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.

(7) H. R. A. Chance and J. Lobstein, *J. Pharmacol. Exp. Ther.*, **82**, 203 (1944).

(8) M. A. Patel, *J. Exp. Biol.*, **6**, 1, 64 (1968).

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

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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.

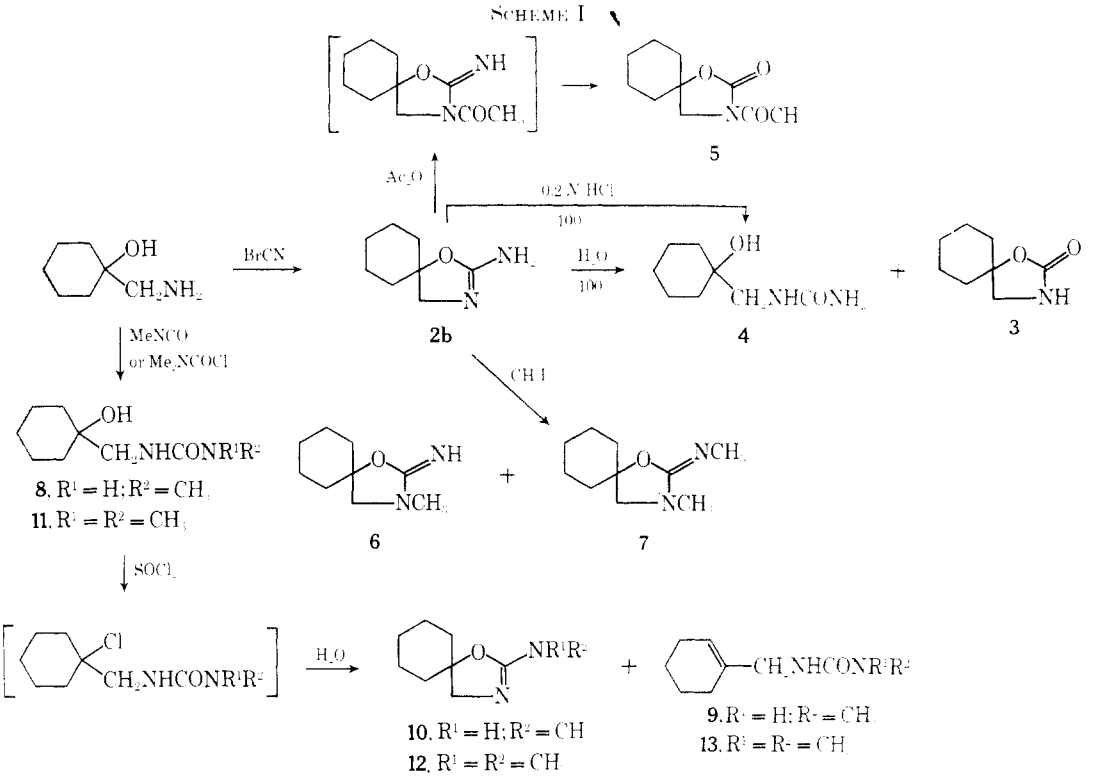
The 5-spiro-substituted compounds **2a–m** were synthesized from cyclic ketones by a previously described procedure[2] involving reduction of the ketone cyanohydrins and reaction of the resultant 2-hydroxyethylamines (**1a–m**) with CNBr.

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

(1) M. R. Harnden and R. R. Rasmussen, *J. Med. Chem.*, **12**, 919 (1969).

(2) G. I. Poos, J. R. Carson, J. D. Rosenau, A. P. Roszkowski, N. M. Kelley, and J. McGowin, *ibid.*, **6**, 266 (1963).

SCHEME I



the desired methyl-substituted derivatives **10** and **12** and also considerable amounts of a by-product which was in each case identified as the corresponding cyclohexenylurea (**9** and **13**).

