their experimental procedure differs from ours in the use of Ib as a hydrate for the Grignard reaction, and in their use of distillation and chromatography in the purification of II, whereas we achieved final purification of IIb through the direct formation of the oxalate salt.

Experimental Section[5]

1-Benzyl-3,4-dimethylpyridinium Chloride (Ib).—A solution of 42.2 g of $C_6H_5CH_2Cl$ and 35.7 g of 3,4-lutidine in 100 ml of Me_2CO was allowed to stand overnight at room temperature. The product, obtained in 81–89% yield in two crops, melted at 196–197.5°. *Anal.* ($C_{14}H_{16}ClN$) C, H, N.

1-Benzyl-2-(*p*-methoxybenzyl)-3,4-dimethyl-1,2,5,6-tetrahydropyridine (IIb).—The Grignard reagent from 36.3 g of *p*-methoxybenzyl chloride (using 3 l. of Et_2O/mole to reduce coupling) was added to 32.8 g of Ib in Et_2O. The mixture was stirred and refluxed for 1.5 hr and poured into a solution of 14 g of NH_4Cl in H_2O. Crude bianisyl was removed by filtration, the Et_2O layer separated and washed with H_2O, and the dihydropyridine isolated as a crude residue (57.5 g) by removal of the Et_2O. This was reduced in EtOH with 3.9 g of $NaBH_4$ in H_2O. The reaction mixture was stirred overnight at room temperature and the EtOH then removed *in vacuo*. The aqueous phase was extracted with Et_2O and the latter extracted in several portions with a total of 17.5 g of 85% H_3PO_4 in 400 ml of H_2O. Addition of excess 35% aqueous NaOH to the acid extracts, extraction of the resultant oil into Et_2O, drying, filtration, and concentration afforded 32.5 g of crude base. This was added to 9.1 g of oxalic acid in 100 ml of Me_2CO to precipitate 31.2 g of IIb·oxalate, mp 153–158°. *Anal.* ($C_{22}H_{27}NO \cdot C_2H_2O_4$) C, H, N.

3-Benzyl-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocin-8-ol·HBr (IIIb).—A mixture of 53.8 g of crude IIb·oxalate, 145 ml of HOAc, and 285 ml of 62% HBr was refluxed for 22 hr, concentrated *in vacuo*, and diluted with 800 ml of *i*-PrOH. The slurry was stirred, concentrated to about 250 ml, cooled, and filtered. The product was taken up in EtOH and precipitated with about an equal volume of Et_2O to give 23.7 g of IIIb as the hydrobromide, mp 259–262°. *Anal.* ($C_{21}H_{25}NO \cdot HBr$) C, H, Br.

The *i*-PrOH mother liquors contain some of the *trans* isomer, mp 275–276° corrected. *Anal.* ($C_{21}H_{25}NO \cdot HBr$) C, H, N.

1,2,3,4,5,6-Hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocin-8-ol (III, R = H).—Reduction of 11.8 g of IIIb·HBr in DMF using a 10% Pd-C catalyst gave, after removal of the catalyst and solvent and basification with NH_4OH, 6.0 g of product, mp 234–235°.[6] *Anal.* ($C_{14}H_{19}NO$) C, H, N.

Alkylation of this base with 1-bromo-3-methyl-2-butene to give pentazocine has been described.[7]

(5) Melting points are not corrected for emergent stem errors.

(6) E. M. Fry and E. L. May [*J. Org. Chem.*, **24**, 116 (1959)] report mp 232–235° corrected.

(7) S. Archer, N. F. Albertson, L. S. Harris, Anne K. Pierson, and J. G. Bird, *J. Med. Chem.*, **7**, 123 (1964).

Substituted Benzamides. Analogs of β-Hydroxyethylcyclohexylamine with CNS Depressant and Hypotensive Activity

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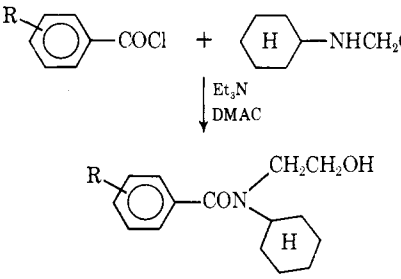
In a previous publication[1] we reported the synthesis and pharmacological evaluation of a series of ring-substituted *N*-(β-cyanoethyl)-*N'*-cyclohexylbenzamides. The biological activity of these compounds was studied in mice and rats for their effect on spontaneous motor activity and blood pressure. They were found to exert a depressant action on the spontaneous activity of mice at a dosage level of 4 mg/kg and effect a prolonged reduction in blood pressure of normotensive rats at this dosage. It was noted that the most active analogs studied were the *p*-chloro- and the *p*-methoxy-*N*-(β-cyanoethyl)-*N'*-cyclohexylbenzamides.

