$ using DMF as solvent. The compounds were tested against gram-positive bacteria *S. citrus* and *S. aureus* and fungi *Aspergillus niger* and *Aspergillus flavus* (Table 2).

TABLE 1.

No.	M.P°C	Yield, % solvent	Formula/ M. wt.	Analysis Calc./Found C	H	N
1a	225-6	73	$C_{15}H_8Br_4O_3$	32.41	1.45	—
		Toluene	(555.84)	32.39	1.41	—
1b	244-6	65	$C_{15}H_7Br_4ClO_3$	30.52	1.20	—
		Toluene	(590.29)	30.46	1.18	—
1c	230-2	50	$C_{14}H_4Br_4Cl_2O_3$	27.53	0.66	—
		Benzene	(610.71)	27.36	0.060	—
2a	155-6	63	$C_{15}H_7Br_4NO_2$	32.59	1.28	2.53
		Ethanol	(552.84)	32.49	1.19	2.46
2b	181-3	60	$C_{15}H_6Br_4ClNO_2$	30.68	1.03	2.38
		Ethanol	(587.29)	30.23	1.00	2.31
2c	195-6	55	$C_{14}H_3Br_4Cl_2NO_2$	27.67	0.50	2.30
		Toluene	(607.74)	27.30	0.41	2.28
3a	285-6	85	$C_{15}H_9Br_4N_2O$	31.78	1.60	7.41
		Toluene	(566.87)	31.55	1.58	7.39
3b	300	72	$C_{15}H_8Br_4ClN_3O$	29.96	1.34	6.96
		Toluene	(601.32)	29.62	1.30	6.88
3c	300	63	$C_{14}H_5Br_4Cl_2N_3O$	27.05	0.81	6.76
		Toluene	(621.74)	27.00	0.70	6.72
4	195-7	70	$C_{16}H_{11}Br_4N_5OS$	29.98	1.73	10.93
		DMF	(640.97)	29.76	1.70	10.75
5a	211-2	73	$C_{23}H_{15}Br_4N_5OS$	37.89	2.07	9.61
		Ethanol	(729.08)	37.73	2.00	9.53
5b	233-5	69	$C_{24}H_{17}Br_4N_5OS$	38.79	2.31	9.43
		Ethanol	(743.11)	38.68	2.24	9.22
5c	236-7	65	$C_{23}H_{14}Br_4ClN_5OS$	36.18	1.85	9.17
		Ethanol	(763.53)	36.00	1.78	9.03
6	180	80	$C_{22}H_{14}Br_4N_4OS$	37.64	2.01	7.98
		Ethanol	(702.06)	37.43	1.99	7.89
7	150-2	70	$C_{25}H_{14}Br_4N_4O_3S$	38.99	1.83	7.28
		Ethanol	(770.09)	38.64	1.79	7.12
8a	188-9	72	$C_{31}H_{18}Br_4N_6O_3S$	42.59	2.08	9.61
		Ethanol	(874.20)	41.38	2.00	9.43
8b	211-13	45	$C_{32}H_{20}Br_4N_6O_3S$	43.27	2.27	0.46

(Table 1 continue...)

(Table 1 continue)

		Ethanol	(888.23)	43.14	2.22	9.03
8c	205-7	42	$C_{31}H_{17}Br_4ClN_6O_3S$	40.98	1.89	9.25
		Ethanol	(908.64)	40.78	1.77	9.00
9	144-5	55	$C_{17}H_{10}Br_4ClN_3O_2$	31.74	1.57	6.53
		Benzene	(643.35)	31.57	1.53	6.42
10a	203-5	55	$C_{25}H_{18}Br_4N_4O_2S_2$	38.00	2.30	7.09
		Acetic acid	(790.18)	37.99	2.03	7.00
10b	222-5	60	$C_{25}H_{18}Br_4ClN_4O_3O_2$	35.68	2.16	6.66
		Acetic acid	(841.63)	35.55	2.03	6.49
11	195-7	73	$C_{23}H_{16}Br_4N_4O$	40.39	2.36	8.19
		Ethanol	(684.02)	40.28	2.28	8.02

TABLE 2.

Compd.	*S. citrus*	*S. aureus*	*E. coli*	*M. serratia*	*A. niger*	*A. flavus*
3a	–	–	–	–	–	–
3b	++	+	+++	++	–	–
3c	+	+++	–	–	++	–
4	+++	++	+++	+	+++	+
5c	+++	+++	++	+	+	+
6	–	–	–	–	+	+
7	+++	+	–	+++	+++	++
8a	++	–	–	+	–	–
9	+	+++	++	++	++	++
10a	+	+	+	+	+++	+
10b	+	++	+++	+	+++	+
11	++	–	+++	++	–	–

The width of the zone of inhibition indicates the potency of antimicrobial activity.
– = No antibacterial activity, + = Mild activity, ++ = Modrate activity, +++ = Marked activity.

All compounds were found to be moderately active against both species. Compounds having 4-chloro substitutions were most active against substitutions were active against E. coli at low concentrations (50 $\mu g/cm^{-1}$). Compounds 4,7a, 10a-b were also tested for their antifungal activity against *A. niger* using agar-plate [10] method with Diathan M-45 as standard commercial. The data indicate that the presence of the dithiocarbamate moeity plays key role in the fungitoxicity of the compounds.

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