Biological Data.—Effects on the CNS were investigated by observation of albino Swiss–Webster mice for gross changes in behavior following administration of test compounds. In Table I the CNS stimulant activity and toxicity of the most active members of the series (**2c**, **e**, **f**, **k**, **10**) are compared with similar data obtained for *d*-amphetamine sulfate. It is of interest that, of the 2-amino-2-oxazolines synthesized (**2a–m**), the most active stimulants (**2c**, **e**, **f**, **k**) all possess 5-spiro substituents containing seven carbon atoms.

TABLE I
COMPARISON OF BIOLOGICAL DATA

Compound[a]	Min. dose causing significant increase in spontaneous motor activity, mg/kg I.P.	Oral	Approx LD_{50}, mg/kg I.P.	Oral
2c	2	20	7.5	30
2e	5	20	15	30
2f	5	10	10	30
2k	20	50	50	100
10	1	20	15	75
d-Amphetamine sulfate	0.1	1	10	20

[a] Administered as a 2% suspension in 0.3% tragacanth.

Experimental Section[3]

2-Hydroxyethylamines (1a–m).—A solution of the appropriate cyanohydrin[1,4] in AcOH (400 ml) containing PtO_2 (2.0 g) in suspension was hydrogenated at 20° and 2.8 kg/cm² pressure. H_2 uptake was complete in 1 hr. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure to a viscous syrup. Upon trituration of the syrup with Et_2O (200 ml) white crystals of the 2-hydroxyethylamine acetate deposited. The salts were recrystallized from *i*-PrOH–Et_2O.

1-Aminomethylcyclopentanol acetate (**1a**), mp 117–119°, 29.4% yield, *Anal.* ($C_7H_{15}NO \cdot AcOH$) C, H, N; 1-aminomethylcyclohexanol acetate (**1b**), mp 122–124°, 52.8% yield, *Anal.* ($C_7H_{15}NO \cdot AcOH$) C, H, N; 1-aminomethylcycloheptanol acetate (**1c**), mp 93–95°, 26.4% yield, *Anal.* ($C_8H_{17}NO \cdot AcOH$) C, H, N; 1-aminomethyl-4-methylcyclohexanol acetate (**1e**), mp 109–111°, 41.3% yield, *Anal.* ($C_8H_{17}NO \cdot AcOH$) C, H, N; 1-aminomethyl-3-methylcyclohexanol acetate (**1f**), mp 126–135°, 48.2% yield, *Anal.* ($C_8H_{17}NO \cdot AcOH$) C, H, N; 1-aminomethyl-3,5-dimethylcyclohexanol acetate (**1g**), mp 152–155°, 45.2% yield, *Anal.* ($C_9H_{19}NO \cdot AcOH$) C, H, N; 1-aminomethyl-3,3,5-trimethylcyclohexanol acetate (**1h**), mp 148–150°, 24.2% yield, *Anal.* ($C_{10}H_{21}NO \cdot AcOH$) C, H, N; 1-aminomethyl-3,4,5-trimethylcyclohexanol acetate (**1i**), mp 154–156°, 44.5% yield, *Anal.* ($C_{10}H_{21}NO \cdot AcOH$) C, H, N; 1-aminomethyl-3,3,5,5-tetramethylcyclohexanol acetate (**1j**), mp 143–144°, 70.0% yield, *Anal.* ($C_{11}H_{23}NO \cdot AcOH$) C, H, N; 2-aminoethyl-2-norbornanol acetate (**1k**), mp 92–119°, 33.7% yield, *Anal.* ($C_8H_{15}NO \cdot AcOH$) C, H, N; 2-aminomethyl-2-decalol acetate (**1l**), mp 124–144° 68.5% yield, *Anal.* ($C_{11}H_{21}NO \cdot AcOH$) C, H, N.

In the case of 1-aminomethylcyclooctanol (**1d**) and 1-methyl-4-aminomethyl-4-piperidol (**1m**) a crystalline acetate could not be obtained. The free base was therefore liberated with 50% aqueous NaOH and the solution concentrated at reduced pressure. The residue was dissolved in CH_2Cl_2 (2 l.) and the solution dried (Na_2CO_3) and concentrated at reduced pressure. Distillation of the oil that was obtained yielded the pure 2-hydroxyethylamine; compound **1d**, bp 102–104° (1.1 mm), 5.0% yield, *Anal.* ($C_9H_{19}NO$) C, H, N; **1m**, bp 92–94° (2.0 mm), 52.3% yield, *Anal.* ($C_7H_{16}N_2O$) C, H, N; dihydrochloride, mp 202–204°. *Anal.* ($C_7H_{16}N_2O \cdot 2HCl$) C, H, N, Cl.

