THE ANTICONVULSANT PROPERTIES OF 2-METHYL-3-*p*-BROMOPHENYL-3*H*-4-QUINAZOLONE HYDROCHLORIDE (B.D.H. 1880) AND SOME RELATED COMPOUNDS

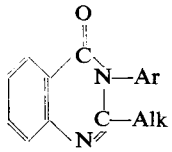
BY CAMILLO BIANCHI AND ALAN DAVID

From the Biological Laboratories, The British Drug Houses, Ltd., Godalming, Surrey

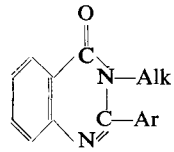
Received April 25, 1960

Twenty-five 2-alkyl-3-aryl-3*H*-4-quinazolone derivatives, eight 2-aryl-3-alkyl-3*H*-4-quinazolone derivatives and six 2-alkyl-3-aryl-3*H*-4-thioquinazolone derivatives were examined for orala nticonvulsant properties against leptazol induced convulsions in mice. 2-Methyl-3-*p*-bromophenyl-3*H*-4-quinazolone hydrochloride (B.D.H. 1880) was the most active compound and was therefore examined more fully. It is fourteen times more active than troxidone against leptazol and eight times more active against electroshock induced convulsions. B.D.H. 1880 also has a better therapeutic index than troxidone. It has approximately one-quarter the activity of phenytoin against leptazol and one-twelth the activity against electroshock-induced convulsions. B.D.H. 1880 and primidone have similar anticonvulsant properties against leptazol induced convulsions but B.D.H. 1880 is only one-third as active as primidone against electroshock induced convulsions.

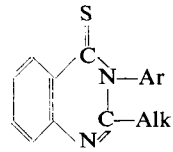
A NUMBER of 2-alkyl-3-aryl-3*H*-4-quinazolones (I), 2-aryl-3-alkyl-3*H*-4-quinazolones (II), and some 2-alkyl-3-aryl-3*H*-4-thioquinazolones (III) were examined for oral anticonvulsant activity following Gujral, Saxena and Tiwari's[1] findings that some related compounds possessed central nervous system depressant properties.



(I)

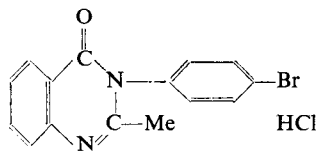


(II)



(III)

Forty compounds, prepared by Jackman, Petrow and Stephenson[2], were examined for anticonvulsant properties against leptazol induced convulsions in mice. The most active compound in this test, 2-methyl-3-*p*-bromophenyl-3*H*-4-quinazolone hydrochloride B.D.H. 1880 (IV) was also examined for its anticonvulsant activity in electroshock induced convulsions in mice. Troxidone, phenytoin and primidone were used as reference compounds. The new compound is a stable white powder, slightly soluble in water with a molecular weight of 351·6.



(IV)

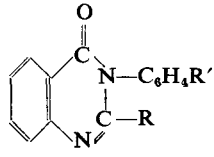
METHODS

Acute Oral Toxicity

The acute oral toxicity of troxidone and B.D.H. 1880 was estimated in unfasted albino mice weighing approximately 20 g. Ten animals were used at each of the seven doses and the mortalities after 7 days recorded. The LD50 was estimated using Kärber's formula[3]. B.D.H. 1880 and troxidone were given as suspensions in 10 per cent gum acacia and all volumes were adjusted to 0·5 ml./20 g. weight.

