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Basic Derivatives of 5-Benzoyl-10,11-dihydro-5*H*-dibenz[*b,f*]azepine

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Synthesis and pharmacological properties of *N*-disubstituted (aminomethyl)benzoylazepines are described. The new compounds show interesting neuroleptic properties comparable to those of droperidol.

Basische 5-Benzoyl-10,11-dihydro-5H-dibenz[b,f]azepin-derivate

Synthesen und pharmakologische Wirkungen einiger N-disubstituierter Aminomethylbenzoyl-azepine werden beschrieben. Die neuen Verbindungen zeigen interessante, mit jenen von Droperidol vergleichbare, neuroleptische Eigenschaften.

As a part of a program to design new triciclyc antidepressive drugs, we have prepared and tested the N-disubstituted 5-aminomethylbenzoyl-10,11-dihydro-5H-dibenz[b,f]azepine derivatives **1–15**, in which the basic chain can occupy alternatively the ortho, meta and para positions.

These compounds have been synthesized by condensing the iminodibenzyl with o-, m- and p-chloromethylbenzoyl chlorides and subsequent amination of the chloromethylbenzamido intermediates with selected secondary bases.

Pharmacology

1. *Methods*

All experiments were carried out in Swiss female mice. The compounds as HCl salts were given (i.p. and s.c.) dissolved in saline; imipramine and droperidol were used as reference standard. The following tests were made:

a) Determination of acute LD_{50} by s.c. and i.p. route.

b) Motor coordination evaluation by rolling bar[1], by means of the road-rod treadmil for mice (Basile, Milan) at 16 turn/min; the fall time from 10 to 15 sec was determined 15 min after s.c. injection (ED_{50} s.c.).

Dedicated to Prof. Dr. *Michele Amorosa* with the best wishes on the occasion of the 70th birthday.

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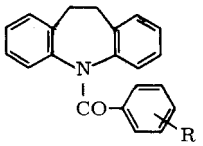
c) Psychomotor excitation test with amphetamine[2]. The motor activity changes were evaluated by an actometer for 25 min, following i.p. administration of half LD_{50}. Amphetamine antagonism was tested for an equal period after 10 mg/kg s.c. amphetamine; full antagonism against the above standard amount of amphetamine was determined by increasing doses of test compounds (ED_{50} i.p.).



1-15

2. *Results and discussion*

Among the many methods for the experimental evaluation of antidepressants, we have chosen, for a preliminary study, the more characteristic tests able to screen neuroleptic from thymoleptic activities of the drugs.

The neuroleptic activity was studied by means of the evaluation of motor coordination and the thymoleptic activity by means of the antagonism against amphetamine-induced hyperactivity. It was reasonable to predict that modifications or stereoisomeric changes in the side chain of imipramine could affect either neuroleptic or thymoleptic properties.

Table 1 summarized the ED_{50} evaluated on the bases of the motor coordination test and of the psychomotor excitation test, as well as The LD_{50} and prelethal symptomatology, for the fifteen compounds tested, in comparison with imipramine and droperidol.

Actue toxicity. The LD_{50} values of the synthesized compounds following s.c. injection were generally lower than LD_{50} of imipramine, except the morpholinomethyl derivatives (compounds **13**, **14** and **15**). However, following i.p. administration, only for 5 of the 15 compounds the LD_{50} was lower than that of imipramine. While for this drug LD_{50} s.c. to LD_{50} i.p. ratio was equal to 5, for all the other compounds, except for the o-morpholinomethyl derivative the ratio was equal to 3 or lower. These findings, i.e. the lower difference between the toxicity related to the different routes of administration, as compared to imipramine, may be interpreted as the result of a lower first pass effect.

It should be stressed that for the morpholinomethyl derivatives the above mentionated ratio was equal to 8, 1, 0.4 for the o-, m- and p-isomers, respectively; this may indicate an increase of the metabolic inactivation, that would be inversely to the LD_{50} s.c. to LD_{50} i.p. ratio.