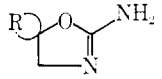
The low yield of the cyclooctyl compound **1d** was a consequence of the predominance of reductive alkylation during the reduction of the cyanohydrin. Distillation of the crude basic product also yielded 1-cyclooctylaminomethylcyclooctanol, bp 182–184° (1.1 mm), 58.4% yield. *Anal.* ($C_{17}H_{33}NO$) C, H, N.

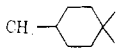
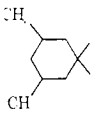
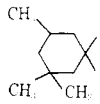
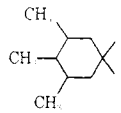
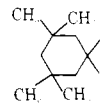
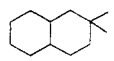
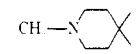
2-Amino-2-oxazolines (2a–m).—The 2-hydroxyethylamine acetate (0.1 mol) and anhydrous NaOAc (8.2 g, 0.1 mol) were dissolved in MeOH (150 ml) and a solution of NaOMe (5.4 g, 0.1 mol) in MeOH (100 ml) added. In the case of **1d** and **1m** the

(3) Melting points were determined with a Thomas–Hoover capillary apparatus and are corrected. Ir and nmr spectra of all compounds listed here and in Table II were consistent with the structures given. Elemental analyses were performed by Mr. V. Rauschel and his associates in the analytical department of Abbott Laboratories. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

(4) M. R. Harnden, *J. Chem. Soc. C*, 960 (1969).

TABLE II
5-SPIRO-SUBSTITUTED 2-AMINO-2-OXAZOLONES



Compound	R	Formula[a]	Mp, °C	Yield, %
2a		$C_7H_{12}N_2O$	154–156	69.2
b		$C_8H_{14}N_2O$	126–128	59.7
c		$C_9H_{16}N_2O$	132–134	68.0
d		$C_{10}H_{18}N_2O$	136–138	34.0
e		$C_9H_{16}N_2O$	147–162	57.8
f		$C_9H_{16}N_2O$	107–108	30.8
g		$C_{10}H_{18}N_2O$	147–149	45.8
h		$C_{11}H_{20}N_2O$	154–156	47.6
i		$C_{11}H_{20}N_2O$	178–180	60.0
j		$C_{12}H_{22}N_2O$	142–143	58.3
k		$C_9H_{14}N_2O$	159–161	55.7
l		$C_{12}H_{20}N_2O$	154–161	38.2
m		$C_8H_{15}N_3O$	185–186	13.3

[a] All compounds analyzed correctly (C, H, N).

free base (0.1 mol) and NaOAc (16.4 g, 0.2 mol) were dissolved in MeOH (250 ml). The solution was cooled to 0° and a solution of BrCN (10.6 g, 0.1 mol) in MeOH (30 ml) added over a period of 15 min. The solution was stirred at 0° for 1 hr. The solvent was evaporated under reduced pressure and the residue dissolved in the minimum volume of H_2O necessary to obtain solution. A concentrated solution of K_2CO_3 was added and a white solid precipitated. The solid was collected, dried, and recrystallized from C_6H_6–n-C_6H_{14} to give the pure product (**2a–l**). In the case of the H_2O soluble compound **2m** the solution was extracted with $CHCl_3$ (four portions of 150 ml) and the $CHCl_3$ solutions dried (K_2CO_3) and concentrated under reduced pressure. On treatment of the residue with EtOAc (25 ml) **2m** was obtained as a white solid.

Chemical Reactions of 2-Amino-1-oxa-3-azaspiro[4.5]dec-2-ene (2b). A. Hydrogenation.—The conditions described by Poos, *et al.*,[2] for hydrogenolysis of *cis*-2-amino-4-methyl-5-phenyloxazoline were used. No reaction occurred.

