Synthesis of 2-Substituted Styryl-6-bromo-4-quinazolone 3-(4-Benzhydrazides) as Possible Monoamine Oxidase Inhibitors

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Nine ethyl 2-substituted styryl-6-bromo-4-oxoquinazoline-3-(4-benzoates) were prepared by condensing bromoacetanthranil with ethyl-4-aminobenzoates. These esters were converted to the corresponding hydrazides with hydrazine hydrate in order to study their monoamine oxidase inhibitory and anticonvulsant properties.

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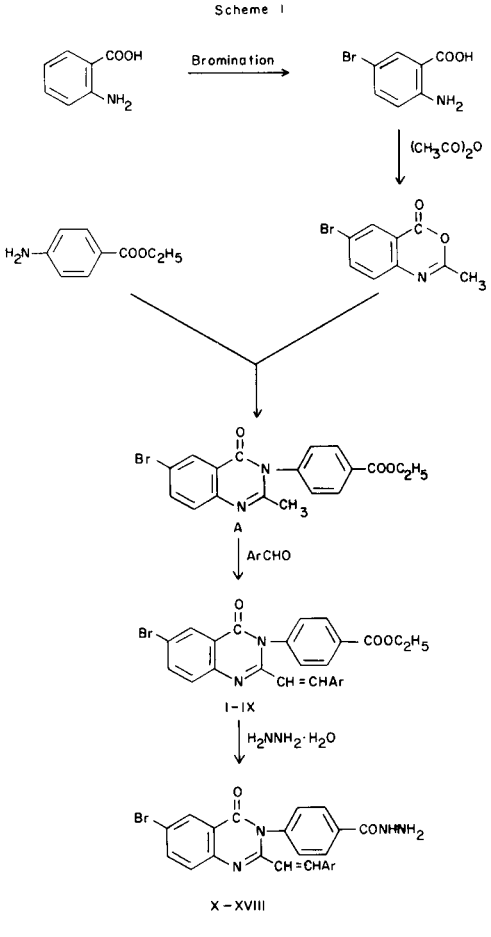
Several quinazolone hydrazides have been synthesized and studied for their monoamine oxidase inhibitory property (3-7). A high degree of monoamine oxidase inhibition for styryl quinoliniums has been reported by Taylor, *et al.* (8). Inhibition was proposed to be related to the presence of the styryl group and specifically, to its ethylenic moiety (9). In an attempt to find a better monoamine oxidase inhibitor, a number of 2-substituted styryl-6-bromo-4-quinazolone 3-(4-benzhydrazides) were synthesized according to methods outlined in Scheme 1.

Anthranilic acid was brominated by the method of Wheeler, *et al.* (10), and was converted to the corresponding acetanthranil by reaction with 2 moles of acetic anhydride. The acetanthranil was condensed with ethyl 4-aminobenzoate resulting in the formation of ethyl 2-methyl-4-oxoquinazoline-3-(4-benzoate) (A). This quinazalone was further condensed with substituted benzaldehydes, resulting in the synthesis of ethyl 2-substituted styryl-4-oxoquinazoline-3-(4-benzoates) (I-IX) and these esters on reaction with hydrazine hydrate yielded the corresponding hydrazides (X-XVIII). All the styryl quinazolone esters (I-IX) and hydrazides (X-XVIII) were investigated for their monoamine oxidase inhibitory property. These results will be published elsewhere.

Scheme I



EXPERIMENTAL

All styrylquinozolone esters and hydrazides were analyzed for their carbon, hydrogen and nitrogen contents. Melting points were taken in open capillary tubes with an immersion thermometer. The infrared spectra of these styrylquinazolones show characteristic bands for -CON (~ 1640 cm^{-1}) and $COOC_2H_5$ (~ 1735 cm^{-1}) (esters), and for CON (~ 1640 cm^{-1}) and NH_2 (~ 3350 cm^{-1}) (hydrazides).

5-Bromoanthranilic Acid.

To a solution of 40 g. of anthranilic acid in 500 ml. of glacial acetic acid, 19 ml. of bromine was added at a temperature of 16°. The resulting mixture of 5 bromo- and 3,5-dibromoanthranilic acid was extracted with 1 liter of water containing 50 ml. of hydrochloric acid followed by filtration. 5-Bromoanthranilic acid crystallized out by cooling the filtrate, m.p. 208° (reported m.p. 210°) (10).

5-Bromoacetanthranil.

5-Bromoanthranilic acid (0.1 mole) was refluxed with 0.2 moles of acetic anhydride for 20 minutes. Excess acetic anhydride was then distilled; bromoacetanthranil separated out as a solid mass. The product was filtered and dried and was used for the synthesis of the quinazolone without further purification (3).

Ethyl 6-Bromo-2-methyl-4-oxoquinazoline-3-(4-benzoate).

A mixture of 5-bromoacetanthranil (0.1 mole) and ethyl 4-aminobenzoate was heated on a free flame for 15 minutes. A jelly like mass which separated on cooling was treated with ethanol, resulting in the separation of a solid mass. This crude product was collected by filtration, dried and recrystallized from ethanol.

