Synthesis of Substituted 2-Methyl-3-(3,4-dimethoxy/dihydroxyphenylethyl)-4-quinazolones as Possible Antiparkinson Drugs

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Several substituted 2-methyl-3-(3,4-dimethoxy/dihydroxyphenylethyl)-4-quinazolones were synthesized as possible antiparkinsonism agents. The structure of these compounds were confirmed by their elemental and spectral analysis.

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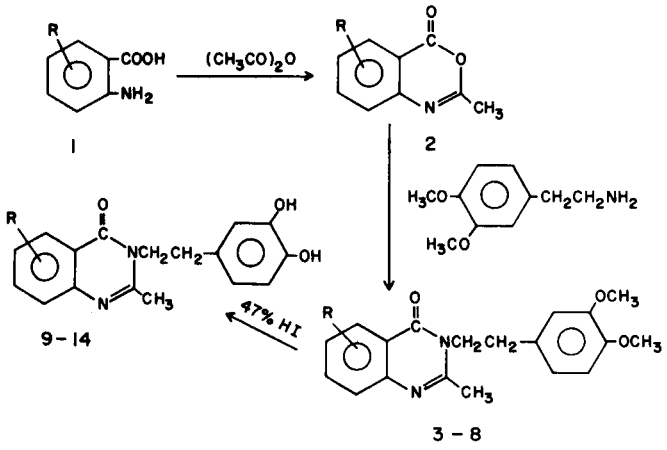
The deficiency of dopamine in the basal ganglia of parkinsonian patients has been established as a biochemical lesion in all forms of parkinsonism. The levodopa (L-DOPA), a precursor of dopamine, acts on the biochemical defect of parkinsonism and is the most effective drug available for treatment of disease (1). However, abundance of dopa-decarboxylase in peripheral tissues has necessitated the use of large doses and prolonged use of L-DOPA for its possible entry to brain to liberate dopamine by dopa-decarboxylase and thereby maintaining optimal dopamine concentration for desired beneficial effects. In addition, the various side effects associated with L-DOPA therapy (2) prompted synthesis of substituted quinazolones containing dopamine and 3,4-dimethoxydopamine moiety in their structure in an attempt to provide preferential transport of these compound to brain and their possible biotransformation to liberate dopamine and/or dopamine like substances by the actions of the drug metabolizing enzyme systems and thus being independent of the use of brain dopa-decarboxylase. The synthesis of various substituted 2-methyl-3-(3,4-dimethoxy/dihydroxyphenylethyl)-4-quinazolones was carried out according to the steps outlined in Scheme 1.

Scheme 1



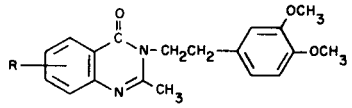
Various substituted acetanthranils **2** were prepared by the condensation of appropriate substituted anthranlic acids **1** and acetic anhydride. The reaction of β-(3,4-dimethoxyphenyl)ethylamine with substituted acetanthranils **2** resulted the formation of substituted 2-methyl-3-(3,4-dimethoxyphenylethyl)-4-quinazolones **3-8**. Finally, the substituted 2-methyl-3-(3,4-dihydroxy-phenylethyl)-4-quinazolones **9-14** were obtained by refluxing the substituted quinazolones **3-8** with 47% hydroiodic acid.

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. Ultraviolet (uv) spectra were recorded on Cary Model 14 spectrophotometer. Infrared (ir) spectra of these compounds were obtained on Beckman IR-12 spectrophotometer

Table I

Physical Constants of Substituted-2-Methyl-3-(3,4-dimethoxyphenylethyl)-4-quinazolones



Compound No.	R	Yield %	Molecular Formula	M.p. °C	Analysis % Calculated C	H	N	Found C	H	N
3	H	85	$C_{19}H_{20}N_2O_3$	130	70.37	6.17	8.64	70.66	6.14	8.71
4	6-CH_3	80	$C_{20}H_{22}N_2O_3$	116	71.01	6.51	8.28	71.12	6.58	8.42
5	8-CH_3	70	$C_{20}H_{22}N_2O_3$	136	71.01	6.51	8.28	71.09	6.67	8.31
6	6-Cl	75	$C_{19}H_{19}ClN_2O_3$	134	63.58	5.29	7.80	63.62	5.31	7.89
7	7-Cl	83	$C_{19}H_{19}ClN_2O_3$	104	63.58	5.29	7.80	63.52	5.28	7.84
8	6-I	78	$C_{19}H_{19}IN_2O_3$	138	50.67	4.22	6.22	50.61	4.18	6.32

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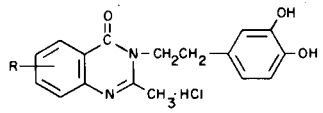
Table II

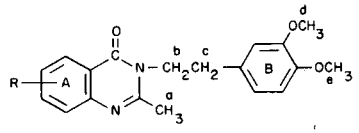
Physical Constants of Substituted-2-Methyl-3-(3,4-dihydroxyphenylethyl)-4-quinazolone Hydrochlorides