B. Hydrolysis.—(a) A solution of **2b** (5.0 g) in H_2O (200 ml) was maintained at 100° for 4 hr, cooled, and extracted with $CHCl_3$ (five portions of 200 ml). The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated under reduced pressure. An oil was obtained which on trituration with n-C_6H_{14} yielded a white solid. Recrystallization from EtOH–n-C_6H_{14} gave pure 1-oxa-3-azaspiro[4.5]decan-2-one (**3**), mp 98–100°, 1.4% yield. *Anal.* ($C_8H_{13}NO_2$) C, H, N. The aqueous solutions were concentrated under reduced pressure and a white solid was obtained. On recrystallization from Me_2CO this gave pure (2-hydroxy-2-spirocyclohexyl)ethylurea (**4**), mp 137–138°, 71.7% yield. *Anal.* ($C_8H_{16}N_2O_2$) C, H, N.

(b) A solution of **2b** (3.0 g) in 0.2 N HCl (200 ml) was maintained at 100° for 4 hr. The reaction mixture was cooled, diluted with H_2O (500 ml), and passed through a column packed with Dowex 1-X4 resin. The effluent was concentrated under reduced pressure to an oil (2.1 g). Tlc of the oil on silica gel indicated that it contained only **2b** and the hydroxyurea **4** (identified by comparison with authentic sample obtained from basic hydrolysis). From the nmr spectrum of the oil it was determined that it contained 71.4% **2b** and 28.6% **4**.

C. Acetylation.—A solution of **2b** (5.0 g) and Ac_2O (9.1 ml) in C_5H_5N (74 ml) was allowed to remain at 20° for 72 hr, then acidified with 4 N HCl, and extracted with Et_2O (three portions of 250 ml). The Et_2O solutions were dried ($MgSO_4$) and concentrated under reduced pressure to a viscous oil. Upon trituration with a small amount of H_2O this yielded a white solid. The solid was filtered, dried, and recrystallized from n-C_6H_{14} to give 3-acetyl-1-oxa-3-azaspiro[4.5]decan-2-one (**5**), mp 64–65°, 79.7% yield. *Anal.* ($C_{10}H_{15}NO_3$) C, H, N. The acidic aqueous solution was basified with 5 N NaOH and reextracted with CH_2Cl_2 (three portions of 250 ml). The extracts were dried ($MgSO_4$) and concentrated under reduced pressure to an oil which upon trituration with H_2O yielded a further quantity (6.4%) of **5**.

D. Methylation.—To a solution of **2b** (5.0 g, 0.032 mol) in MeOH (100 ml) was added K_2CO_3 (13.8 g) and MeI (6.3 ml, 0.096 mol). The mixture was heated under reflux for 5 hr. The solution was concentrated under reduced pressure and the residue extracted with n-C_6H_{14} (250 ml). The solution was filtered, dried, and concentrated under reduced pressure to a viscous oil (6.0 g). The oil was dissolved in MeOH (25 ml) and fumaric acid (3.4 g) added. Et_2O was then added to the clear solution until crystallization commenced. The crystals were filtered and recrystallized from MeOH–Et_2O two more times to give the pure fumarate salt of 2-imino-3-methyl-1-oxa-3-azaspiro[4.5]decane (**6**), mp 171–172°, 49.6% yield. *Anal.* ($C_9H_{16}N_2O \cdot C_4H_4O_4$) C, H, N. The fumarate (1.0 g) was dissolved in MeOH (20 ml) and a solution of NaOMe (0.4 g) in MeOH (10 ml) added. The mixture was stirred at 20° for 15 min and then filtered. The filtrate was concentrated under reduced pressure to an oil. The oil was dissolved in n-C_6H_{14} (50 ml) and the solution filtered and concentrated under reduced pressure to give **6** as the free base: nmr:[5] 3-NCH_3, δ 2.89 (s); 4-CH_2, 3.25 (s).

