Synthesis of Some 6-Bromo-3-[(arylamino)methyl]- and 2-Styryl-3-[4′-(carboalkoxy)phenyl]-4(3*H*)-quinazolinones†

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Some substituted 6-bromo-3-[(arylamino)methyl]-4(3*H*)-quinazolinones have been synthesized under the conditions of the Mannich reaction. In addition, a few unsubstituted and substituted 2-styryl-4(3*H*)-quinazolinones, 6-bromo-2-styryl-4(3*H*)-quinazolinones, and 6-bromo-2-styryl-3-[4′-(carboethoxy)phenyl]-4(3*H*)-quinazolinones have also been synthesized by condensing the corresponding 2-methyl derivative with an appropriate aromatic aldehyde. Representative compounds have been screened for their central neural system and antiviral activity.

Quinazolinones possess a wide range of pharmacological activities. For instance, 2-methyl-3-(2′-methylphenyl)-4(3*H*)-quinazolinone is a potent hypnotic agent, and various other derivatives possess diuretic, antihypertensive, antiinflammatory, bronchodilatory, antiviral, and antitubercular activity (*1–3*). These observations gave us impetus to synthesize certain newer quinazolinone derivatives, described in this article.

6-Bromo-4(3*H*)-quinazolinone (I) obtained from 6-bromoanthranilic acid and formamide has been condensed with aryl amines and formaldehyde in equimolar proportions to furnish 6-bromo-3-[(arylamino)methyl]-4(3*H*)-quinazolinones (II) (Chart I). Condensation of IV with 4-(carboalkoxy)anilines has yielded 3-[4′-(carboalkoxy)phenyl]-2-methyl-4(3*H*)-quinazolinones (IVa,b). Heating IVb with an aromatic aldehyde in glacial acetic acid for several hours gave rise to VI. Similar reaction of aldehydes with 6-bromo-2-methyl-4(3*H*)-quinazolinone (IVc) as well as with (VII) has been employed to prepare corresponding 2-styryl derivatives (V and VIII). All of the compounds have been adequately characterized by their correct elemental analyses and spectral (IR, NMR, and mass) data.

The mass spectrum of II (R = H) is characterized by the presence of an intense molecular ion peak at *m/e* 329/331 with a typical bromine isotopic pattern. The compound then undergoes Mclafferty rearrangement with charge residing on both of the fragments. The fragment at *m/e* 105 ejects a hydrogen radical to yield an ion at *m/e* 104 from which loss of HCN and CH≡CH occurs in a stepwise manner leading to ions at *m/e* 77 and 51. The other fragment at *m/e* 224/226 can lose either HCN or CO, giving rise to fragments at *m/e* 197/199 or 196/198. Further loss of HCN and Br from the ion at *m/e* 196/198 furnishes ions at *m/e* 169/171 and *m/e* 90. The ion at *m/e* 196/198 could also eliminate Br (*m/e* 117). The ion at *m/e* 168/170 is generated from the ion at *m/e* 197/199 by the loss of a CHO radical. The mass spectra of compounds II (R = Cl and Br) confirm the fragmentation pattern shown in Chart II.

Central Neural System Activity. All of the compounds were administered ip at different dosages such as 200, 400, 1000 mg to groups of five, four, and four mice, respectively. During gross observation, it was found that spontaneous motor activity and reactivity of the animals were increased. A LD_{50} of all these compounds was >1000 mg/kg. The compounds did not show any anticonvulsant activity, maximum electro seizure (MES).

Antiviral Activity. Compounds **1–6** (Table I) have been tested for their inhibitory effect against tobacco mosaic virus. Four compounds (**1**, **2**, **3**, and **6**) have inhibited the virus.