TABLE I

ANTICONVULSANT ACTIVITY OF SOME 2-ALKYL-3-ARYL-3*H*-4-QUINAZOLONE COMPOUNDS



Compound	R	R′	Relative activity to troxidone
2-Methyl-3-*o*-tolyl	-Me	-*o*-Me	3·3
2-Methyl-3-*o*-anisyl	-Me	-*o*-OMe	2·2
2-Methyl-3-*p*-anisyl	-Me	-*p*-OMe	2·1
2-Methyl-3-*o*-phenetyl	-Me	-*o*-OEt	2·0
2-Methyl-3-*m*-phenetyl	-Me	-*m*-OEt	<0·5
2-Methyl-3-p-phenetyl	-Me	-*p*-OEt	<0·3
2-Methyl-3-*o*-chlorophenyl	-Me	-*o*-Cl	10·0
2-Methyl-3-*m*-chlorophenyl	-Me	-*m*-Cl	7·0
2-Methyl-3-*p*-chlorophenyl	-Me	-*p*-Cl	13·0
2-Methyl-3-*o*-bromophenyl	-Me	-*o*-Br	14·0
2-Methyl-3-*m*-bromophenyl	-Me	-*m*-Br	1·5
2-Methyl-3-*p*-bromophenyl	-Me	-*p*-Br	14·0
2-Methyl-3-*p*-iodophenyl	-Me	-*p*-I	6·7
2-Methyl-3-*p*-fluorophenyl	-Me	-*p*-F	2·6
2-Methyl-3(2,4-dichlorophenyl)	-Me	2,4-di-Cl	2·1
2-Methyl-3(2,5-dichlorophenyl)	-Me	2,5-di-Cl	14·0
2-Methyl-3(2,3-xylyl)	-Me	2,3-di-OMe	inactive at 600 mg./kg.
2-Methyl-3(2,4-xylyl)	-Me	2,4-di-Me	—
2-Methyl-3(2,5-xylyl)	-Me	2,5-di-Me	—
2-Methyl-3(2,6-xylyl)	-Me	2,6-di-Me	4·5
2-Methyl-3(3,4-xylyl)	-Me	3,4-di-Me	—
2-Methyl-3(3,5-xylyl)	-Me	3,5-di-Me	1·3
2-Methyl-3(3,4,5-trimethoxyphenyl)	-Me	3,4,5-tri-OMe	inactive at 600 mg./kg.
2-Methyl-3(4-bromo-2,3-dimethylphenyl)	-Me	4Br-2,3-di-Me	2·5
2-Ethyl-3-phenyl	-Et	H	2·0
2-Ethyl-3-*o*-chlorophenyl	-Et	-*o*-Cl	2·0
-2-Ethyl-3-*p*-bromophenyl	-Et	-*p*-Br	<2·5
-2-Propyl-3-*p*-bromophenyl	-Pr	-*p*-Br	2·4

Anticonvulsant Activity

This was estimated in unfasted male albino mice weighing between 15 and 20 g. The compounds, with the exception of phenytoin sodium which is water soluble, were administered by stomach tube as suspensions in 10 per cent gum acacia or in the following aqueous suspending medium.

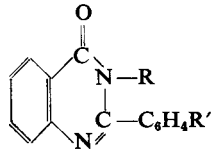
Sodium carboxymethylcellulose 1·2 g. Tween 80 1·5 g. Methyl *p*-hydroxybenzoate 0·06 g. Propyl *p*-hydroxybenzoate 0·03 g. Distilled water to 100 ml.

Doses were administered to groups of five to ten animals 2 hours before the convulsive stimuli. The volumes were adjusted to 0·5 ml./20 g. weight.

Leptazol convulsions were induced by 50 mg./kg. given intravenously. Electroshock seizures were induced through ear electrodes by a current of 15 mA for a 0·2 seconds duration using an apparatus described by Woodbury and Davenport[4].

TABLE II

ANTICONVULSANT ACTIVITY OF EIGHT 2-ARYL-3-ALKYL-3*H*-4-QUINAZOLONE COMPOUNDS



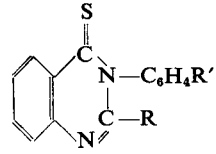
Compounds	R	R′	Relative activity to troxidone
2-Phenyl-3-methyl	-Me	-H	3·0
2-*o*-Tolyl-3-methyl	-Me	-*o*-Me	7·4
2-*p*-Chlorophenyl-3-methyl ..	-Me	-*p*-Cl	<0·7
2-*o*-Bromophenyl-3-methyl ..	-Me	-*o*-Br	6·3
2-*p*-Bromophenyl-3-methyl ..	-Me	-*p*-Br	<1·0
2-Phenyl-3-ethyl	-Et	-H	1·3
2-Phenyl-3(βγ-dihydroxypropyl) ..	$-CH_2.CHOH.CH_2OH$	-H	2·3
2-*p*-Bromophenyl-3-ethyl	-Et	-*p*-Br	<0·7

Positive protection was recorded if the tonic hindleg extensor component of the seizure was abolished. From the number of mice protected the ED50's values were estimated according to Kärber's formula[3] or Litchfield and Wilcoxon's method[5].

The duration of effect of B.D.H. 1880 against electroshock induced convulsions was estimated in four groups of twenty mice given varying amounts orally. The ED50 value was estimated from the number of mice

TABLE III

ANTICONVULSANT ACTIVITY OF SIX 2-ALKYL-3-ARYL-3*H*-4-THIOQUINAZOLONE COMPOUNDS



Compound	R	R′	Relative activity to troxidone
2-Methyl-3-*o*-tolyl	-Me	-*o*-Me	2·3
2-Methyl-3-*p*-chlorophenyl	-Me	-*p*-Cl	<0·7
2-Methyl-2-*o*-bromophenyl	-Me	-*o*-Br	<0·7
2-Methyl-3-*p*-bromophenyl	-Me	-*p*-Br	<0·7
2-Methyl-3-*p*-fluorophenyl	-Me	-*p*-F	Inactive at 600 mg./kg.
2-Ethyl-3-*p*-bromophenyl	-Et	-*p*-Br	Inactive at 600 mg./kg.

protected at 1, 2, 3, 5, 7 and 23 hours after administration. The convulsions were induced by a current of 30 mA for 0·2 seconds applied through ear electrodes.