Prelethal symptomatology. Like imipramine 4 out of the 15 compounds tested induced only non specific symptoms (sedative pattern) before death, which occurred within few min. For the other derivatives convulsive seizures were observed. These were followed by a depressive state and death occurred after about 30 min.

Motor coordination test[3]. In this test the ED_{50} of the morpholinomethyl derivatives was always higher than that of imipramine: twice as high for m- and p-compounds and 4 times for the o-. For the piperidinomethyl derivatives the experimental values were very similar to those of the parent drugs, except for the m-derivative. The ED_{50} of pyrrolidinomethyl, diethylaminomethyl (except for compound **6**) and dimethylaminomethyl derivatives were

Tab. 1: *N-Disubstituted 5-(aminomethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepines*

Compound	R	LD_{50}(10^{-5} mole/kg) s.c.	i.p.	Prelethal symptomatology	ED_{50}(10^{-5} mole/kg) motor coordination test s.c.	T.I.	psychomotor excitation test s.c.	T.I.
1	o-$CH_2N(CH_3)_2$	85	28	c→s	21	4.0	20	1.4
2	m-$CH_2N(CH_3)_2$	58	35	c→s	28	2.1	18	1.9
3	p-$CH_2N(CH_3)_2$	86	29	c→s	23	3.7	15	1.9
4	o-$CH_2N(C_2H_5)_2$	53	33	c→s	47	1.1	19	1.7
5	m-$CH_2N(C_2H_5)_2$	63	51	c→s	38	1.6	26	2.0
6	p-$CH_2N(C_2H_5)_2$	133	55	c→s	107	1.2	35	1.6
7	o-CH_2N⬡	38	19	c→s	27	1.4	12	1.6
8	m-CH_2N⬡	42	18	c→s	19	2.2	14	1.3
9	p-CH_2N⬡	67	55	c→s	55	1.2	30	1.8
10	o-CH_2N⬡	78	41	s	76	1.0	26	1.6
11	m-CH_2N⬡	66	25	c→s	41	1.6	16	1.6
12	p-CH_2N⬡	85	30	s	71	1.2	18	1.7
13	o-CH_2N⬡O	402	50	c→s	310	1.3	23	2.2
14	m-CH_2N⬡O	152	145	c→s	142	1.1	75	1.9
15	p-CH_2N⬡O	200	529	s	129	1.5	345	1.5
Imipramine		158	31	s	72	2.2	7	4.4
Droperidol		55	21	s	46	1.2	13	1.6

c = convulsive seizures, s = sedative pattern, → = followed by

lower as compared to imipramine. For the latter group the ED_{50} was about 65 % lower but it should be stressed that their therapeutic index (T.I.) was equal to or even 80 % higher (o-derivative) of imipramine T.I..

These results on the whole show that the newly synthesized compounds are similar to imipramine as far as the depressive properties on motor activity are concerned.

Psychomotor excitation test[4]. In this test the ED_{50} values were always higher than the ED_{50} of imipramine. It should be noticed that the doses used in this test were able to abolish the response to amphetamine (Fig. 1). Thus they have a neuroleptic effect which has to be correlated with the result of the motor coordination test. Nevertheless, in the present test, the T.I. values were always lower than for imipramine.

