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Short communication

11-Alkoxy-dibenzo[*b,e*]azepin-6-ones with anti-convulsant activity

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Summary — Data relative to the synthesis and anti-convulsant properties of new 5,6-dihydro-dibenzo[*b,e*]azepin-6-ones are presented. Structure—activity relationships of various derivatives substituted in positions 5 and 11, as well as the importance of the steric hindrance of the substituents on biological activity are shown.

Résumé — **Alkoxy-11 dibenzo[*b,e*]azépinones-6 à activité anti-convulsivante.** *La synthèse et l'activité anti-convulsivante de certaines nouvelles dihydro-5,6 dibenzo*[b,e]*azépinones-6 ainsi que les rapports entre la structure et l'activité de plusieurs dérivés substitués en position 11 et 5 sont décrits. La grande importance de l'encombrement stérique des substituants sur l'activité est démontrée.*

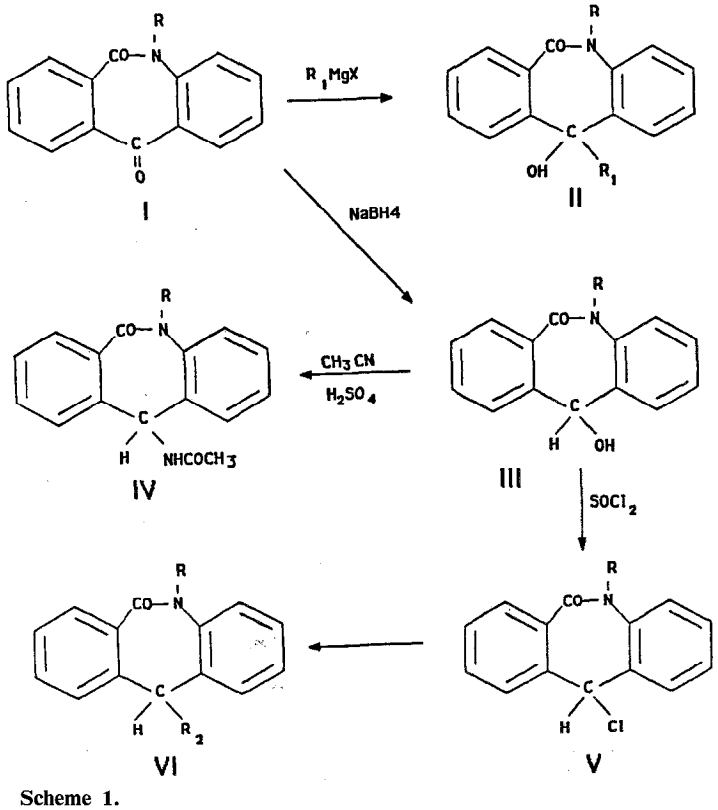
dibenzo[*b,e*]azepines / dibenzo[*b,e*]azepin-6-ones / anti-convulsant agents

Introduction

Considerable interest has been given to tricyclic structures, such as dihydro-dibenzo[*b,e*]azepines, due to their effects on the central nervous system (CNS). Among these compounds, some 11-alkylamino-5,6-dihydro-dibenzo[*b,e*]azepin-6-ones have been shown to possess anti-convulsant properties [1]. In order to better elucidate the structure—activity relationship and, in particular, the importance of substitution in position 11, new derivatives with either amino or non-basic groups, such as acylamino and ethereal ones, have been prepared.

Chemistry

Derivatives of 5,6-dihydro-dibenzo[*b,e*]azepine, substituted in position 11 (Scheme 1, **VI**) were obtained in good yield by treating 11-Cl derivatives **V** with nucleophilic agents, such as amines and alkaline salts of alcohols or phenols. Unlike other nucleophiles used, the amines reacted according to the pathway outlined in Scheme 1 only when no substituent was present in position 5. The presence of an N—H group in position 5 was not required for substitution in position 11 with alkyloxy or phenyloxy groups. Unlike other amines, ammonia did not react with chloride **V**, so the 11-acetyl-amino derivative **IV** was obtained by subjecting compound **III** to a Ritter reaction. Treatment



Scheme 1.

