Substituted Benzamides with Potential CNS-Depressant and Hypotensive Activity

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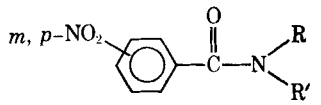
Abstract □ A series of 14 *N*-alkyl, *N*-aryl, and *N*-aralkyl analogs of *N*-cyclohexyl nitrobenzamide has been synthesized and characterized. The compounds have been studied for their ability to depress the spontaneous motor activity of mice and for their hypotensive activity in rats. Four of the compounds, which are structurally characterized by small alkyl groups attached to the amide nitrogen and a *p*-nitro group, showed the greatest CNS-depressant activity. The hypotensive action of these compounds paralleled their depressant action.

Keyphrases □ Nitrobenzamide, *N*-cyclohexyl—synthesis, *N*-alkyl, *N*-aryl, *N*-aralkyl analogs; evaluation, CNS-depressant activity □ CNS-depressant activity—synthesis, pharmacological evaluation of *N*-cyclohexyl nitrobenzamide analogs.

In previous publications (1, 2) the synthesis and pharmacological evaluation of two series of ring-substituted benzamides of *N*-(β-cyanoethyl)- and *N*-(β-hydroxyethyl)-*N*-cyclohexylamine were reported. The biological activity of these compounds was studied in mice and rats for their effect on spontaneous motor activity and blood pressure. They were found to exert a depressant action on the spontaneous activity of mice at a 4–5-mg./kg. dosage level and to effect a prolonged reduction in blood pressure of normotensive rats at this dosage. Of the β-cyanoethyl analogs, the most active compounds were the *p*-chlorobenzamides and *p*-methoxybenzamides.

This paper reports a convenient synthesis and preliminary pharmacological evaluation for a series of amides of *m*-nitro- and *p*-nitro-substituted benzoic acids represented by the formula (I):



R = cyclohexyl; R′ = alkyl, aryl, or aralkyl

I

To study the *in vivo* effects of the test compounds, C_3H mice weighing between 20–25 g. were used. All test compounds were dissolved in propylene glycol and administered orally and intraperitoneally. Dose–response curves were obtained using eight mice (rats) at each of four dosage levels, and the median effective dose (ED_{50}) was calculated.

Concurrent with the toxicity range studies in mice and rats, careful gross observation of the intact animals was made at several dosage levels, and signs of CNS depression (decreased spontaneous motor activity, *etc.*) were noted. The general type of pharmacological activity encountered in these compounds was predominantly evinced by their effects on the CNS.

At a dose of 5 mg./kg., i.p., the test compounds caused sedation without sleep in mice and rats. The animals developed a persistent state of tranquility within 10 min. following administration, and this activity persisted for several hours. The animals could be handled with essentially no resistance, although they were otherwise seemingly unaltered. They were calm but

Table I—Effects on Spontaneous Activity in Mice

Compound Number	Dose, mg./kg.	Reduction in Spontaneous Activity, %
Chlorpromazine	1.0	2.5
	3.0	42.4
	5.0	60.0
	7.0	75.2
	1.0	32.4
	3.0	72.0
	5.0	91.1
	7.0	—
2	1.0	23.1
	3.0	62.9
	5.0	80.4
	7.0	95.2
3	1.0	30.8
	3.0	66.4
	5.0	86.0
	7.0	—
4	1.0	4.5
	3.0	44.1
	5.0	61.9
	7.0	76.5
5	1.0	32.0
	3.0	73.9
	5.0	93.4
	7.0	—
6	1.0	0.5
	3.0	39.0
	5.0	57.2
	7.0	72.0
7	1.0	32.5
	3.0	71.8
	5.0	89.6
	7.0	—
8	1.0	18.5
	3.0	57.6
	5.0	75.8
	7.0	90.4
9	1.0	18.5
	3.0	58.4
	5.0	76.0
	7.0	91.0
10	1.0	6.0
	3.0	45.2
	5.0	63.1
	7.0	76.8
11	1.0	18.8
	3.0	58.1
	5.0	76.5
	7.0	90.9
12	1.0	20.2
	3.0	60.0
	5.0	77.4
	7.0	92.5
13	1.0	—
	3.0	36.1
	5.0	54.2
	7.0	69.0
14	1.0	23.8
	3.0	63.4
	5.0	80.4
	7.0	95.2

Table II—Hypotensive Activity

Compound Number	Minutes following Administration 15	30	60	90	120
	Blood Pressure, % Reduction of Control				
1	50.0	28.6	20.5	15.0	0.0
3	49.4	32.0	22.6	14.2	2.5
5	50.4	31.6	20.8	12.5	3.1
7	48.3	30.2	20.0	5.1	0.0

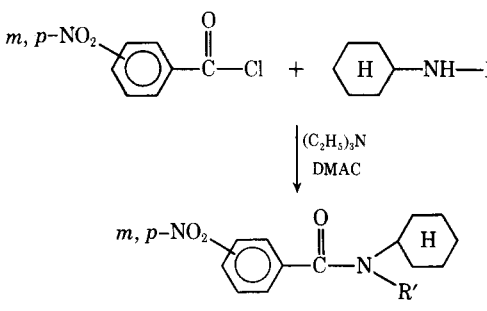
alert to attention. The animals walked normally and their movements were coordinated. Respiration was reduced and somewhat irregular during the 1st hr. following administration. In comparison to control animals, urination and defecation seem to be suppressed, which may be indicative of antispasmodic activity. Side reactions such as tremors were not noted in this study. The test compounds potentiated the sedative activity of barbiturates (amobarbital, pentobarbital, and secobarbital) and reserpine.