Chart I

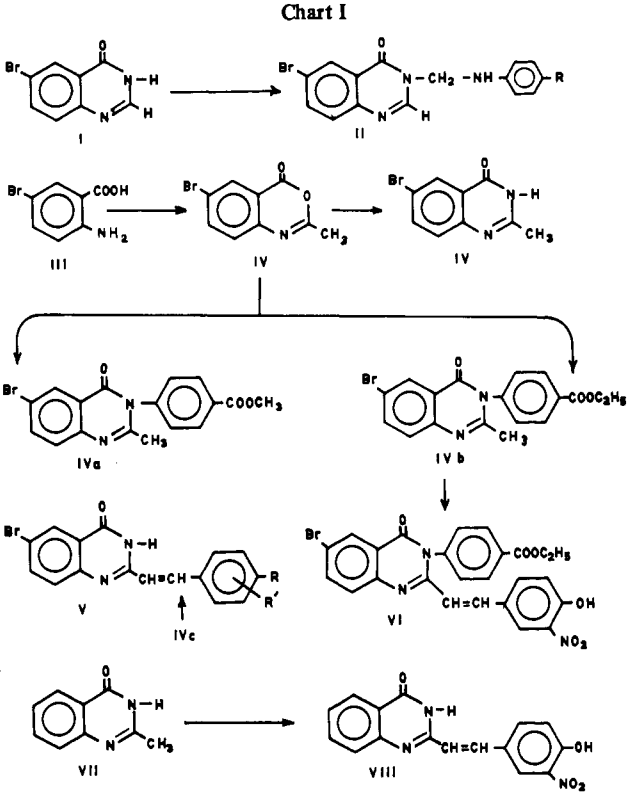

Table I. 6-Bromo-3-[(arylamino)methyl]-(3*H*)-quinazolinones (II)

s no.	R	yield, %	mp, °C	mol formula	% inhibition of the virus
1[b]	H	45	179-180	$C_{15}H_{12}BrN_3O$	52
2	4-CH_3	30	173	$C_{16}H_{14}BrN_3O$	61
3	4-Cl	40	207-208	$C_{16}H_{11}BrClH_3O$	62
4	4-$COOC_2H_5$	30	193[a]	$C_{18}H_{16}BrN_3O_3$	nil
5	4-OC_2H_5	40	134-135	$C_{17}H_{16}BrN_3O_2$	nil
6	4-OCH_3	35	145-146	$C_{16}H_{14}BrN_3O_2$	67
7[c]	4-Br	40	197-198	$C_{15}H_{11}Br_2N_3O$	

[a] Softens at 193 °C; completely melts at 244 °C. [b] IR 3266 (NH), 1665 (C=O), 1600 (C=N) cm^{-1}. [c] NH δ 5.50 (NCH_2N), 6.80–8.60 (ArH and NH).

Experimental Section

Melting points were taken in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 177 instrument in KBr, and NMR spectra were recorded in Me_2SO-d_6 on a Varian A60D instrument, while mass spectra

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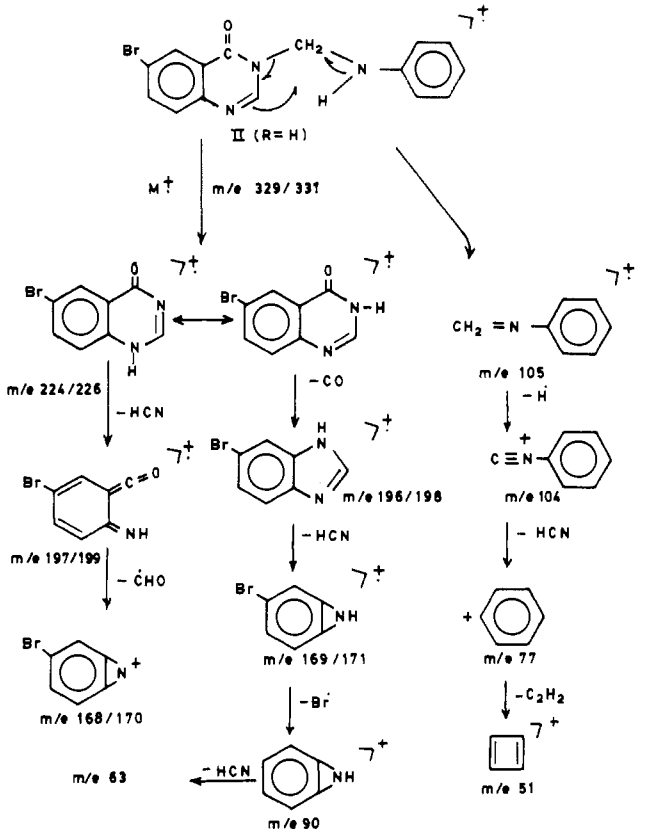
Chart II



were recorded on a Perkin-Elmer-Hitachi RMU6E mass spectrometer fitted with a direct inlet system.

6-Bromo-4(3*H*)-quinazolinone (I). It was prepared by direct bromination of 4(3*H*)-quinazolinone. 4(3*H*)-Quinazolinone (1.46 g, 0.01 mol) was stirred overnight in 30 mL of water containing bromine (1.6 g, 0.01 mol) and KBr (1.19 g, 0.01 mol). The resulting orange white slurry was warmed until the orange color due to bromine disappeared. The reaction mixture was then cooled, filtered, washed with a little acetone, and dried in air. Recrystallization from ethanol–DMF gave fine white crystals: 94%, mp 262–264 °C, lit. (ref 4) mp 260–264 °C.

