Some Newer Quinazolones as Possible Anticonvulsants

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(Received 25th June 1983)

Summary: In view of their expected MAO inhibitory, CNS depressant and anticonvulsant properties, twenty four new 2-(O-methoxy-phenoxymethyl) -3-(α-substituted carboxamidomethyl)-6,8-substituted-4-quinazolones were synthesised (Scheme 1). Some of the compounds were tested for their anticonvulsant activity but none of them showed significant activity.

Introduction

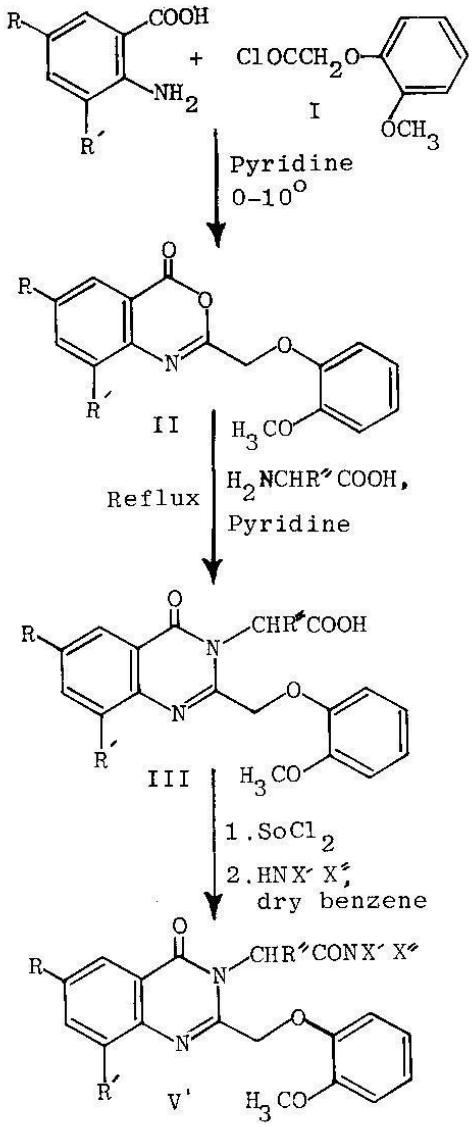
A number of workers have reported that several derivatives of 4-quinazolone exhibit CNS [1], hypnotic [2], anticonvulsant [3,4] and analgesic activities. Numerous drugs exerting action on CNS have amide linkage as their common structural unit. The lower aminoacids like glycine, leucine, β-alanine and γ-aminobutyric acid have been found to be inhibitory neurotransmitters [5,6]. More recently, quinazolone substituted acids and their amides have also shown strong anticonvulsant activity. Inspired by these observations, it was considered worthwhile to prepare the title quinazlones containig o-methoxy phenoxymethyl moiety with the hope that the presence of the latter might enhance the anticonvulsant activity of these compounds.

Experimental

All m.p.'were determined in open capillaries and are uncorrected. The purity of the compounds was checked by tlc on silica gel.

O-(Methoxy) phenoxyacetyl chloride (I)

It was prepared according to the method reported in literature [9,10].



Scheme-1

2-(O-Methoxyphenoxymethyl)-6,8-substituted anthranils (II)

Substituted anthanalic acid (0.03 mole) was dissolved in pyridine (30 ml) and the solution cooled to 0°C. To this solution was added O-methoxy-phenoxyacetyl chloride (0.03 mole) slowly in small portions with shaking, the temperature being maintained at 0-10°C. Thereafter, the mixture was kept at the room temperature for 12 to 13 hours. It was then poured into cold dilute HCl with stirring. After being kept overnight, it was filtered. The solid mass thus obtained was dried and used as such in the next step without crystallization. The anthranils prepared are:-

(i) 2-(O-Methoxy-phenoxymethyl)-6,8-dibromoanthranil

m.p.222°C. Found: N, 2.83%. Calcd. for $C_{16}H_{11}NO_4Br_2$,N,3.17%.

