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THE BIOCHEMORPHOLOGY OF CYCLOBUTANECARBOXAMIDES

KARIMULLAH A. ZIRVI*

PCSIR Laboratories, Peshawar

CHARLES H. JARBOE

Department of Pharmacology, School of Medicine, University of Louisville, Louisville, Kentucky 40202, *U.S.A.*

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Abstract. Several *N*-alkylcyclobutanecarboxamides have been synthesized and examined for general central nervous system depressant properties, barbiturate potentiation, myorelaxant, antitremorine and anticonvulsant potency. Water solubility seems to play a major role in the activity of these compounds. *N*-4-Chlorophenylcyclobutanecarboxamide appears to be the most active myorelaxant while *N*-cyclopentyl- and *N*-furfurylcyclobutanecarboxamides appear to be most active as anti-Parkinson agents. None of the compounds is active against pentylenetetrazole-induced convulsions.

It has been reported[1,2] that several imides of cyclobutanecarboxylic acid have sedative and hypnotic properties; these effects are limited by aqueous solubility. Furthermore, it has been shown that these effects appear to be structure related since a variety of small ring imides and several imides of cyclobutane-1,1-dicarboxylic acid[3] are not depressant. We have also reported[4] that although the imides of cyclobutane-1,1-dicarboxylic acid are inactive, the amides of the acid are active central nervous system depressants. This observation prompted us to better elucidate the biochemorphology of cyclobutane compounds by studying amides of cyclobutanecarboxylic acid for biological activity. To that end we have synthesized and evaluated a family of amides (Table 1). The compounds have been evaluated for general central nervous system depressant properties, barbiturate potentiation, myorelaxant, antitremorine and anticonvulsant potency. Furthermore, the biological activity of these compounds has been correlated with molecular structure and aqueous solubility.

Experimental

Chemical Methods. The compounds were prepared using a conventional route involving acylation of an amide with cyclobutanecarbonyl chloride in pyridine.[2] Analytical data and m.p. of the compounds have been reported earlier.[5]

Pharmacological Tests. In all of the bioassays mice were used once only. They were previously untreated with drug and permitted to feed *ad libitum*. Methods used to evaluate the compounds in Table 1 for sedative and hypnotic properties, barbiturate potentiation, myorelexant, antitremorine and anticonvulsant potency, were as described before.[2]

Discussion

To better elucidate the biochemorphology of the cyclobutanecarboxamides the compounds in Table 1 were arranged according to their stereochemical and physiochemical properties. When tested for general depressant activity it was apparent that the parent compound, cyclobutanecarboxamide (Table 1, no.1), was the most active in that long term loss of the righting reflex was observed. Any substitution at the amide nitrogen depressed the activity. There was marked depression of spontaneous activity in mice treated with the straight-chain derivative (2), and intermediate depression in the case of branched-chain derivatives (3–5). Branched-chain derivatives (3–5), by comparison to alicyclic derivatives (6–9), showed a smaller decrease of activity. One of the branched derivatives (5), showed considerable depressant activity but this was followed by convulsions and death (LD_{50}=1000 mg/kg). In the alicyclic series 6 was the most active compound. It caused intermediate loss of spontaneous activity. The effect produced by ring size changes paralleled an earlier finding[6] that alicyclic carbonylcholines show decreased activity as the ring size increases. Water solubility seems to play a major part in the activity of compounds. The parent compound 1 was highly water-soluble; any kind of substitution at the amide nitrogen reduced water solubility. This was the probable cause of reduction in activity. The introduction of an electron-withdrawing group on the amide nitrogen of the highly water-soluble and highly active cyclobutanecarboxamide (1) rendered the resulting molecules (10–12) less water-soluble and less

*Now at Department of Pharmacology, School of Medicine, Pahlavi University, Shiraz, Iran.

TABLE 1. BIOLOGICAL DATA FOR *N*-ALKYLCYCLOBUTANECARBOXAMIDES.[a]

Compound	Alkyl group	Gross effect[b]	*R*[c]	CNS[d] activity	SLT[e] Partial	SLT[e] Complete	ATA[f]
1.	Cyclobutanecarboxanide amide	C*	6.6	C	2/4	2/4	+
2.	Propyl	M	7.7	C	0/4	0/4	++
3.	Isobutyl	I	6.7	C	0/4	0/4	+++
4.	Isopropyl	I	5.2	C	0/4	0/4	++
5.	*t*-Butyl	D	11.7[g]	C	0/4	0/4	+++
6.	Cyclopentyl	I	3.8	C	0/4	0/4	+++
7.	Cyclohexyl	S	1.5	A	0/4	0/4	+++
8.	Cycloheptyl	S	3.8	C	0/4	0/4	+++
9.	1-Adamantyl	S	2.8	C	1/4	1/4	+
10.	Benzyl	M	10.3	C	1/4	1/4	+++
11.	Furfuryl	S	2.2	C	3/4	2/4	+++
12.	Phenyl	N	1.2	—	1/4	0/4	—
13.	2-Methoxycarbonylphenyl	N	2.4	B	2/4	2/4	—
14.	2-Ethoxycarbonylphenyl	N	2.0	B	2/4	2/4	—
15.	4-Chlorophenyl	N	2.1	B	4/4	3/4	++
16.	3-Carboxyphenyl	P	1.1	A	1/4	1/4	—
17.	2-Carboxyphenyl	N	2.5	B	1/4	1/4	—
18.	4-Carboxyphenyl	N	0.9	—	2/4	1/4	++