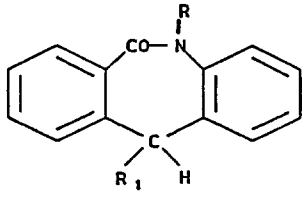
*Author to whom correspondence should be addressed.

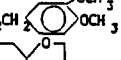
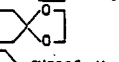
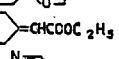
of 5,6-dihydro-dibenzo[*b*,*e*]azepin-6,11-dione **I** with alkyl-magnesium halides gave the corresponding 11-hydroxy-11-alkyl derivatives **II**. Many of these compounds had ^{1}H NMR spectra in which, like those described by Ackermann *et al.* [2] for similar systems, split peaks relative to substituents attached to C-11 and, sometimes, N-5 were observed.

Results and Discussion

Data relative to the anti-convulsant properties of various 5,6-dihydro-dibenzo[*b*,*e*]azepin-6-ones substituted in position 11 are shown in Table I. 11-Isopropyl amino-5,6-dihydro-dibenzo[*b*,*e*]azepin-6-one **1** antagonized markedly MES-induced convulsions. Acetylation of **1** (compound **7**) or replacement of isopropyl amino moiety with other hindered amines (**2**, **3**, **5** and **6**), abolished anti-convulsant properties; the same resulted when an acetamido group was present in position 11, **9**. However, phenylurea **8** and compound **4** retained some activity. Unexpectedly compounds **10** and **11** with an ethereal group in position 11 reduced markedly or even abolished MES- and MET-induced convulsions. These findings drew our attention to the potential usefulness of these derivatives. Data relative to anti-convulsant properties of compounds with either an ethereal or an alcoholic function in position 11, are summarized in Table II. The dimension of the substituent in position 11 or 5, has great importance, since a decreased anti-convulsant activity was found with increasing steric hindrance (compounds **14**—**24**). Compounds **11** and **13** were the most active against MES- and MET-induced convulsions. Unlike **13**, compound **11** protected mice and rats against MES-

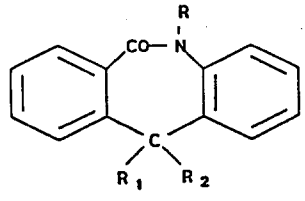
Table I. Effect of various compounds administered orally at a dose of 400 mg/kg on convulsions induced by electroshock (MES) or metrazole (MET) at various times.



No	R	R_1	Yield %	m.p.[e]	percentage of mice protected MES 0.5	MES 4h	MET 0.5	MET 4h
1	H	$NHCH(CH_3)_2$	80[a]	190-191°C methanol	100	100	10	20
2	H		85[a]	185-187°C ethanol	0	0	0	0
3	H		65[a]	173-174°C ethanol	0	0	10	20
4	H		80[a]	224-225°C acetone	30	10	10	10
5	H		70[b]	228-229°C toluene	0	0	10	0
6	H		87[a]	257-258°C acetone	0	0	0	0
7	H	$N(COCH_3)CH(CH_3)_2$	62[c]	140-141°C cyclohexane	0	0	0	0
8	H	$N(CONHC_6H_6)CH(CH_3)_2$	95[c]	162-163°C toluene	0	57	10	0
9	CH_3	$NHCOCH_3$	40[d]	258-259°C ethanol	0	10	0	0
10	H	OC_2H_5	70[a]	165-166°C ethanol	100	100	100	100
11	CH_3	OC_2H_5	84[a]	98-100°C isopropanol	100	100	100	100

Yields are based on [a]chloride **V** (Scheme 1); [b]compound **4**; [c]compound **1**; [d]alcohol **III** (Scheme 1).
[e]Melting point (uncorrected) and recrystallization solvent.