(ii) 2-(O-Methoxy-phenoxymethyl)-6-iodo anthranil

m.p. 228°C. Found: N, 3.13%. Calcd. for $C_{16}H_{12}NO_4I$, N, 3.42%.

2-(O-Methoxy-phenoxymethyl)-3- α -substituted carboxymethyl-6,8-substituted-4-quinazolones (II)

These were prepared by refluxing equimolar quantities of substituted anthranil and an appropriate amino-acid in pyridine for 12 hours. The pyridine was distilled off under reduced pressure and the residue poured into acidified ice cold water. The solid thus obtained was filtered, dried and characterized by its sharp m.p., analysis and I.R.spectra (table 1).

Table-1: 2-(o-Methoxy-phenoxymethyl)-3-α-substituted carboxymethyl-6, 8-substituted-4-quinazolones (III)

S.No.	R	R'	R"	M.P. °C	Molecular formula	N %	
						Found	Calcd.
1*.	Br	Br	H	201-203	$C_{18}H_{14}N_2O_5Br_2$	5.39	5.62
2.	Br	Br	CH_3	222-225	$C_{19}H_{16}N_2O_5Br_2$	5.14	5.46
3*.	Br	Br	i-C_3H_7	218	$C_{21}H_{20}N_2O_5Br_2$	5.97	5.78
4.	Br	Br	i-C_4H_9	210	$C_{22}H_{22}N_2O_5Br_2$	4.81	5.05
5.	I	H	H	230	$C_{18}H_{15}N_2O_5I$	5.79	6.00
6*.	I	H	CH_3	195-198	$C_{19}H_{17}N_2O_5I$	5.61	5.83
7.	I	H	i-C_3H_7	222	$C_{21}H_{21}N_2O_5I$	5.37	5.51
8*.	I	H	i-C_4H_9	210	$C_{22}H_{23}N_2O_5I$	5.13	5.36

*Showed I.R.bands at 1660 cm^{-1} (-N-C=O) and 1725-1700 cm^{-1} (CO of COOH).

2-(O-Methoxy-phenoxymethyl)-3- α-substituted chlorocarbonylmethyl-6,8-substituted-4-quinazolones (IV)

The III (0.002 M) was converted into its acid chloride by refluxing with excess of thionyl chloride in anhydrous benzene for 5 to 6 hours. The excess of $SOCl_2$ was distilled off. The acid chloride obtained as residue was used as such in the next step.

2-(O-Methoxy-phenoxymethyl)-3- α-substituted carboxamidomethyl)-6,8-substituted-4-quinazolones (V)

IV (0.002 M) was refluxed with a secondary amine (0.002M) in anhydrous benzene for two hours. The reaction mixture was cooled and excess benzene was distilled off under reduced pressure. The solid obtained was washed successively with 5% HCl and 5% $NaHCO_3$ and recrystallized from ethanol. The compounds thus prepared were characterized by their sharp m.p., elemental analysis and the presence of bands at 1660 cm^{-1} (N-C=O) in the infra red spectra (table.2).

Biological activity

(A) Determination of Approximate Lethal dose in mice

As per method of Horn [11], an initial dose of 464 mg/kg of the compound (later varied depending on mortaility) was administered i.p. in groups of 4 albino mice of either sex and each weighing between 16 to 20 gm. Mice were fasted for 24 hours and the mortality was recorded at the end of 24 hours.

Gross behavioural effects

These were observed according to the method of Turner [12]. Different doses of the compound including 1/5th of ALD_{50} were administered i.p. in groups of animals, which were then observed at intervals of 6 and 24 hours for the signs of stimulation or depression.

(B) Anticonvulsant activity

(a) Metrazole - induced seizure Test

It was carried out according to the method of Swinyard [13]. A group of 5 albino mice of either sex each weighing 16-20 gm and pretreated with 1/5th of ALD_{50} dose of compounds i.p. was injected pentylenetetrazole (80 mg/kg) subcutaneously after one hour. The number of animals not exhibiting convulsions during 60 minutes after injection of pentylenetetrazole were expressed in terms of percentage protection.

