V. K. Rastogi, S. S. Parmar, S. P. Singh and T. K. Akers

Jawahar Lal Nehru Laboratory of Molecular Biology, Department of Pharmacology and Therapeutics, King George's Medical College, Lucknow University, Lucknow 226003, India

and

Department of Physiology, University of North Dakota, School of Medicine, Grand Forks, North Dakota 58202

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A series of 2-methyl-3-(3,5-diallyl-4-hydroxyphenyl)-4-quinazolones were prepared as possible anticonvulsants. All compounds were evaluated for their anticonvulsant activity against pentylenetetrazol-induced seizures and their ability to potentiate sodium pentobarbital sleeping time in albino mice.

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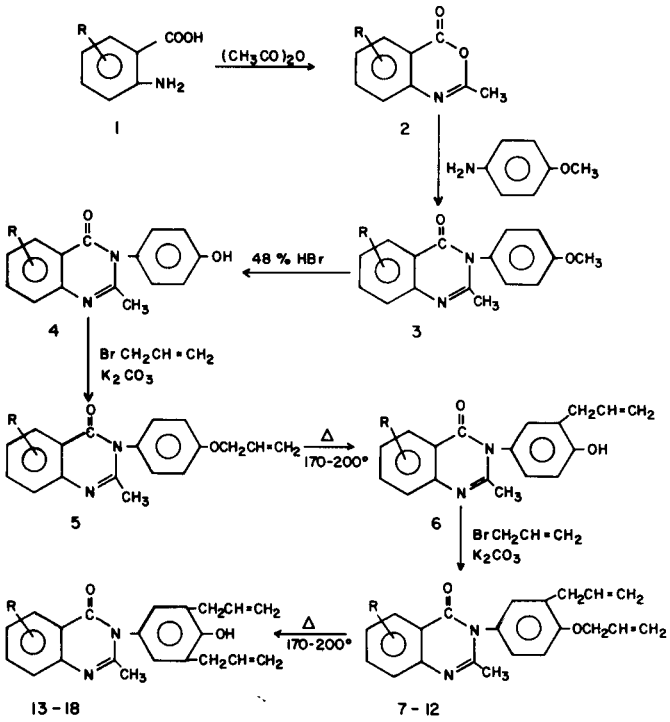
Quinazolones have attracted considerable attention in recent years due to the clinical use of methaqualone (2-methyl-3-*o*-tolyl-4-quinazolone) as an anticonvulsant (1) and hypnotic-sedative (2) drug. In addition, the ability of substituted 2-methyl-3-(3-allyl-4-hydroxyphenyl)/(3-allyloxy-4-hydrazinocarbonylphenyl)-4-quinazolones to exhibit central nervous system depressant properties (3,4) prompted synthesis of substituted 2-methyl-3-(3,5-diallyl-4-hydroxyphenyl)-4-quinazolones. The various substituted quinazolones were synthesized according to the steps outlined in Scheme 1.

Various substituted acetanthranils **2** (5), obtained by the reaction of the appropriate anthranilic acids **1** (6-8) with acetic anhydride, were condensed with *p*-anisidine to give substituted 2-methyl-3-(4-methoxyphenyl)-4-quinazolones **3** (3). These substituted quinazolones **3** on treatment with 48% hydrobromic acid yielded substituted demethylated quinazolones **4** (3) which were converted to the corresponding substituted 2-methyl-3-(4-allyloxyphenyl)-4-quinazolones **5** (3) by the reaction of allyl bromide in presence of anhydrous potassium carbonate. These compounds **5** were converted into substituted 2-methyl-3-(3-allyl-4-hydroxyphenyl)-4-quinazolones **6** (3) on heating at 170-200° for 2 hours. The conversion of **6** to substituted 2-methyl-3-(3-allyl-4-allyloxyphenyl)-4-quinazolones **7-12** was achieved by the same procedure as was followed for the conversion of **4** to **5**. Finally, various substituted 2-methyl-3-(3,5-diallyl-4-hydroxyphenyl)-4-quinazolones **13-18** were obtained by heating **7-12** on an oil bath at 170-200° for 2 hours.

All substituted quinazolones, **13-18**, were investigated for their anticonvulsant activity and their ability to potentiate sodium pentobarbital induced sleeping time (9). Three substituted quinazolones, **14**, **17** and **18**, provided 40% protection, while **13** provided 20% protection and **15** and **16** were devoid of protective ability against pentylenetetrazol-induced convulsions. The average sleeping time of 43.6 ± 5.2 minutes by sodium pentobarbital was increased by 69.4 ± 11.3 to 132.8 ± 18.5 minutes by substituted



SCHEME 1

quinazolones. In these studies **15** exhibited maximum and **18** produced minimum potentiation of sleep induced by sodium pentobarbital. These results have failed to provide any relationship between anticonvulsant activity of substituted quinazolones and their ability to potentiate pentobarbital-induced sleep. All substituted quinazolones possessed low toxicity which was reflected by approximate LD_{50} values of >800 mg./kg.

EXPERIMENTAL

All compounds were analyzed for their carbon, hydrogen and nitrogen contents. Melting points were taken in an open capillary tube with an immersion thermometer and are corrected.

Substituted Acetanthranils (**2**).