Ethyl 6-Bromo-2-substitutedstyryl-4-oxoquinazoline-3-(4-benzoates) (I-IX).

Ethyl 6-bromo-2-methyl-4-oxoquinazoline-3-(4-benzoate) (0.005 mole) was treated with a suitable substituted benzaldehyde (0.005 mole) at 170-180° for 10-12 hours. The mixture was cooled and triturated with ethanol. The yellow solid products obtained by chilling the mixture were

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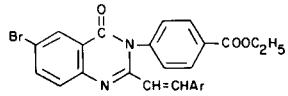
Table I

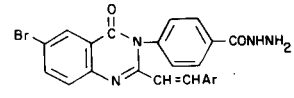
Ethyl 2-Substituted Styryl-6-bromo-4-oxoquinazoline-3-(4-benzoates)



Compound No.	Ar	M.p. °C	Yield %	Recrystallization Solvent	Molecular Formula	Analyses % Calculated C	H	N	Found C	H	N
I	C_6H_5	220	75	Benzene	$C_{25}H_{19}BrN_2O_3$	63.15	4.00	5.89	63.38	3.86	5.74
II	2-ClC_6H_4	160	60	Benzene	$C_{25}H_{18}BrClN_2O_3$	58.88	3.53	5.49	58.60	3.68	3.26
III	4-ClC_6H_4	222	82	Benzene	$C_{25}H_{18}BrClN_2O_3$	58.88	3.53	5.49	59.12	3.40	5.34
IV	2-OH-3,5-$Cl_2C_6H_2$	235	38	Ethanol	$C_{25}H_{17}BrCl_2N_2O_4$	53.57	3.03	5.00	53.28	3.16	4.84
V	3-OHC_6H_4	204	66	Ethanol	$C_{25}H_{19}BrN_2O_4$	61.10	3.87	5.70	61.32	3.70	5.54
VI	3-OCH_3-4-OHC_6H_3	199	62	Ethanol	$C_{26}H_{21}BrN_2O_5$	59.88	4.03	5.37	59.52	4.20	5.18
VII	4-$N(CH_3)_2C_6H_4$	192	67	Benzene	$C_{27}H_{24}BrN_3O_3$	62.54	4.63	8.10	62.86	4.42	7.92
VIII	3-$NO_2C_6H_4$	200	65	Benzene	$C_{25}H_{18}BrN_3O_5$	57.69	3.46	8.07	57.96	3.30	7.84
IX	4-$NO_2C_6H_4$	252	70	Benzene	$C_{25}H_{18}BrN_3O_5$	57.69	3.46	8.07	57.88	3.34	7.90

Table 2

2-Substituted Styryl-6-bromo-4-quinazolone 3-(4-Benzhydrazides)



Compound No.	Ar	M.p. °C	Yield %	Recrystallization Solvent	Molecular Formula	Analyses % Calculated C	H	N	Found C	H	N
X	C_6H_5	249	55	Ethanol	$C_{23}H_{17}BrN_4O_2$	59.86	3.68	12.14	59.54	3.90	12.28
XI	2-ClC_6H_4	224	45	Ethanol	$C_{23}H_{16}BrClN_4O_2$	55.70	3.22	11.30	56.02	3.10	11.16
XII	4-ClC_6H_4	253	59	Benzene	$C_{23}H_{16}BrClN_4O_2$	55.70	3.22	11.30	55.46	3.36	11.12
XIII	2-OH-3,5-$Cl_2C_6H_2$	251	40	Ethanol	$C_{23}H_{15}BrCl_2N_4O_3$	50.55	2.74	10.25	50.80	2.58	10.06
XIV	3-OHC_6H_4	230	52	Ethanol	$C_{23}H_{17}BrN_4O_3$	57.86	3.56	11.74	57.58	3.72	11.60
XV	3-OCH_3-4-OHC_6H_3	220	50	Ethanol	$C_{24}H_{19}BrN_4O_4$	56.80	3.74	11.04	57.14	3.52	10.86
XVI	4-$N(CH_3)_2C_6H_4$	248	55	Ethanol	$C_{25}H_{22}BrN_5O_2$	59.52	4.36	13.88	59.28	4.54	13.66
XVII	3-$NO_2C_6H_4$	262	48	Benzene	$C_{23}H_{16}BrN_5O_4$	54.54	3.16	13.83	54.30	3.38	13.66
XVIII	4-$NO_2C_6H_4$	266	50	Benzene	$C_{23}H_{16}BrN_5O_4$	54.54	3.16	13.83	54.76	3.02	13.70

collected by filtration, dried and recrystallized from suitable solvents. Their physical constants are recorded in Table 1.

6-Bromo-2-substitutedstyryl-4-quinazolone 3-(4-Benzhydrazides) (X-XVIII).

A mixture of the appropriate ester (0.0025 mole) in absolute ethanol and 0.005 mole of hydrazine hydrate (99-100%) was refluxed on a steam bath for 16-20 hours. The excess solvent was distilled and the solids which separated were filtered and recrystallized from suitable solvents. Their physical constants are listed in Table 2.

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