The original mother liquors from which **6** fumarate crystallized were concentrated under reduced pressure. The oil obtained was dissolved in MeOH and Et_2O added until crystallization commenced. The mixture was kept at 5° for 2 hr and filtered, and the filtrate concentrated under reduced pressure. This process was repeated twice and the oil obtained crystallized upon standing. After recrystallization from MeOH (20 ml) by addition of Et_2O (200 ml) there was obtained the pure fumarate salt of 2-methylimino-3-methyl-1-oxa-3-azaspiro[4.5]decane (**7**), mp 149–151°, 24.7% yield. *Anal.* ($C_{10}H_{18}N_2O \cdot C_4H_4O_4$) C, H, N. The free base **7** was liberated in the same manner as described above for **6**: nmr:[5] 2-NCH_3, δ 2.80 (s); 3-NCH_3, 2.92 (s); 4-CH_2, 3.14 (s).

2-Methylamino-1-oxa-3-azaspiro[4.5]dec-2-ene (10).—A solution of MeNCO (8.55 g, 0.15 mol) in CH_2Cl_2 (15 ml) was added to a solution of 1-aminomethylcyclohexanol (19.4 g, 0.15 mol) in CH_2Cl_2 (85 ml) at 0°. The mixture was stirred for 2 hr and the resulting white precipitate obtained, was filtered and dried to give pure 1-(2-hydroxy-2-spirocyclohexyl)ethyl-3-methylurea (**8**), mp 136–137°, 91.0% yield. *Anal.* ($C_9H_{18}N_2O_2$) C, H, N.

A solution of $SOCl_2$ (11.9 g, 0.1 mol) in CH_2Cl_2 (40 ml) was added to a vigorously stirred suspension of **8** (18.6 g, 0.1 mol) in CH_2Cl_2 (400 ml) at 0°. The clear solution obtained was heated at reflux temperature for 30 min and then concentrated under reduced pressure. The residue was triturated with boiling H_2O (250 ml) and the aqueous solution separated from an oil which crystallized upon standing. Recrystallization from cyclohexane afforded 1-(cyclohex-1-enyl)methyl-3-methylurea (**9**), mp 91–93°, 33.9% yield. *Anal.* ($C_9H_{16}N_2O$) C, H, N. The aqueous solution was basified with a saturated solution of K_2CO_3 and the white precipitate that was obtained filtered, dried, and recrystallized twice from n-C_6H_{14} to give pure **10**, mp 97–99°, 40.7% yield;

(5) Determined by Mrs. R. Stanaszek for solutions in $CDCl_3$ using a Varian Model A60 spectrometer and Me_4Si as an internal standard.

nmr[3] 2-NCH_3, δ 2.85 (s); 4-CH_2, 3.50 (s). *Anal.* ($C_9H_{16}N_2O$) C, H, N.

2-Dimethylamine-1-oxa-3-azaspiro[4.5]dec-2-ene (12).—Dimethylcarbamoyl chloride (21.5 g, 0.2 mol) was added to a solution of 1-aminomethylcyclohexanol (25.9 g, 0.2 mol) and Et_3N (30.3 g, 0.3 mol) in dry PhMe (400 ml) at 0°. A precipitate formed immediately. The mixture was stirred at 20° for 2 hr and filtered. The solid obtained was extracted with hot Et_2O (3 portions of 500 ml). The Et_2O solutions were dried ($MgSO_4$) and concentrated to yield pure 1-(2-hydroxy-2-spirocyclohexyl)-ethyl-3,3-dimethylurea (**11**), mp 96–97°, 61.3% yield. *Anal.* ($C_{10}H_{20}N_2O_2$) C, H, N.