A mixture of appropriate anthranilic acid (1 mole) and acetic

Table I

Physical Constants of Substituted 2-Methyl-3-(3-allyl-4-allyloxyphenyl)-4-quinazolones

Compound No.	R	M.p. °C	Yield %	Molecular Formula	Analyses % Calculated C	H	N	Found C	H	N
7	H	109	90	$C_{21}H_{20}N_2O_2$	75.90	6.00	8.43	75.75	5.82	8.18
8	6-Cl	100	85	$C_{21}H_{19}ClN_2O_2$	68.75	5.18	7.64	69.02	4.99	7.38
9	6-Br	98	85	$C_{21}H_{19}BrN_2O_2$	61.31	4.62	6.81	60.94	4.78	6.90
10	6-I	120	83	$C_{21}H_{19}IN_2O_2$	55.02	4.14	6.11	55.31	4.00	5.92
11	6,8-Cl_2	110	90	$C_{21}H_{18}Cl_2N_2O_2$	62.84	4.48	7.00	62.92	4.23	7.26
12	6,8-Br_2	124	75	$C_{21}H_{18}Br_2N_2O_2$	51.42	3.67	5.71	51.33	3.50	5.98

Table II

Physical Constants of Substituted 2-Methyl-3-(3,5-diallyl-4-hydroxyphenyl)-4-quinazolones

Compound No.	R	M.p. °C	Yield %	Molecular Formula	Analyses % Calculated C	H	N	Found C	H	N
13	H	154	82	$C_{21}H_{20}N_2O_2$	75.90	6.00	8.43	76.21	5.98	8.21
14	6-Cl	178	80	$C_{21}H_{19}ClN_2O_2$	68.75	5.18	7.64	68.85	4.92	7.42
15	6-Br	177	78	$C_{21}H_{19}BrN_2O_2$	61.31	4.62	6.81	61.54	4.87	7.06
16	6-I	187	78	$C_{21}H_{19}IN_2O_2$	55.02	4.14	6.11	54.92	6.18	6.02
17	6,8-Cl_2	194	65	$C_{21}H_{18}Cl_2N_2O_2$	62.84	4.48	7.00	62.80	4.22	7.28
18	6,8-Br_2	197	63	$C_{21}H_{18}Br_2N_2O_2$	51.42	3.67	5.71	51.71	3.47	5.96

anhydride (2 moles) was refluxed for 1 hour on a free flame under anhydrous conditions. Removal of the excess of acetic anhydride under reduced pressure yielded crude **2** (5) which were used in the next step without further purification.

Substituted 2-Methyl-3-(4-methoxyphenyl)-4-1uinazolones (**3**).

Equimolar quantities of **2** (0.1 mole) and *p*-anisidine (0.1 mole) were heated on a free flame for 10 minutes. The jelly-like mass on workup and recrystallization from ethanol gave **3**. The melting points of **3** were comparable with those reported earlier (3).

Substituted 2-Methyl-3-(4-hydroxyphenyl)-4-quinazolones (**4**).

The demethylation of compounds **3** was carried out by refluxing these compounds (15.0 g.) with a mixture of 48% hydrobromic acid (150 ml.) and acetic anhydride (350 ml.) for 6 hours. The reaction mixture was evaporated under reduced pressure. The residue thus obtained was dissolved in sodium hydroxide solution and filtered. The filtrate on neutralization with hydrochloric acid gave crude solid products which were collected by filtration and recrystallized from ethanol (3).

Substituted 2-Methyl-3-(4-allyloxyphenyl)-4-quinazolones (**5**).

Equimolar quantities of **4** (0.05 mole), allyl bromide (0.05 mole) and anhydrous potassium carbonate (0.05 mole) in 200 ml. of dry acetone were refluxed on a water bath for 8 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. On cooling, the solid mass which separated out, was filtered and recrystallized from ethanol (3).

Substituted 2-Methyl-3-(3-allyl-4-hydroxyphenyl)-4-quinazolones (**6**).

These quinazolones were prepared by heating **5** on an oil bath at 170-200° for 2 hours. The product was cooled, dissolved in sodium hydroxide solution and filtered. The alkaline filtrate on neutralization with acetic acid gave colourless solids **6** which were recrystallized from ethanol (3).

Substituted 2-Methyl-3-(3-allyl-4-allyloxyphenyl)-4-quinazolones (**7-12**).

Various quinazolones were synthesized from **6**, according to the procedure described above for the preparation of **5**. These compounds were characterized by their sharp melting points and elemental analyses (Table I).

Substituted 2-Methyl-3-(3,5-diallyl-4-hydroxyphenyl)-4-quinazolones (**13-18**).

The method for the preparation of **6** was used to synthesis of **13-18**. The various quinazolones **13-18** thus obtained were recrystallized from ethanol and characterized by their sharp melting points and elemental analyses (Table II).

Pharmacological Studies.

The anticonvulsant activity was determined in mice after intraperitoneal administration of 100 mg./kg. of substituted quinazolones against convulsions in albino mice induced by subcutaneous administration of 90 mg./kg. of pentylenetetrazol (9). The ability of substituted quinazolones (100 mg./kg., i.p.) to potentiate sleeping time was evaluated in albino mice after intraperitoneal administration of 35 mg./kg. of sodium pentobarbital (9). The toxicity

was reflected by their approximate LD_{50} values determined by intraperitoneal administration of substituted quinazolones in albino mice by following the method reported earlier (10).

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