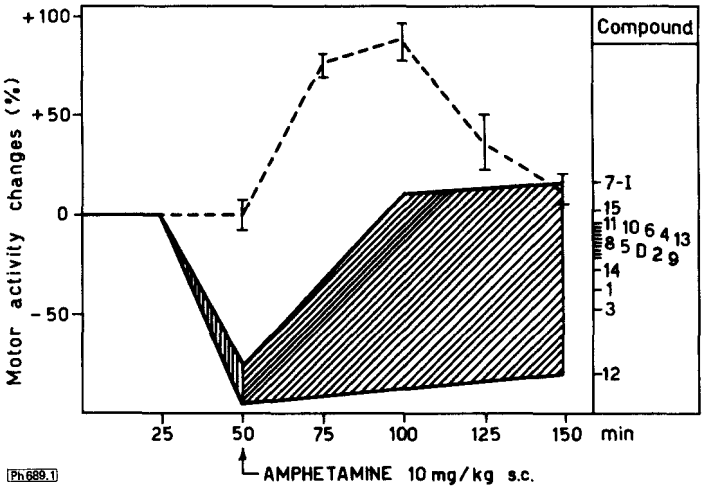


Fig. 1: Effect of amphetamine alone (-----) and after i.p. administration of the tested compounds (see Table 1) (———) I = imipramine, D = droperidol.

The only derivatives which did not affect the psychomotor excitatory action of amphetamine were the o-pyrrolidinomethyl derivative (compound **7**) and the p-morpholinomethyl derivative (compound **15**).

The results obtained in the present study show that the modifications in the side chain of imipramine have allowed the maintenance of its neuroleptic activity, while the T.I. values of the most active compounds (dimethylaminomethyl-derivatives) are higher as compared not only to imipramine, but also to a typical butyrophenone neuroleptic, droperidol.

A thymoanaleptic (antidepressant) activity was shown only for two derivatives (compounds **7** and **15**), but their T.I. is lower than that of the parent drug. Therefore in these two compounds a neuroplegic effect, which is common to analogs of the phenothiazine and butyrophenone series, appears to be associated with a more specific stimulating-antidepressant activity on cortical and subcortical structures.

It can also be concluded that the modifications in the side chain of imipramine have increased the neuroplegic properties of the parent drug more than the antidepressant ones.

Experimental Part

5-(o-Chloromethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(16)**

A mixture of 19.5 g (0.1 mole) of 10,11-dihydro-5H-dibenz[b,f]azepine and 18.9 g (0.1 mole) of o-chloromethylbenzoyl chloride was heated at 140–150° for 2 h. After cooling the reaction product was extracted with EtOH and gave 30 g (86 % yield), m.p. 178–180°. $C_{22}H_{18}ClNO$ (347.6) Calcd.: C 76,0 H 5.22 N 4.0 Cl 10.2; Found: C 75.9 H 5.20 N 4.0 Cl 10.1.

5-(m-Chloromethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(17)**

With the same procedure from 19.5 g (0.1 mole) of 10,11-dihydro-5H-dibenz[b,f]azepine and 18.9 g (0.1 mole) of m-chloromethylbenzoyl chloride 24.2 g (70 % yield) of product m.p. 102–104° (ligroin) were obtained. $C_{22}H_{18}ClNO$ (347.6) Calcd.: C 76,0 H 5.22 N 4.0 Cl 10.2; Found: C 75.8 H 5.18 N 4.0 Cl 10.1.

5-(p-Chloromethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(18)**

With the same procedure from 19.5 g (0.1 mole) of 10,11-dihydro-5H-dibenz[b,f]azepine and 18.9 g (0.1 mole) of p-chloromethylbenzoyl chloride 26 g (75 % yield) of product m.p. 150–153° (ligroin) were obtained. $C_{22}H_{18}ClNO$ (347.6) Calcd.: C 76,0 H 5.22 N 4.0 Cl 10.2; Found: C 75.9 H 5.30 N 4.1 Cl 10.2.

Preparation of compounds **1–15** (General procedure)

To a solution of 0.01 mole of **16**, **17** or **18** in 100 ml benzene, 0.02 mole of the selected secondary base were added and the mixture was refluxed for 2 h. After cooling, the reaction mixture was tranferred to a separatory funnel, washed with water and then extracted with HCl dil. The hydrochloric extract was alkalized with solid K_2CO_3 and the separated layer taken up in $CHCl_3$. After removing the solvent the residue was crystallized from ligroin.

5-(o-Dimethylaminomethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(1)**

White product, m.p. 134–136°. Yield 75 %. $C_{24}H_{24}N_2O$ (356.2) Calcd.: C 80.9 H 6.79 N 7.9; Found: C 80.8 H 6.71 N 7.8.