Compound No.	R	Yield %	Molecular Formula	M.p. °C	Analysis % Calculated C	H	N	Found C	H	N
9	H	80	$C_{17}H_{16}N_2O_3HCl$	210 dec.	61.35	5.11	8.42	61.31	5.02	8.27
10	6-CH_3	60	$C_{18}H_{18}N_2O_3HCl$	252 dec.	62.33	5.48	8.08	62.41	5.44	8.28
11	8-CH_3	65	$C_{18}H_{18}N_2O_3HCl$	240 dec.	62.33	5.48	8.08	62.24	5.57	7.64
12	6-Cl	70	$C_{17}H_{15}ClN_2O_3HCl$	260 dec.	55.58	4.36	7.63	55.39	4.46	7.63
13	7-Cl	80	$C_{17}H_{15}ClN_2O_3HCl$	204	55.58	4.36	7.63	55.47	4.21	7.78
14	6-I	82	$C_{17}H_{15}IN_2O_3HCl$	270 dec.	44.49	3.49	6.10	44.47	3.45	6.12

Table III

Infrared and Nuclear Magnetic Resonance Spectral Data of Substituted 2-Methyl-3-(3,4-dimethoxyphenylethyl)-4-quinazolones

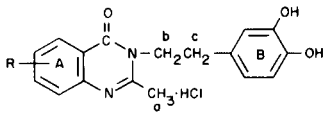


Compound No.	R	Characteristic Bands in Ir. Spectra (Cm^{-1}) C=C	C-N /C=N	Nmr Chemical Shifts (δ) (a) a (CH_3)	b (CH_2)	c (CH_2)	d (OCH_3)	e (OCH_3)	Ring B Protons	Ring A Protons
3	H	1600	1670	2.43 (s)	4.20 (t)	2.93 (t)	3.63 (s)	3.70 (s)	6.66-6.90 (m)	7.36-8.16 (m)
4	6-CH_3	1590	1685	2.40 (s)	4.20 (t)	2.90 (t)	3.63 (s)	3.70 (s)	6.63-6.86 (m)	7.33-7.86 (m)
5	8-CH_3	1600	1680	2.46 (s)	4.20 (t)	2.90 (t)	3.63 (s)	3.70 (s)	6.66-6.90 (m)	7.20-8.00 (m)
6	6-Cl	1595	1685	2.43 (s)	4.16 (t)	2.86 (t)	3.63 (s)	3.70 (s)	6.63-6.86 (m)	7.43-8.00 (m)
7	7-Cl	1590	1680	2.43 (s)	4.16 (t)	2.86 (t)	3.63 (s)	3.70 (s)	6.63-6.68 (m)	7.36-8.10 (m)
8	6-I	1600	1675	2.40 (s)	4.20 (t)	2.86 (t)	3.63 (s)	3.70 (s)	6.63-6.86 (m)	7.23-8.30 (m)

(a) Signal multiplicity: s = singlet, t = triplet and m = multiplet.

Table IV

Infrared and Nuclear Magnetic Resonance Spectral Data of Substituted 2-Methyl-3-(3,4-dihydroxyphenylethyl)-4-quinazolones

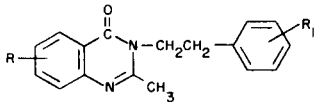


Compound No.	R	Characteristic Bands in Ir Spectra (cm^{-1}) C=C	C-N	C=N	OH	Nmr Chemical Shifts (δ) (a) a (CH_3)	b (CH_2)	c (CH_2)	Ring B Protons	Ring A Protons	3,4-$(OH)_2$
9	H	1610	1650	1715	3200	2.83 (s)	4.20 (t)	2.83	6.40-6.80 (m)	7.53-8.30 (m)	9.70 (b)
10	6-CH_3	1600	1650	1710	3210	2.86 (s)	4.20 (t)	2.86	6.40-6.80 (m)	7.70-8.06 (m)	9.60 (b)
11	8-CH_3	1600	1640	1695	3330	2.70 (s)	4.20 (t)	2.80 (t)	6.40-6.76 (m)	7.30-8.10 (m)	7.50 (b)
12	6-Cl	1600	1650	1715	3240	2.70 (s)	4.20 (t)	2.83 (t)	6.40-6.73 (m)	7.60-8.13 (m)	8.90 (s)
13	7-Cl	1580	1640	1690	3240	2.60 (s)	4.20 (t)	2.80 (t)	6.40-6.80 (m)	7.30-8.20 (m)	7.30 (b)
14	6-I	1600	1640	1705	3210	2.56 (s)	4.20 (t)	2.83 (t)	6.30-6.90 (m)	7.30-8.33 (m)	9.43 (b)

(a) See footnote in Table III.