RESULTS

Table I records the oral anticonvulsant activity of twenty-five 2-alkyl-3-aryl-3*H*-4-quinazolone derivatives taking troxidone as unity. Tables II and III record the anticonvulsant activity of eight 2-aryl-3-alkyl-3*H*-4-quinazolone derivatives and of six 2-alkyl-3-aryl-3*H*-4-thioquinazolone derivatives respectively.

In the 2-alkyl-3-aryl-3*H*-4-quinazolone group a number of compounds, particularly the halo phenyl derivatives, are more active than troxidone.

TABLE IV

THE ORAL ANTICONVULSANT ACTIVITY OF B.D.H. 1880, TROXIDONE, PHENYTOIN SODIUM AND PRIMIDONE IN MICE, TEN PER GROUP

Compound	*ED50 mg./kg. (Fiducial limits P = 0·05)		Therapeutic index	
	Leptazol	Electroshock	Leptazol	Electroshock
B.D.H. 1880	30 (23–38)	140 (104–189)	11·7	2·5
Troxidone	425 (371–480)	1200 (876–1644)	5·3	1·9
Phenytoin sodium	12 (9–17)	12 (8–18)	—	—
Primidone	41 (29–59)	40 (21–75)	—	—

* Litchfield and Wilcoxon's method.

Table III shows that the related thioquinazolone derivatives are invariably less active. The 2-aryl-3-alkyl-3*H*-4-quinazolone compounds are also less active than the related 2-alkyl-3-aryl compounds with the exception of the *o*-tolyl derivative which is more active.

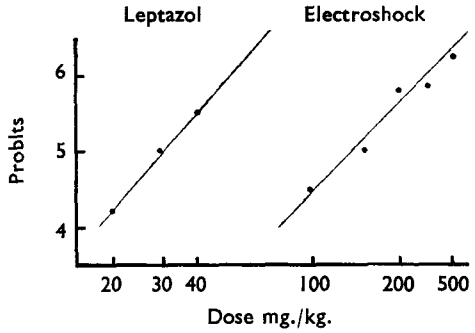


FIG. 1. The oral anticonvulsant activity of B.D.H. 1880 against leptazol and electro-shock induced convulsions in mice.

Acute Toxicity and Anticonvulsant Activity of B.D.H. 1880

This compound, one of the most active against leptazol induced convulsions, was examined more fully. It has an oral LD50 in mice of 353·5 mg./kg. compared to 2291·0 mg./kg. for troxidone. The ED50 values against leptazol and electroshock induced convulsions for B.D.H. 1880, troxidone, phenytoin and primidone are recorded in Table IV.

The anticonvulsant activity of B.D.H. 1880 has been repeatedly confirmed and Table IV records the results of a typical experiment. There is a linear relation between log dose and the probits of the animals protected against both leptazol and electroshock induced convulsions (Fig. 1). The anticonvulsant activity of B.D.H. 1880 is still present 7 hours after administration. Table V records the ED50 values at intervals.

TABLE V

THE ORAL ED50 OF B.D.H. 1880 IN MICE AGAINST ELECTROSHOCK INDUCED CONVULSIONS AT INTERVALS FOLLOWING ADMINISTRATION

Time in hours	ED50 mg./kg.
1	>175
2	108
3	115
5	120
7	125
23	>175

DISCUSSION

The results reported in this paper show that the 2-alkyl-3-phenyl-3*H*-4-quinazolone structure can yield compounds with marked anticonvulsant properties: for example, the 2-methyl-3-*p*-bromophenyl derivative, B.D.H. 1880, has a similar or a greater activity than most commonly used anti-epileptic drugs.

The thioquinazolone analogue of B.D.H. 1880 has less anticonvulsant properties than troxidone which suggests that the oxygen in the fourth position in the quinazolone ring is essential for good anticonvulsant activity.

There is some reduction in activity when the 2-methyl group in B.D.H. 1880 is substituted by an ethyl or butyl group. There is, however, a marked reduction in activity when the *p*-bromophenyl group is moved from the third to the second position in the quinazolone nucleus as in 2-*p*-bromophenyl-3 methyl-3*H*-4-quinazolone.

The introduction of a bromo radical in the benzene ring of the heterocyclic nucleus as in 6-bromo-2-methyl-3-*o*-tolyl-3*H*-4-quinazolone does not influence anticonvulsant activity.

REFERENCES

1. Gujaral, Saxena and Tiwari, *Ind. J. med. Res.*, 1955, **43**, 637.
2. Jackman, Petrow and Stephenson, *J. Pharm. Pharmacol.*, 1960, **12,** in the press.
3. Karber, *Arch. exp. path. pharmacol.*, 1931, **162**, 480.
4. Woodbury and Davenport, *Arch. int. Pharmacodyn.*, 1952, **112**, 97.
5. Litchfield and Wilcoxon, *J. Pharmacol.*, 1949, **96**, 99.