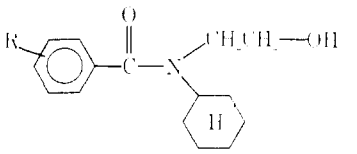
TABLE I
MONOSUBSTITUTED
N-β-HYDROXYETHYL-N'-CYCLOHEXYLBENZAMIDE
DERIVATIVES



R	Yield, %	Mp,[a] °C	Formula[c]
p-MeO	75	81.4–82.6	$C_{16}H_{23}NO_3$
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	61.0
	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	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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Received September 22, 1969

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

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(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).

TABLE I

No.	X	Yield, %	Mp, °C	Formula[a]	Mp, °C (hydrochloride)	Mp, °C (picrate)
1	H	64	52–53	$C_{13}H_{15}N_3O_2S$	212–214	227–228
2	4-CH_3	70	135–136	$C_{14}H_{17}N_3O_2S$	202–204	183–185
3	6-CH_3	68	116–117	$C_{14}H_{17}N_3O_2S$	244–246	199–200
4	4,7-$(CH_3)_2$	75	126–127	$C_{15}H_{19}N_3O_2S$	186–188	238–240
5	5-Cl	65	155–156	$C_{13}H_{14}ClN_3O_2S$	226–228	254–256
6	6-Cl	58	44–45	$C_{13}H_{14}ClN_3O_2S$	144–145	191–192
7	6-Br	60	73–74	$C_{13}H_{14}BrN_3O_2S$	172–174	217–219
8	5-OCH_3	66	90–91	$C_{14}H_{17}N_3O_3S$	152–154	211–212
9	6-OCH_3	64	34–35	$C_{14}H_{17}N_3O_3S$	215–217	200–202

[a] All compounds were analyzed for N, S and gave satisfactory analytical results (±0.4%).

TABLE II

	Surface anesthesia					Intradermal anesthesia				
No.	Drug concentration, %	% anesthesia	Duration, min	Potency (cocaine = 1)	Potency (lidocaine = 1)	Drug concentration, %	% anesthesia	Duration, min	Potency (procaine = 1)	Potency (lidocaine = 1)
1	0.2	100	26	0.5	1	0.2	100	70	2	1
2	0.4	100	40	0.25	0.5	0.2	95	68	2	1
3	0.2	100	52	0.5	1	0.2	98	80	2	1
4	0.2	95	29	0.5	1	0.4	95	90	1	0.5
5	0.2	90	70	0.5	1	0.4	100	60	1	0.5
6	0.2	100	28	0.5	1	0.2	100	68	2	1
7	0.4	100	38	0.25	0.5	0.2	96	65	2	1
8	0.2	95	28	0.5	1	0.4	98	75	1	0.5
9	0.2	100	39	0.5	1	0.1	90	85	4	2
Cocaine	0.1	96.66	21							
Lidocaine	0.2	100	14.83			0.2	98.33	44.10		
Procaine						0.4	100	55.53		

cornea[7] and (2) intradermal anesthesia (block anesthesia) in the guinea pig.[8] The activity was compared with the reference drugs, *viz.* cocaine·HCl, procaine·HCl, and lidocaine·HCl (see Table II).

Acknowledgment.—The authors are thankful to Professor W. U. Malik for providing necessary laboratory facilities, and to Dr. M. A. Patel of Drugs Laboratory, Baroda, for carrying out the biological screening of these compounds.

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Synthesis of Compounds with Potential Central Nervous System Stimulant Activity. II. 5-Spiro-Substituted 2-Amino-2-oxazolines

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Received November 1, 1969

In part I[1] of this series the synthesis and biological activity of some 5-spiro-substituted 2-amino-2-oxazolin-4-ones were discussed. In the present publication we wish to report the synthesis of some 5-spiro-substituted 2-amino-2-oxazolines and their effects on the central nervous system.

The 5-spiro-substituted compounds **2a–m** were synthesized from cyclic ketones by a previously described procedure[2] involving reduction of the ketone cyanohydrins and reaction of the resultant 2-hydroxyethylamines (**1a–m**) with CNBr.

The chemical reactions of 2-amino-1-oxa-3-azaspiro[4.5]dec-2-ene (**2b**), a representative member of the series, were investigated (Scheme I). As a consequence of the absence of the benzylic moiety **2b** did not undergo the hydrogenolytic ring opening reported for 2-amino-4-methyl-5-phenyl-2-oxazoline,[2] and was recovered unchanged. Hydrolysis of **2b** with H_2O at 100° yielded predominantly the hydroxyurea **4** and a small quantity of the 2-oxazolidinone **3**. Heating a solution of **2b** in 0.2 *N* HCl at 100° for the same period of time, however, rather surprisingly resulted in much less hydrolysis and the sole hydrolysis product was the hydroxyurea **4**. Acetylation of **2b** with Ac_2O in pyridine yielded the 3-acetyl-2-oxazolidinone **5**. The 2-imino derivative is probably formed first and undergoes facile hydrolysis during the isolation procedure. Methylation of **2b** with 3 mol of MeI gave a mixture of the 3-methyl derivative **6** and the 2,3-dimethyl derivative **7**. The positions of the Me substituents were readily determined by comparison of the nmr spectra obtained for **6** and **7** with the spectra obtained for 2-methylamino-1-oxa-3-azaspiro[4.5]dec-2-ene (**10**) and 2-dimethylamino-1-oxa-3-azaspiro[4.5]dec-2-ene (**12**). The latter two compounds were synthesized by an alternative unequivocal route involving conversion of 1-aminomethylcyclohexanol into the substituted hydroxyureas **8** and **11** with methyl isocyanate and dimethylcarbamoyl chloride, respectively. Reaction of **8** and **11** with $SOCl_2$ and treatment of the intermediate chloroureas, without isolation, with boiling H_2O gave

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