STRUCTURE-ACTIVITY RELATIONSHIP IN CNS-DEPRESSANT QUINAZOL-4-ONES—PART 1 2, 3-DISUBSTITUTED QUINAZOL-4-ONES

by

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In several communications from this laboratory, a number of 2-alkyl-3-aryl-quinazol-4-ones have been shown to exert a profound influence on the normal functional activity of the brain. Some of these compounds were found to possess clinically useful hypnotic (Gujral et al., 1955 a & b; 1956 a, b & c), antiepileptic (Gujral et al., 1956 d; 1957 a & b) and antipyretic and hypothermic properties (Saxena and Khanna, 1958) when given orally. Parentral administration of the potent hypnotic extended the depressant action to general and local anesthesia (Gujral et al., 1959). Hypnotic properties of QZ-2 were also confirmed by Hays (1957) and by Boissier, Dumont and Malen under their Code No. TR 495 (1958) and the anticonvulsant properties were confirmed by Becker and Swift (1959). They were found to be devoid of any morphine-like analgesic action (Gujral et al., 1955 a; Hays, 1959) although it has been found that codeine analgesia in rats is potentiated (Becker, 1958; Becker and Hays, 1958; Cass and Frederik, 1959). Detailed pharmacology of the most potent hypnotic agent of this series (QZ-2) was studied by Gujral et al.

(1959) and by Becker and Swift (1959). As these compounds were totally different from the conventional barbiturates, hydantoinates and their congeners, it was considered desirable to investigate structure-activity relationship in this promising and entirely new class of central depressants particularly with a view to enhance their potency and to resolve the properties found overlapping in some of the more active compounds. This paper deals only with their hypnotic and antiepileptic actions.

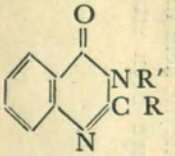
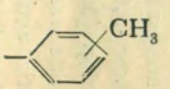
As several compounds intimately associated with the essential life processes of the neurones, like some vitamins and coenzymes and both RNA and the DNA of the mitochondria and the nuclei, contain a pyrimidine moiety, quite a large number of CNS-depressants are derived from this ring system. Amongst the quinazolines (5, 6-benzopyrimidines) certain 3-aryl-6-alkyl or alkoxy-3,4-dihydroquinazolinium salts were found to have CNS-depressant action (Maffei, 1929 a b & c, and 1931; Valenti, 1930). 3-Phenyl-quinazol-4-one was found by Chen (1948) to be equal to acetylsalicylic acid in antipyretic action in febrile rats. Quinazol-2,4-diones have been studied by Wenzel (1955) for their anticonvulsant effect.

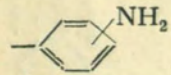
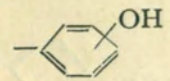
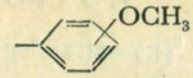
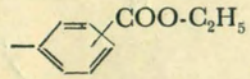
METHODS AND MATERIALS

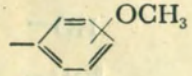
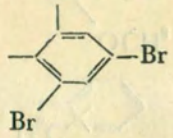
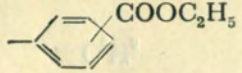
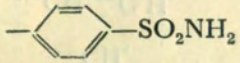
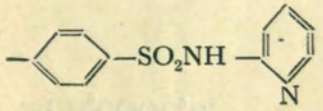
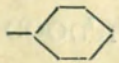
Albino rats (CDRI strain) of either sex weighing between 75 to 100 gm. were selected. They were divided into groups of six rats each, keeping the total group weight constant. Food was withheld the previous evening but water was freely allowed except during the actual performance of the test. 200 mg./kg. of each drug, in the form of a homogenised aqueous suspension in 5 per cent gum acacia, was administered to each group, except the control group, by means of a stomach cannula attached to a tuberculin syringe. The hypnotic activity was screened by the method previously described (Gujral et al., 1955 b). The anticonvulsant activity was screened by using the maximal electroshock seizure test (Swinyard, 1949; Swinyard, Brown and Goodman, 1952). The current, of intensity 210 ma for 0.4 seconds, was delivered through an electroshock machine (Gujral et al., 1957 b) two hours after the administration of the drugs. The end point was the abolition of hind leg tonic extensor component of the seizure. Percentage of the rats protected by each drug was noted.