5-(m-Dimethylaminomethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(2)**

White product, m.p. 104–106°. Yield 70 %. $C_{24}H_{24}N_2O$ (356.2) Calcd.: C 80.9 H 6.79 N 7.9; Found: C 80.7 H 6.58 N 7.8.

5-(p-Dimethylaminomethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(3)**

White product, m.p. 130–131°. Yield 75 %. $C_{24}H_{24}N_2O$ (356.2) Calcd.: C 80.9 H 6.79 N 7.9; Found: C 80.8 H 6.72 N 7.7.

5-(o-Diethylaminomethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(4)**

White product, m.p. 122–123°. Yield 70 %. $C_{26}H_{28}O$ (370.2) Calcd.: C 81.2 H 7.34 N 7.3; Found: C 81.1 H 7.26 N 7.2.

5-(m-Diethylaminomethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(5)**

White product, m.p. 68–70°. Yield 65 %. $C_{26}H_{28}N_2O$ (370.2) Calcd.: C 81.2 H 7.34 N 7.3; Found: C 81.2 H 7.22 N 7.2.

5-(p-Diethylaminomethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(6)**

White product, m.p. 118–120°. Yield 70 %. $C_{26}H_{28}N_2O$ (370.2) Calcd.: C 81.2 H 7.34 N 7.3; Found: C 81.3 H 7.40 N 7.1.

5-(o-Pyrrolidinomethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(7)**

White product, m.p. 129–132°. Yield 70 %. $C_{26}H_{26}N_2O$ (368.2) Calcd.: C 81.6 H 6.86 N 7.3; Found: C 81.6 H 6.91 N 7.4.

5-(m-Pyrrolidinomethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(8)**

White product, m.p. 83–84°. Yield 70 %. $C_{26}H_{26}N_2O$ (368.2) Calcd.: C 81.6 H 6.86 N 7.3; Found: C 81.7 H 6.81 N 7.2.

5-(p-Pyrrolidinomethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(9)**

White product, m.p. 93–95°. Yield 70 % $C_{26}H_{26}N_2O$ (368.2) Calcd.: C 81.6 H 6.86 N 7.3 Found: C 81.8 H 6.91 N 7.2.

5-(o-Piperidinomethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(10)**

White product, m.p. 150–152°. Yield 75 %. $C_{27}H_{28}N_2O$ (382.2) Calcd.: C 81.8 H 7.12 N 7.1; Found: C 81.6 H 7.01 N 7.0.

5-(m-Piperidinomethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(11)**

White product, m.p. 106–108°. Yield 75 %. $C_{27}H_{28}N_2O$ (382.2) Calcd.: C 81.8 H 7.12 N 7.1; Found: C 81.7 H 7.06 N 7.1.

5-(p-Piperidinomethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(12)**

White product, m.p. 112–115°. Yield 80 %. $C_{27}H_{28}N_2O$ (382.2) Calcd.: C 81.8 H 7.12 N 7.1; Found: C 81.8 H 7.15 N 7.2.

5-(o-Morpholinomethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(13)**

White product, m.p. 175–177°. Yield 80 %. $C_{26}H_{26}N_2O_2$ (384.2) Calcd.: C 78.4 H 6.58 N 7.0; Found: C 78.5 H 6.61 N 7.0.

5-(m-Morpholinomethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(14)**

White product, m.p. 163–165°. Yield 75 %. $C_{26}H_{26}N_2O_2$ (384.2) Calcd.: C 78.4 H 6.58 N 7.0; Found: C 78.4 H 6.51 N 7.1.

5-(p-Morpholinomethylbenzoyl)-10,11-dihydro-5H-dibenz[b,f]azepine **(15)**

White product, m.p. 124–126°. Yield 80 %. $C_{26}H_{26}N_2O_2$ (384.2) Calcd.: C 78.4 H 6.58 N 7.0; Found: C 78.4 H 6.62 N 7.1.

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