(1) W. D. Roll, *J. Pharm. Sci.*, **57**, 1671 (1968).

This paper reports a convenient synthesis and pharmacological evaluation for a series of amides of *ortho*-, *meta*-, and *para*-monosubstituted benzoic acids (**1**–**9**).



1, **2**, **3**, R = *p*-, *m*-, *o*-OCH_3
4, **5**, **6**, R = *p*-, *m*-, *o*-Cl
7, **8**, **9**, R = *p*-, *m*-, *o*-CH_3

Effects on the Central Nervous System of Mice. Gross Observation.—At a dose of 5 mg/kg, administered intraperitoneally (i.p.), **1**–**9** caused sedation without sleep in mice. A persistent state of tranquility developed within 10 min following administration and lasts for several hours. The animals' overall response pattern was similar to that observed with chlorpromazine with **1**, **3**, **4**, **5**, **7**, and **9**, demonstrating greater depressant activity. The test compounds potentiate the sedative action of reserpine.

Experimental Section[2]

General Method of Preparation of Amides.—Equimolecular amounts of the substituted benzoyl chloride and *N*-(β-hydroxyethyl)cyclohexylamine (Abbott Laboratories, North Chicago, Ill.) were dissolved in freshly distilled DMAC. The acyl halide solution was then added to a cooled, well-stirred mixture of the *N*-(β-hydroxyethyl)cyclohexylamine solution and Et_3N. When the addition of the acyl halide solution was completed, the crude substituted benzamide was precipitated by the addition of cold H_2O and collected. The crude product was recrystallized from EtOH–H_2O to give the pure compounds listed in Table I.

Pharmacologic Methodology. Gross Observations.—To study the *in vivo* effects, C3H mice weighing between 20 and 25 g were used. All test compounds were dissolved in propylene glycol and administered orally and i.p. Dose–response curves were obtained using 8 mice (rats) at each of four dose levels, and the median effective dose (ED_{50}) was calculated.

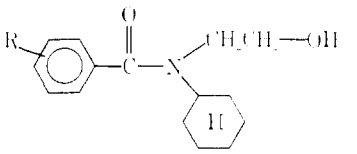
The effect of the compounds on reserpine-induced sedation was studied in mice by injecting them i.p. 4 hr following the administration of 2.5 mg/kg of reserpine i.p. and compared with that of the control groups at varying intervals.

Wistar rats dosed simultaneously with amphetamine (0.4%) 4 mg/kg i.p. and test compounds **1**, **3**, **4**, **7**, and **9** did not exhibit the characteristic symptoms (tremors, pacing, piloerection) noted in control animals receiving only the aforementioned dose of amphetamine.

Spontaneous Activity.—The depressant activity of the test compounds was determined in mice with actophotometers (Metro Industries, Inc., New York, N. Y.). The total body

(2) Melting points were determined using a Mettler FP-1 melting and boiling point apparatus and are corrected. Analyses (C, H) were obtained with a Coleman C-H analyzer, and where they are indicated only by symbols of the elements analytical data obtained for these elements were within ±0.4% of the theoretical values. Ir spectra were obtained with a Perkin-Elmer spectrophotometer Model 137-B (KBr).

TABLE I
MONOSUBSTITUTED
N-β-HYDROXYETHYL-N'-CYCLOHEXYLBENZAMIDE
DERIVATIVES



R	Yield, %	Mp,[a] °C	Formula[c]
p-MeO	75	81.1–82.6	$C_{16}H_{23}NO_2$
m-MeO	75	101–102	$C_{16}H_{23}NO_3$
o-MeO	73	Oil[b]	$C_{16}H_{23}NO_3$
p-Cl	78	88.5–89.7	$C_{15}H_{20}ClNO_2$
m-Cl	76	Oil[b]	$C_{15}H_{20}ClNO_2$
o-Cl	78	58.3–58.8	$C_{15}H_{20}ClNO_2$
p-Me	74	60.4–60.9	$C_{16}H_{23}NO_2$
m-Me	73	55.2–56.2	$C_{16}H_{23}NO_2$
o-Me	72	64.2–64.5	$C_{16}H_{23}NO_2$

[a] Determined at 2°/min. [b] An oil which was purified by chromatography. [c] All compounds were analyzed for C, H.