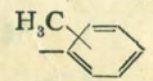
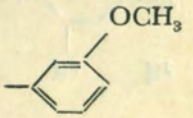
RESULTS

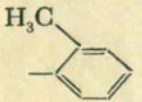
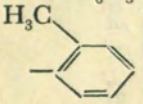
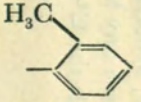
The results of the screening of 62 compounds have been tabulated below :

Sr. No.	Code No.	Name	 R	R′	Hypnotic activity	Anticonvulsant activity (Percentage protection)
		A. Parent nucleus :				
1.	HAC-1	Quinazol-4-one	H	H	0	0
		B. Substituted-quinazol-4-ones :				
2.	HAC-2	methyl	H	CH_3	0	0
3.	HAC-3	allyl	H	$-CH_2-CH=CH_2$	0	0
4	HAC-4	benzyl	H	$-CH_2-C_6H_5$	0	0
5.	HAC-5	phenyl (QZ-21)	H	$-C_6H_5$	40 mg./kg.=0 200 mg./kg.=100	0 33
6.	HAC-6	o-tolyl	H		40 mg./kg.=80 200 mg./kg.=100	0 33
7.	HAC-7	p-tolyl	H		0	0

8.	HAC-8	o-aminophenyl	H		0	0
9.	HAC-9	p-aminophenyl	H		0	0
10.	HAC-10	o-hydroxyphenyl	H		0	0
11.	HAC-11	p-hydroxyphenyl	H		0	0
12.	HAC-12	o-anisyl	H		Slight activity	0
13.	HAC-13	m-anisyl	H		,,	0
14.	HAC-14	p-anisyl	H		,,	0
15.	HAC-15	o-carbethoxyphenyl	H		0	0
16.	HAC-16	p-carbethoxyphenyl	H		0	0
17.	HAC-17	amino	H	$-NH_2$	0	0
18.	HAC-18	hydroxy	H	$-OH$	0	0
19.	HAC-19	carbethoxy	H	$-COOC_2H_5$	0	0
20.	HAC-20	carbethoxymethyl	H	$-CH_2COOC_2H_5$	0	0

31.	HAC-31	p-hydroxphenyl	CH_3		0	0
32.	HAC-32	o-anisyl	CH_3		Slight activity	33
33.	HAC-33	m-anisyl	CH_3		,,	50
34.	HAC-34	p-anisyl	CH_3		,,	33
35.	HAC-35	o-bromo	CH_3		100 mg./kg.=100	16
36.	HAC-36	2′,4′,6′-tribromo	CH_3		0	0
37.	HAC-37	o-carbethoxyphenyl	CH_3		0	0
38.	HAC-38	p-carbethoxyphenyl	CH_3		0	0
39.	HAC-39	p-sulphonamidophenyl	CH_3		0	0
40.	HAC-40	p-N(*a*-pyridyl)-sulphon-amidophenyl	CH_3		0	0
41.	HAC-41	cyclohexyl	CH_3		0	0
42.	HAC-42	amino	CH_3	$-NH_2$	0	0

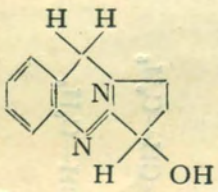
43.	HAC-43	hydroxy	CH_3	—OH	0	0
44.	HAC-44	carbethoxy	CH_3	$—COOC_2H_5$	0	0
45.	HAC-45	carbethoxymethyl	CH_3	$—CH_2COOC_2H_5$	0	0
	D. 2-Phenyl-3-substituted-quinazol-4-ones :					
46.	HAC-46	methyl	C_6H_5	$—CH_3$	0	0
47.	HAC-47	benzyl	C_6H_5	$—CH_2—C_6H_5$	0	0
48.	HAC-48	phenyl	C_6H_5	$—C_6H_5$	0	0
49.	HAC-49	o-tolyl	C_6H_5		0	0
50.	HAC-50	p-tolyl	C_6H_5		0	0
51.	HAC-51	m-anisyl	C_6H_5		0	0
52.	HAC-52	amino	C_6H_5	$—NH_2$	0	0
53.	HAC-53	hydroxy	C_6H_5	—OH	0	0
	E. BZ-halogenated compounds :					
54.	HAC-54	6-bromo-QZ-1	CH_3	$—C_6H_5$	Active	33

55.	HAC-55	6-bromo-QZ-2	CH_3		Active	50
56.	HAC-56	6-bromo-QZ-4	C_2H_5	$-C_6H_5$	Active	50
	F. 2-Benzylidenoalkyl-3-aryl-quinazol-4-ones :					
57.	HAC-57	2-benzylidenomethyl-3-phenyl	$-CH=CH-C_6H_5$	$-C_6H_5$	0	50
58.	HAC-58	2-benzylidenomethyl-3-o-tolyl	$-CH=CH-C_6H_5$		0	50
59.	HAC-59	2-*a*-benzylidenoethyl-3-phenyl	$-C(CH_3)=CH-C_6H_5$	$-C_6H_5$	0	50
60.	HAC-60	2-benzylidene derivative of 6-Br-QZ-1 (HAC-54)	$-CH=CH-C_6H_5$	$-C_6H_5$	0	50
61.	HAC-61	2-benzylidene derivative of 6-Br-QZ-2 (HAC-55)	$-CH=CH-C_6H_5$		0	50
62.	HAC-62	2-benzylidene derivative of 6-Br-QZ-4 (HAC-56)	$-C(CH_3)=CH-C_6H_5$	$-C_6H_5$	0	50