The most active compounds were Compounds 1, 3, 5, and 7 (Tables I and II). The *p*-nitro analogs were generally more potent depressants than the *m*-nitro derivatives, except those compounds where R′ (Table III) contained an aromatic ring (Compounds 11–14). Analogs where R′ was small (C_1–C_3) had the greatest CNS-depressant and blood pressure-depressor activity. Compounds that contained an OH functional group at R′ (Compounds 7, 8, 13, and 14) had a shorter duration of action. In all cases, the compounds' relative depressor activity paralleled their depressant activity (Table II).

PHARMACOLOGICAL RESULTS

Spontaneous Activity—The depressant activity of the test compounds was determined in mice with actophotometers.[1] The total body movements of single animals were measured at 15-min. intervals for a period of 1 hr. The mice were placed in the photocell unit immediately after intraperitoneal administration of the test compounds. Eight animals were used to study the effect of each compound at each dosage level, and the mean activity of each series of test animals was compared with the mean activity of a comparable number of control animals to ascertain the percent reduction in activity.

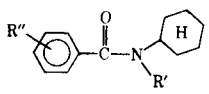
Hypotensive Activity—Indirect blood pressure measurements were performed using a photoelectric tensometer.[1] The test compounds were administered intraperitoneally to normotensive Wistar rats, and the systolic blood pressure was determined for a period of 2 hr. The mean response of eight test animals was used to determine the percent reduction in blood pressure produced by each test compound.



Scheme I

[1] Metro Industries, Inc., New York, N. Y.

Table III—Substituted Nitrobenzamides



Compound No.	R″ R′	Yield, %	M.p.	Anal., % Calcd.	Found
1	*p*-NO_2—CH_3	76.5	102.5°	C, 64.11 H, 6.92	C, 64.40 H, 6.95
2	*m*-NO_2—CH_3	72.2	94.5°	C, 64.11 H, 6.92	C, 64.35 H, 6.91
3	*p*-NO_2—C_2H_5	70.5	72.3°	C, 65.44 H, 6.96	C, 65.40 H, 6.97
4	*m*-NO_2—C_2H_5	72.3	45.0°	C, 65.44 H, 6.96	C, 65.46 H, 6.94
5	*p*-NO_2—$CH(CH_3)_2$	69.5	107.8°	C, 66.18 H, 7.64	C, 65.99 H, 7.67
6	*m*-NO_2—$CH(CH_3)_2$	74.8	35.6°	C, 66.18 H, 7.64	C, 66.10 H, 7.61
7	*p*-NO_2—CH_2CH_2—OH	75.0	210.5°	C, 61.63 H, 6.90	C, 61.59 H, 6.93
8	*m*-NO_2—CH_2OH—OH	74.2	Oil[a]	C, 61.63 H, 6.90	C, 61.66 H, 6.91
9	*p*-NO_2—CH_2CH_2CN	72.5	120.1°	C, 63.77 H, 6.35	C, 63.82 H, 6.30
10	*m*-NO_2—CH_2CH_2CN	69.6	93.1°	C, 63.77 H, 6.35	C, 63.90 H, 6.38
11	*p*-NO_2—C_6H_5	71.3	132.4°	C, 70.37 H, 6.21	C, 70.39 H, 6.20
12	*m*-NO_2—C_6H_5	75.0	105.1°	C, 70.37 H, 6.21	C, 70.31 H, 6.19
13	*p*-NO_2 —CH_2—CH(OH)—C_6H_5	65.8	126.1°	C, 68.46 H, 6.57	C, 68.40 H, 6.55
14	*m*-NO_2 —CH_2—CH(OH)—C_6H_5	66.9	25.2°	C, 68.46 H, 6.57	C, 68.55 H, 6.60

[a] Purified by chromatography (eluted by petroleum ether) on silica gel. TLC showed single spot.

EXPERIMENTAL

Melting points were determined using a Mettler FP-1 melting- and boiling-point apparatus. Analyses for carbon and hydrogen were obtained with a Coleman C-H analyzer; IR spectra were obtained with a Perkin-Elmer spectrophotometer model 137-B in KBr, and UV spectra were obtained with a Coleman model 124 Hitachi double-beam grating spectrophotometer. IR and UV spectra were as expected.

General Method of Preparation of Amides—Equimolecular amounts of *m*- and *p*- nitrobenzoyl chloride and *N*-substituted cyclohexylamine (Abbott Laboratories, North Chicago, Ill.) were dissolved in purified dimethylacetamide. The nitrobenzoyl chloride solution was then added to a cooled, well-stirred mixture of the substituted cyclohexylamine solution and triethylamine (Scheme I). When the addition of the acyl chloride solution was completed, the crude substituted benzamide was precipitated by the addition of ice water and collected on a filter. The crude product was recrystallized from EtOH/H_2O or Skelly Solve C/Skelly Solve B to give the pure compounds listed in Table III.

REFERENCES

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(2) W. D. Roll, *J. Med. Chem.*, **13**, 303(1970).

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