TABLE II
EFFECTS ON THE SPONTANEOUS ACTIVITY IN MICE

Compound	Dose, mg/kg	% reduction in spontaneous act
Chlorpromazine	1.0	2.5
	3.0	42.4
	5.0	60.0
	7.0	75.2
1	1.0	9.8
	3.0	55.0
	5.0	58.4
	7.0	80.8
2	1.0	7.5
	3.0	47.8
	5.0	48.6
	7.0	69.4
3	1.0	12.8
	3.0	61.0
	5.0	65.9
	7.0	88.5
4	1.0	11.5
	3.0	64.0
	5.0	66.2
	7.0	89.8
5	1.0	9.0
	3.0	52.2
	5.0	55.3
	7.0	76.5
6	1.0	7.0
	3.0	45.0
	5.0	45.2
	7.0	64.9
7	1.0	13.6
	3.0	66.1
	5.0	73.5
	7.0	97.7
8	1.0	4.9
	3.0	37.8
	5.0	35.5
	7.0	53.6
9	1.0	11.0
	3.0	58.8
	5.0	63.3
	7.0	86.1

TABLE III
HYPOTENSIVE ACTIVITY IN NORMOTENSIVE RATS

Compound[a]	% reduction of control blood pressure (Min following administration) (15)	(30)	(60)	(90)	(120)
3[b]	26.7	30.0	35.0	0.0	0.0
4[b,c]	13.6	29.4	31.8	4.5	0.0
7[b,d]	40.3	25.0	16.6	8.3	0.0

[a] Administered 5 mg/kg i.p. [b] Direct measurement showed (*b*) 30; (*c*) 40; (*d*) 50 mm drop in blood pressure.

movements of single animals were measured at 15-min intervals for 1 hr. The mice were placed in the photocell unit immediately after i.p. 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 in order to determine the percent reduction in activity (Table II).

Antiamphetamine Activity.—Groups of male Wistar rats (4 each) received i.p. injections of 4 mg/kg of amphetamine (0.4%) followed immediately with 5 mg/kg of test compound. A similar number of control animals received amphetamine only.

Hypotensive Activity.—Indirect blood pressure measurements were performed using a photoelectric tensometer (Metro Industries, Inc., New York, N. Y.). The test compounds were administered i.p. to normotensive Wistar rats, and the systolic blood pressure was determined for a period of 2 hr. The methodology was that of Coates, *et al.*[3] The mean response of 8 test animals and 8 control animals was used to determine the percent reduction in blood pressure produced by each test compound (Table III).

Direct blood pressure determinations were made as described in a previous paper.[1]

(3) D. W. Coates, J. P. Buckley, and W. J. Kinnard, *J. Pharm. Sci.*, **52**, 71 (1963).

Synthesis of Some Local Anesthetics

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Some derivatives of 2-aminobenzothiazoles[1,2] and 2-aminothiazoles[3,4] are reported to possess considerable local anesthetic activity. We have now synthesized some morpholinoacetyl-2-aminobenzothiazole derivatives, by condensation of chloroacetyl chloride with different 2-aminobenzothiazoles followed by treatment with morpholine.

Experimental Section

Different-2-aminobenzothiazoles were prepared by the Hugershoff[5] method, and the chloroacetyl-2-aminobenzothiazoles were prepared by known methods.[6]

Morpholinoacetyl-2-aminobenzothiazole.—To chloroacetyl-2-aminobenzothiazole (5 g) dissolved in EtOH (50 ml), morpholine (4 ml) was added, and the mixture was refluxed for 6 hr. After the reaction, excess EtOH and morpholine were recovered by distillation and the residue was washed ($NaHCO_3$, H_2O). The product was crystallized from EtOH, mp 53°. The other morpholinoacetyl derivatives were prepared similarly.

Local Anesthetic Testing.—The local anesthetic activity was evaluated by employing: (1) surface anesthesia on the guinea-pig

(1) P. N. Bhargava and B. T. Baliga, *J. Indian Chem. Soc.*, **35**, 807 (1958).
(2) P. N. Bhargava and K. A. Jose, *ibid.*, **37**, 314 (1960).
(3) P. N. Bhargava and M. G. R. Nair, *ibid.*, **34**, 42 (1957).
(4) P. N. Bhargava and P. R. Singh, *ibid.*, **37**, 241 (1960).
(5) A. Hugershoff, *Ber.*, **34**, 3130 (1901); **36**, 3121 (1903).
(6) P. N. Bhargava and G. C. Singh, *J. Indian Chem. Soc.*, **38**, 77 (1961).