Supramaximal Electroshock seizures test:

As per method of Swinyard [13] a group of 5 albino mice of either sex each weighing between 10 to 20 grams was pretreated one hour earlier with 1/5th ALD_{50} dose of the compound. A current stimulus of 48 m.A. for 0.2 second delivered through ear electrodes produced tonic extension of hind limbs in 100% of the mice in control group. Abolition of this response by the compound was taken as criteria of their anticonvulsant activity.

Acknowledgement

We thank Professor V.S.Misra, Head, Chemistry Department, Lucknow University, Lucknow for providing departmental facilities and Dr. Nityanand, Director C.D.R.I., Lucknow for anticonvulsant screening of the compounds.

Table 2: 2-[o-Methoxy-phenoxymethyl]-3-[α-substituted carboxamidomethyl]-6,8-substituted-4-quinazolone (V)

S.No.	R	R'	R''	NX' NX''	M.P.°C	Molecular formula	N % Found	N % Calcd.
1.	Br	Br	CH_3	Piperidino	70	$C_{24}H_{25}N_3O_4Br_2$	7.02	7.25
2.	Br	Br	i-C_3H_7	"	69-70	$C_{26}H_{29}N_3O_4Br_2$	6.59	6.91
3.	Br	Br	i-C_4H_9	"	78-80	$C_{27}H_{31}N_3O_4Br_2$	6.55	6.76
4.	I	H	H	Morpholino	80	$C_{22}H_{22}N_3O_5I$	7.67	7.85
5.	I	H	CH_3	"	101	$C_{23}H_{24}N_3O_5I$	7.41	7.65
6.	I	H	i-C_3H_7	"	95	$C_{25}H_{28}N_3O_5I$	7.03	7.27
7.	Br	Br	CH_3	Pyrrolidino	80	$C_{23}H_{23}N_3O_4Br_2$	6.98	7.25
8.	Br	Br	i-C_3H_7	"	65-68	$C_{25}H_{27}N_3O_4Br_2$	6.89	7.08
9.	Br	Br	i-C_4H_9	"	83	$C_{26}H_{29}N_3O_4Br_2$	6.63	6.91
10.	I	H	H	Piperidino	73	$C_{23}H_{24}N_3O_4I$	7.63	7.87
11.	I	H	CH_3	"	100	$C_{24}H_{26}N_3O_4I$	7.41	7.67
12.	I	H	i-C_3H_7	"	70-72	$C_{26}H_{30}N_3O_4I$	7.48	7.30
13.	Br	Br	CH_3	Morpholino	60	$C_{23}H_{23}N_3O_5Br_2$	6.83	7.22
14.	Br	Br	i-C_3H_7	"	82-83	$C_{25}H_{27}N_3O_5Br_2$	6.51	6.89
15.	Br	Br	i-C_4H_9	"	80	$C_{26}H_{29}N_3O_5Br_2$	6.92	6.74
16.	I	H	H	Pyrrolidino	103	$C_{22}H_{22}N_3O_4I$	7.82	8.09
17.	I	H	CH_3	"	90	$C_{23}H_{24}N_3O_4I$	8.11	7.87
18.	I	H	i-C_3H_7	"	95-96	$C_{25}H_{28}N_3O_4I$	7.21	7.48
19.	Br	Br	H	Piperidino	63	$C_{23}H_{23}N_3O_4Br_2$	7.15	7.43
20.	I	H	i-C_4H_9	"	98	$C_{27}H_{32}N_3O_4I$	6.94	6.75
21.	Br	Br	H	Morpholino	69	$C_{22}H_{21}N_3O_5Br_2$	6.88	7.40
22.	I	H	i-C_4H_9	"	80	$C_{26}H_{30}N_3O_5I$	6.74	7.10
23.	Br	Br	H	Pyrrolidino	98	$C_{22}H_{21}N_3O_4Br_2$	7.30	7.62
24.	I	H	i-C_4H_9	"	101	$C_{26}H_{30}N_3O_4I$	6.98	7.30

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