Table II. Effect of various compounds administered orally at a dose of 100 mg/kg on convulsions induced by electroshock (MES) or metrazole (MET) at various times.



compound No	R	R_1	R_2	Yield %	m.p. /b.p.*	percentage of mice protected MES 0.5	MES 4h	MET 0.5	MET 4h
12	H	OH	H	a	-	90	90	50	40
13	CH_3	OH	H	b	-	100	100	90	80
10	H	OC_2H_5	H	70[c]	165-166°C ethanol	80	100	90	70
14	CH_3	OCH_3	H	b	-	92	100	80	60
11	CH_3	OC_2H_5	H	84[c]	98-100°C isopropanol	89	92	100	100
15	CH_3	$OCH(CH_3)_2$	H	75[c]	138-139°C methanol	90	90	70	80
16	CH_3	OC_4H_9	H	70[c]	69-70°C isopropanol	40	40	15	50
17	CH_3	OC_8H_{17}	H	50[c]	205°C (0.3 mm Hg)	0	0	20	30
18	H	OC_6H_5	H	85[c]	185-187°C ethanol	0	0	10	10
19	C_3H_7	OC_2H_5	H	55[c]	65-66°C petroleum ether	30	30	10	10
20	C_5H_{11}	OC_2H_5	H	60[d]	70-71°C petroleum ether	0	0	0	10
21	$CH_2CH=CH_2OC_2H_5$		H	90[d]	64-65°C petroleum ether	0	0	10	20
22	$CH_2C_6H_5$	OC2H5	H	60[d]	79-81 ligroin 75-120	0	30	0	0
23	CH_3	CH_3	OH	75[e]	200-202°C ethanol	67	75	10	75
24	CH_3	$CH_2C_6H_5$	OH	65[e]	171-172°C ethanol	0	0	0	25

[a]Known compound, see [3].
[b]Known compound, see [2].
Yields are based on [c]chloride **V** (Scheme 1); [d]compound **10**; [e]ketone I (Scheme 1).
*Melting point (uncorrected) and recrystallization solvent; when the boiling point is given, distillation pressure is shown between parentheses.

and MET-induced convulsions at doses much lower than those which produced neurotoxic effects (Tables III and IV). Compound **11** was shown to be a potent and long-acting anti-convulsant (Table V) with the best protective index when compared with other clinically effective anti-epileptics [4].

Table III. Effect of compounds **11** and **13** administered orally at a dose of 200 mg/kg on rats running on 'rotorod' at various times.

Time (h)	Percentage of rats running on 'rotorod'	
	11	**13**
0.5	71	57
2	93	50
5	79	21
8	79	64

Experimental protocols

Pharmacology

Male Swiss albino mice (Nassan, Milan, Italy), 20—22 g or male CD-COBS rats (Charles River, Calco, Italy), 125—150 g, were used. Each experimental group consisted of 8—10 animals. Electroshock in the mouse (50 Hz, 120 V for 0.4 s) or in the rat (50 Hz, 140 V for 1 s) delivered *via* auricular electrodes (Giunta, Milan, Italy) produced tonic extension of the hind limbs [5]. Metrazole was administered subcutaneously at a dose of 75 mg/kg (rat) or 85 mg/kg (mouse) and produced clonic seizures [6]. Neurotoxic effects were assessed by subjecting rats and mice to the rotorod [7] or traction test [8], respectively.

Chemistry

^{1}H NMR analyses were performed on a Varian spectrometer, EM-360 L using tetramethylsilane (TMS) as an internal standard. Elemental analyses were conducted by the Analytical Department of Menarini.

Table IV. Oral ED_{50} values of compound **11** at the time of peak activity protecting against convulsions induced by electroshock (MES) or metrazole (MET) and inducing neurotoxic effects in mice and rats.

Species	Time[a] (h)	MES[b]	MET[b]	Neurotoxicity[b]	Protective index[c]
Mice	0.5; 0.5; 0.5	27.2 (23.4—31.6)	34.7 (18.1—66.4)	634 (431—1199)	23.3; 18.3
Rats	2; 8; 8	11 (6.8—18)	32 (20.5—50)	501 (317—791)	45.5; 15.7

[a]Time values refer to MES, MET and neurotoxicity, respectively.
[b]Values represent ED_{50} (mg/kg) with 5% confidence limits between parentheses.
[c]Values represent ED_{50} neurotoxicity/ED_{50} MES and ED_{50} neurotoxicity/ED_{50} MET, respectively.

Table V. Effect of compound **11** and diphenylhydantoin (DPH) administered orally at a dose of 50 mg/kg on convulsions induced by electroshock in rats at various times.