[a]In each test the dose used was 1000 mg/kg (oral), except where indicated. [b]S,I,M,C*, slight, intermediate, marked and complete reduction in the spontaneous motor activity respectively. D, depression and death. P, slight loss of activity alongwith hind-limb paralysis. [c]Pentobarbital given i.p. at a dose of 50 mg/kg. *R*, the ratio (drug+barbiturate sleep time)/(barbiturate sleep time + drugsleep time. [d]Central nervous system activity: A, central nervous system depressant ability only. B, barbiturate potentiation only. C, both central nervous system depressant and barbiturate potentiation ability. [e]Strychnine lethality test, (strychnine sulphate 2 mg/kg i.p.) This dose is 100% lethal. The mice die within 10–12 min. Partial: animals protected longer than 30 min from death/animals tested. Complete: animals completely protected from death/animals tested. [f]Antitremorine activity. Tremors were subjectively graded with control animals receiving tremorine HCl 20 mg/kg i.p. — these compounds were not analyzed. + 0% animals are protected. ++ 20–80% mice are moderately protected, but none is completely protected. +++ 20—80% mice are completely protected from tremors. [g]The dose used was 500 mg/kg orally.

active as general depressants. Like *N*-phenylcyclobutanecarboxamide (12), all other *N*-substituted anilides of cyclobutanecarboxylic acid except 16 were also insoluble in water and inactive. Compound 16 though insoluble in water showed unusual activity. It caused a slight depression plus a fugitive paralysis of hind-limbs for about 1 hr.

In summary, the depressant activity of these compounds appeared to be related to their degree of water solubility. Aqueous solubility, however, is not only the factor influencing activity. Steric effects at carbonyl group and electrical factors indirectly influence activity by greatly reducing water solubility and also the hypnotic activity.

To test the previously reported phenomenon[2] that the locus for barbiturate potentiation appeared to be functionally different from sites involved in the directly measured depressant effect, a comparison was made of the barbiturate potentiation and general depressant effect of these compounds. It was presumed that if there were two functionally different loci for these activities we should be able to observe with these compounds three different modes of central nervous system action, i.e. central nervous system depression only (category A), potentiation only (category B), and both central nervous system depression and potentiation (category C). When analyzed for pentobarbital potentiation activity at a dose of 1000 mg/kg a sleep prolongation factor *R* (Table 1) was used as the criterion for effect. For compounds not causing loss of the righting reflex *R* is a measure of true potentiation and becomes significant when greater than 1.5. As is apparent from Table 1 most of the compounds with hypnotic and sedative activity also prolonged pentobarbital sleeping time significantly and thus appear to belong to category C. However, compounds 7 and 16, active as hypnotics and sedatives, were found to be inactive as potentiators and thus belong to category A. On the other hand, four compounds 13–15 and 17 found to be inactive during gross screening potentiated the sleeping time significantly and can be associated with category B. Moreover, during gross screening 1 appeared to be the most active central nervous system depressant. Contradictory to this, in the pentobarbital potentiation analysis, several other compounds (2,3,5 and 10)seemed to be more active than 1, of these 5 was the most active. At a 500 mg/kg dose level 5 prolonged the sleeping time three times more than cyclobutanecarboxamide. However, it was toxic at high doses ($LD_{50} = 1000$ mg/kg). These observations strongly support the hypothesis that there are two mechanistically separate modes of action for the compounds under consideration; one for barbiturate potentiation and the other for depressant ability.

Myorelaxant activity such as shown by meprobamate, is conveniently studied by ascertaining whether a compound antagonizes strychnine lethality.[7-9] In the present series and at a 1000 mg/kg dose (oral), 15 appeared to be the most active compound (75% protection) and 1 to be second (50% protection). However, at 500 mg/kg (oral) 15 showed 0% protection while 1 protected 25% of the animals. This indicated that the dose response curves are not parallel. This also suggested that the parent compound 1 is the more potent myorelaxant at lower doses. This order of activity for 1 paralleled the gross screening and potentiation experiments. Of the four *N*-alicyclic derivatives, contrary to the gross screening and potentiation results (all four were active) only one of these (9) showed strychnine antagonism, indicating that central nervous system depressant activity is remotely related at best to myorelaxant activity. Other active members of the series were 11 and 13–18. All were active at 1000 mg/kg orally and protected 50–25% of the animals while at 500 mg/kg (oral) all appeared to be comparatively inactive. Since these compounds show myorelaxant activity without any hypnotic and sedative effect, they appear to belong to that class of compound which has as the prototype example mephenesin. However, comparatively they are quite weak in activity.

All of the alkyl amides except 12–14, 16 and 17 were tested for ability to antagonize tremorine-induced peripheral parasympathetic stimulation and centrally originating parkinsonian-like tremors.[10-11] The antitremorine activity was limited to 3, 5–8, 10 and 11. All of these showed complete protection in 20–80% of the test animals and were classified as slightly active. Since a highly active compound should be able to protect 100% of the test animals completely at a dose much lower than used to test these compounds. Standard agents such as atropine, scopolamine, or trihexyphenidyl (Artane®) block tremorine effects in doses of 5–10 mg/kg in mice. The most active compound in these series were 6 and 11, which at 1000 mg/kg (oral) protected 80% of the test animals completely. Although many central depressants have anticonvulsant properties,[12] none of the seven alkyl amides, compound 1 and compounds 5–10 tested for such activity were found to protect mice against pentylenetetrazole-induced convulsions.

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