Table V

Absorption Spectra of Substituted 2-Methyl-3-(3,4-dimethoxy/dihydroxyphenylethyl)-4-quinazolones



Compound No.	R	R_1	λ Max (e) (a)
3	H	3,4-$(OCH_3)_2$	278 (4500), 300 (1600), 320 (1200)
4	6-CH_3	"	278 (4800), 312 (1500), 325 (1200)
5	8-CH_3	"	282 (4500), 312 (1650), 324 (1300)
6	6-Cl	"	274 (6000), 316 (1400), 328 (1100)
7	7-Cl	"	280 (4300), 305 (1400), 320 (1200)
8	6-I	"	280 (7600), 320 (1200), 330 (900)
9	H	3,4-$(OH)_2$	278 (10400), 305 (3600), 320 (2400)
10	6-CH_3	"	280 (12600), 313 (3400), 324 (2000)
11	8-CH_3	"	282 (10400), 310 (3800), 324 (2800)
12	6-Cl	"	276 (15400), 316 (3800), 328 (2800)
13	7-Cl	"	282 (11400), 308 (3800), 320 (3200)
14	6-I	"	282 (15800), 318 (2800), 330 (2000)

(a) All spectra were recorded on Carry 14 spectrophotometer in spectrograde methanol at room temperature. The concentrations of various substituted dimethoxyquinazolones (**3-8**) were 1 x $10^{-4}M$ and various substituted dihydroxyquinazolone hydrochlorides (**9-14**) were 5 x $10^{-5}M$. The extinction coefficient is in the paranthesis after each wavelength.

as a suspension in nujol mull. Nuclear magnetic resonance spectra were recorded on a Varian EM-390 instrument using tetramethylsilane as an internal standard and deuterated dimethylsulfoxide as solvent. A Perkin-Elmer MPF-44A spectrophotofluorometer with phosphorescence attachment was used for the measurement of fluorescence and phosphorescence. Spectrograde methanol was purchased from Burdick and Jackson Laboratories, Inc., Muskegon, Michigan. Various substituted anthranilic acids were purchased from Aldrich Chemical Company, Inc., Milwaukee, Wisconsin. β-(3,4-dimethoxyphenyl)ethylamine was obtained from Sigma Chemical Co., St. Louis, Missouri.

Substituted Acetanthranils (2).

A mixture of suitable anthranilic acid (0.1 mole) and acetic anhydride (0.2 mole) was refluxed for 1 hour on a free flame under anhydrous conditions. Removal of the excess of acetic anhydride under reduced pressure gave solid mass of **2** (3-7). These crude acetanthranils **2** were used in the preparation of **3-8** without further purification.

Substituted 2-Methyl-3-(3,4-dimethoxyphenylethyl)-4-quinazolones (**3-8**).

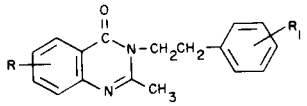
Equimolecular quantities of **2** (0.1 mole) and freshly distilled β-(3,4-dimethoxyphenyl)ethylamine were heated on a free flame for 10 minutes. The jelly-like mass on work up and recrystallization from ethanol yielded various quinazolones **3-8**. These substituted quinazolones were characterized by their sharp melting points and elemental and spectral analyses (Table I, III, V and VI).

Substituted 2-Methyl-3-(3,4-dihydroxyphenylethyl)-4-quinazolones (**9-14**).

Various substituted quinazolones **3-8** (0.05 moles) were refluxed in 250 ml. of 47% hydroiodic acid for 4 hours. The reaction mixture was cooled and filtered. The crude product thus obtained was dissolved in 10% sodium hydroxide solution and filtered. The filtrate was made acidic with dilute hydrochloric acid, cooled, and filtered. The solid quinazolone hydrochlorides **9-14** thus obtained were recyrstallized from ethanol. The various substituted quinazolone hydrochlorides were characterized by their sharp melting points and elemental and spectral analyses (Table II, IV, V and VI).

Table VI

Total Emission Spectra of Substituted 2-Methyl-3-(3,4-dimethoxy/dihydroxyphenylethyl)-4-quinazolones



Compound No.	R	R_1	Excitation λex (nm)	Fluorescence (a) bands (nm)	Phosphorescence (b) bands (nm)
3	H	3,4-(OCH_3)	278	338	399, 424 (c), 450 (sh)
4	6-CH_3	"	278	337	411, 437 (c), 464 (sh)
5	8-CH_3	"	282	337	410, 436 (c), 464 (sh)
6	6-Cl	"	274	339	416, 444 (c)
7	7-Cl	"	280	338	408, 428 (c)
8	6-I	"	280	338	420, 442 (c)
9	H	3,4-$(OH)_2$	278	337	396, 442 (c)
10	6-CH_3	"	280	337	409, 436 (c), 463
11	8-CH_3	"	282	337	409, 436 (c), 460 (sh)
12	6-Cl	"	276	338	411, 437 (c), 463 (sh)
13	7-Cl	"	282	338	405, 427 (c)
14	6-I	"	282	336	398, 423 (c), 434 (sh)

(a) Fluorescence spectra were recorded in methanol (1 x 10^{-5} *M*) at room temperature. Excitation and emission band pass were 14 nm and 5 nm, respectively. (b) Phosphorescence spectra were obtained in methanol (1 x 10^{-5} *M*) at liquid nitrogen temperature. Excitation and emission band pass were 10 nm and 1 nm, respectively. (c) λ Max in phosphorescence, sh = shoulder.

Acknowledgments

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