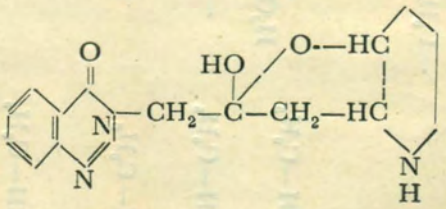
DISCUSSION

The study of the above table shows that the parent compound quinazol-4-one, its 3-(methyl, allyl, benzyl, amino, hydroxy, carbethoxy or carbethoxymethyl)-derivatives, 2,3-dimethyl, 2,3-di-n-propyl (Gujral et al., 1955 a) and 2-methyl-3-(allyl, benzyl, cyclohexyl, amino, hydroxy, carbethoxy or carbethoxymethyl)-derivatives are all devoid of any hypnotic or anticonvulsant activity.

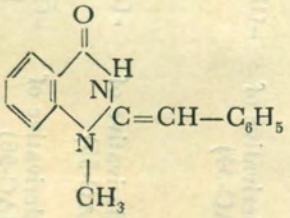
Quinazoline, its di- and tetrahydro-derivatives, 2,3-dialkyl-quinazolines represented by vasicine and some quinazol-4-one alkaloids like febrifugine and isofebrifugine, arborine and rutaecarpine and evodiamine also have not been shown to have any hypnotic activity. 3-Phenyl-3,4-dihydroquinazoline (Orexine, which is the C^4-hydrogenated QZ-21) is, however, a CNS depressant Valenti, 1930).



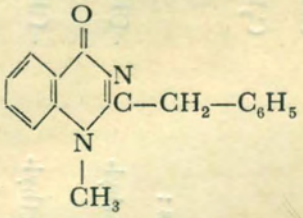
Vasicine



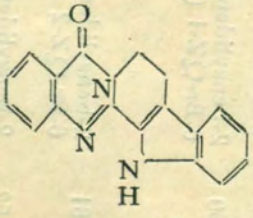
Febrifugine



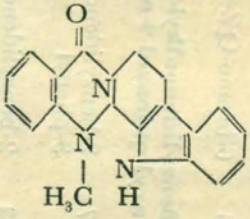
or



Arborine



Rutaecarpine



Evodiamine

The CNS-depressant activity, therefore, seems to be incipient in 3-phenyl-quinazol-4-one (HAC-5 or QZ-21) and reaches a substantial level in the 2-methyl- and the 2-ethyl-analogues (QZ-1 and QZ-4, Gujral et al., 1955 a).

Thus a resonant aromatic nucleus at N^3 with a small alkyl at C^2 in the quinazol-4-one moiety seems to be the essential features of the electron availability and the overall molecular morphology for a favourable depressant action in these compounds. Condensed nuclei like naphthyl at N^3 (Gujral et al., 1955 a), however, are inactive. Higher alkyls as n-propyl at C^2 produced undesirable side effects in the active compounds, while the introduction of a phenyl group in this position, as in the 2,3-diphenyl derivatives (H AC 46-53),caused complete inactivation. The introduction of o-, m- and p-amino and hydroxy, o- and p-methoxy, o- and p-carbethoxy and the p-sulphonamido groups in the N^3-phenyl also led to inactivation. The o-bromo, m-methyl or methoxy and o- and p-nitro groups (Gujral et al., 1955 a), however, retained the activity, although the nitro compounds were toxic. The o-methyl substitution as in HAC-6 and Q Z-2, on the other hand, increased the hypnotic potency while the same substitution in the para position, which apparently should have a similar electron availability at N^3, was found to produce (Gujral et al., 1955 a) a complete block in the activity. A similar deactivating influence, however, has also been observed in some other hypnotics: phenylacetamides (Chapman et al., 1957). Replacement of the N^3-phenyl by the heterocyclic *a*-pyridyl is also not useful. It is interesting to note that conversion of the picolinic methyl into its benzylidene derivative, as in HAC 57-62, resolves the overlapping hypnotic and the anticonvulsant properties of the active compounds. These compounds retain their anticonvulsant action with a loss of the accompanying hypnotic effect.

SUMMARY

1. 3-Phenyl-quinazol-4-one moiety seems to be the seat of CNS-depressant effect in the 2,3-disubstituted quinazol-4-ones. Methyl and ethyl groups at C^2 enhance this activity. 2-Methyl-3-o-tolyl compound (Q Z-2) has so far been found to be the most potent in this series.

2. Introduction of o-bromo and m-methyl or methoxy in the N^3-phenyl retains the activity while that of amino, hydroxy, carbethoxy, sulphonamido and p-methyl groups and the hydrogenation of the N^3-phenyl to cyclohexyl or its replacement by *a*-pyridyl leads to inactivation. 6-Bromo compounds also retain hypnotic activity.

3. Conversion of the picolinic methyl of the active compounds into its benzylidene derivatives (C^2–styryl Compounds) leads to retension of the anticonvulsant activity along with a selective deactivation of the hypnotic effect. These two properties can thus be resolved.

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