6-Bromo-3-[(arylamino)methyl]-4(3*H*)-quinazolinones (II). A mixture of I (2.25 g, 0.01 mol), formalin (1.5 mL), and an appropriate aromatic primary amine (0.01 mol) was taken in ethanol (10 mL). The reaction mixture was heated on a water bath with stirring for few minutes. It was then allowed to stand at room temperature overnight. The solid mass thus deposited was filtered and recrystallized from a suitable solvent. The compounds thus prepared are listed in Table I.

6-Bromo-2-methyl-4(3*H*)-quinazolinone (IVc). A mixture of 6-bromoacetanthranil (7.2 g) and 2.5 g of ammonium acetate was fused at 170–180 °C (oil bath) for 5 min. The crude IVc thus obtained was recrystallized from methanol: mp 296–298 °C, lit. (ref *5*) 298–300 °C.

6-Bromo-2-methyl-3-[4′-(carbomethoxy)phenyl]-4(3*H*)-quinazolinine (IVa). A mixture of acetic anhydride (8 mL) and 5-bromoanthranilic acid (2.25 g) was refluxed for 2 h. Excess acetic anhydride was distilled off, and the crude IV thus obtained was mixed with 4-(carbomethoxy)aniline (1.51 g, 0.01 mol). The reaction mixture was heated in an oil bath at 170 °C for 30 min. The reaction mixture was cooled, 5 mL of methanol was added to it, and then it was left overnight. The solid product thus obtained was recrystallized from methanol: yield 40%, mp 195–196 °C; IR 1712 (C=O, ester), 1680 (C=O, ring) cm^{-1}.

6-Bromo-2-(4′-hydroxy-3′-nitrostyryl)-3-[4′-(carboethoxy)-phenyl]-4(3*H*)-quinazolinone (VI). 5-Bromoanthranilic acid (4.32 g, 0.02 mol) and 10 mL of acetic anhydride were refluxed together for 2 h on a low flame. Excess acetic anhydride was distilled off. The crude IV thus obtained was fused with 3.30 g (0.02 mol) of benzocaine in an oil bath at 170 °C for 30 min. The contents thus obtained were cooled, a little methanol was added to it, and then it was left overnight. The product thus obtained was recrystallized from ethanol: yield 45%, mp 174–176 °C, lit. (ref *6*) mp 176 °C.

Table II. 6-Bromo-2-styryl-4(3*H*)-quinazolinones (V)

s no.	R	R′	yield, %	mp, °C	mol formula
8	H	2-OH	50	>270	$C_{16}H_{11}BrN_2O_2$
9[a]	4-Cl	H	55	>280	$C_{16}H_{10}BrClN_2O$
10	4-OH	3-NO_2	40	>280	$C_{16}H_{10}BrN_3O_4$
11[b]	4-OH	3-OCH_3	30	>275	$C_{17}H_{13}BrN_2O_3$
12	H	3-NO_2	30	>275	$C_{16}H_{10}BrN_3O_3$
13	4-OCH_3	H	35	268–270	$C_{17}H_{13}BrN_2O_2$

[a] IR 3000 (NH), 1670 (C=O), 1580 (C=N), 800 (CCl) cm^{-1}. [b] NMR δ 3.53 (OCH_3), 6.47 (J = 13 Hz, 4-$MeOC_6H_4CH$=), 7.49 (J = 13 Hz, N=C(-N-)CH=), 6.60–8.20 (ArH). O=C–NH proton not observed because sweep offset was not done.

6-Bromo-2-styryl-4(3*H*)-quinazolinones (V). To a refluxing solution of IVc (2.39 g, 0.01 mol) in 20 mL of glacial acetic acid, salicylaldehyde (1.22 g, 0.01 mol) was added, and heating was continued for 12 h. The crystalline product deposited on cooling was recrystallized from DMF–water: yield 45%, mp 270 °C (Table II).

2-(4′-Hydroxy-3′-nitrostyryl)-4(3*H*)-quinazolinone (VIII). 2-Methyl-4(3*H*)-quinazolinone (VII) was prepared by the fusion of 8.0 g of acetanthranil with 4.3 g of ammonium acetate at 170–180 °C (oil bath) for 5 min. This gave a solid mass, which was recrystallized from alcohol: yield 59%, mp 234–236 °C, lit. (ref *7*) mp 234–236 °C.

To a refluxing solution of VII (1.60 g, 0.01 mol) in 10 mL of glacial acetic acid, 1.67 g (0.01 mol) of 4-hydroxy-3-nitrobenzaldehyde was added. The heating was continued for 12 h. The crystalline product deposited on cooling was recrystallized from acetic acid: yield 60%, mp 274 °C.

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