Compd.	Percentage of rats protected from convulsions								
	0.5	2	3	4	8	13	16	24	h
11	37	100	100	100	100	87	25	12	
DPH	50	69	78	50	62	0	0	0	

Conclusion

In conclusion, some 11-alkyloxy derivatives of 5,6-dihydro-dibenzo[*b*,*e*]azepin-6-ones showed anti-convulsant activity. Steric characteristics of the substituent in either the 5 or 11 position seem essential, since activity decreases with the increasing degree of steric hindrance. One of these derivatives, **11**, was selected for further pharmacological evaluation.

Analyses of C, H, N were within ± 0.4% of the theoretical values for all new compounds.

11-Alkylamino-5,6-dihydro-dibenzo[b,e]*azepin-6-ones* (compounds **1**—**4** and **6**) were obtained by reacting 11-chloro-5,6-dihydro-dibenzo-[*b*,*e*]azepin-6-one with the appropriate amine with or without solvent, according to known methods [1].

11-(4 (Ethyloxycarbonyl-methylen)piperidin-1-yl)-5,6-dihydro-dibenzo-[b,e]*azepin-6-one* **5**. Compound **4** (0.024 mol) was hydrolized with 10% hydrochloric acid (150 ml) for 5 h at 50°C. The solution was made alkaline with sodium carbonate and the precipitate was collected and dried. The crude ketone was subjected to a Wittig reaction with triethylphosphonoacetate (0.024 mol).

Compound **1** was treated with: ***a***. a 2-fold excess of acetic anhydride in acetic acid to obtain *11-(*N-*isopropyl*-N-*acetyl-amino)-5,6-dihydro-dibenzo*[b,e]*azepin-6-one* **7**; ***b***. a 10% excess of phenyl isocyanate in tetrahydrofuran (THF) to obtain N-*phenyl*-N′-*isopropyl*-N′-*(5,6-dihydro-dibenzo*[b,e]*azepin-6-one-11-yl)-urea* **8**.

11-Alkyloxy-5-alkyl-5,6-dihydro-dibenzo[b,e]*azepin-6-ones*
Compounds **10**, **11** and **15**—**22** were obtained according to known methods.

A. Reacting 11-chloro-5,6-dihydro-dibenzo[*b*,*e*]azepin-6-ones with an alkaline salt of the appropriate alcohol, treating them with sodium hydride and then alkylating the N in the 5 position with an alkyl bromide.

B. Alkylating the sodium salt of 5,6-dihydro-dibenzo[*b*,*e*]azepin-6,11-diones with an alkyl bromide (compounds **I**, Scheme 1), transforming them into the corresponding chloride **V** (Scheme 1) and reacting them with an alkaline salt of the appropriate alcohol.

Method A was preferred for preparation of compounds **10**, **18**, **19**, **20**, **21**, **22**, whereas method B was used for compounds **11**, **15**, **16**, **17**.

Acknowledgments

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References

1 Waring W. S. & Whittle B. A. (1969) *J. Pharm. Pharmacol.* 21, 520—530
2 Ackermann K., Chapuis J., Horning D. E., Lacasse G. & Muchowski J. M. (1969) *Can. J. Chem.* 47, 4327—4333
3 Winthrop S. O., Davis M. A., Herr F., Stewart J. & Gaudry R. (1962) *J. Med. Pharm. Chem.* 5, 1199—1206
4 Swinyard E. A. & Woodhead J. H. (1982) *in: Antiepileptic Drugs* (Woodbury D. M., Penry J. K. & Pippinger C. E., eds.), Raven Press, New York, pp. 111—126
5 Swinyard E. A., Brown W. C. & Goodman L. S. (1952) *J. Pharmacol. Exp. Ther.* 106, 315—330
6 Krall R. L., Penry J. K., White B. G., Kupferberger H. J. & Swinyard E. A. (1978) *Epilepsia* 19, 409—428
7 Dunham N. M. & Miya T. S. (1957) *J. Am. Pharm. Assoc.* 46, 208—210
8 Boissier J. R. & Simon P. (1960) *Therapie* 15, 1170—1174