The hydroxyurea **11** (20.0 g, 0.1 mol) was treated with $SOCl_2$ and then with boiling H_2O, as described above for the synthesis of **10**, but no H_2O-insoluble fraction was obtained. The aqueous solution was basified with a saturated solution of K_2CO_3 and extracted with CH_2Cl_2 (three portions of 250 ml). The CH_2Cl_2 solution was dried and concentrated under reduced pressure to an oil. The oil was distilled to yield **12** [bp 73–75° (0.85 mm), 30.6% yield; nmr[3] 2-$N(CH_3)_2$, δ 2.91 (s); 4-CH_2, 3.50 (s). *Anal.* ($C_{10}H_{18}N_2O$) C, H, N] and 1-(cyclohex-1-enyl)methyl-3,3-dimethylurea (**13**) [bp 130–132° (0.55 mm), 41.4% yield. *Anal.* ($C_{10}H_{18}N_2O$) C, H N].

Acknowledgments.—We thank Mrs. I. M. Cole for for the biological data, and Dr. C. M. Lee and Mr. B. W. Horrom for helpful discussions.

3-Substituted 1,2,3,4-Tetrahydrocarbazoles

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In previous studies of heterocyclic compounds[1,2] it was found that *N*-alkylated 1,3,4,5-tetrahydrothiopyrano[4,3-*b*]indole had antireserpine activity equal to imipramine with little antimorphine effect. Because this derivative was the sulfur isostere of the 3-carbon atom of 1,2,3,4-tetrahydrocarbazole, it was of interest to prepare various 3-substituted derivatives of 1,2,3,4-tetrahydrocarbazoles and examine their effect on the CNS.

The key intermediate, 3-carbethoxy-1,2,3,4-tetrahydrocarbazole **3**, Table I (III, R′ = H; R = C_2H_5, Scheme I), was prepared by the Fischer indole synthesis[3] employing 4-carbethoxycyclohexanone and phenylhydrazine which was converted into appropriate derivatives through the sequence shown in Scheme I. The compounds prepared are listed in Tables I, II, and III together with pertinent data. Although most of the reactions proceeded smoothly, it is to be noted that the best preparation of the dialkylaminoalkyl esters was by reaction of the potassium salt of **3** (R′ = H or CH_3; R = K) with the appropriate halide.

Representative compounds were submitted to a preliminary pharmacologic screen for general stimulation, depression, and autonomic activity.[1,2] None of the compounds exhibited significant activity. However, it is interesting in view of the studies of Buu-Hoï and coworkers[4] on the carcinogenic activity of large, multiple ring compounds that compound **16** exhibited a growth inhibition at a concentration of 1 μg ml in mammary carcinoma tissue.

Experimental Section[5]

All melting points (Thomas–Hoover capillary-type apparatus) are corrected. Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Ir spectra of all compounds corresponded with assigned structures. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

Materials.—Ketones were prepared by the catalytic hydrogenation of commercially available 4-substituted phenols[6] followed by chromic acid oxidation of the resultant 4-substituted cyclohexanols.[7]

3-Carbethoxy-1,2,3,4-tetrahydrocarbazole (3) (III, R = C_2H_5; R′ = H). Method A.—The previous procedure[3] was employed using PhNHNH$_2$ (108 g, 1.0 mol), 4-carbethoxycyclohexanone (170 g, 1.0 mol), and 360 g of glacial AcOH. The product, mp 94.5–96.0° [C_6H_6–petroleum ether (bp 37–54°), 1:1], amounted to 210 g (86.4%). Compounds **1–11** in Table I were synthesized in this manner. *Anal.* ($C_{15}H_{17}NO_2$) C, H.

Method B.—1,2,3,4-Tetrahydrocarbazole-3-carboxylic acid (10 g, 0.05 mol) (**1**, III, R = R′ = H) was dissolved in 500 ml of absolute EtOH and cooled to 10° and dry HCl passed into the solution at a rapid rate for 4 hr. The solution was refluxed an additional 4 hr and cooled to room temperature and an equal volume of H_2O added. The precipitate was extracted with Et_2O, washed with H_2O and saturated $NaHCO_3$ until neutral, and dried (Na_2SO_4). Evaporation under reduced pressure yielded a brown residue which distilled [bp 183–188° (0.4 mm)], 8.7 g, 71.6%. The product solidified on standing and was recrystallized to give **3**, identical with that synthesized by method A.

Method C. Oxalyl chloride (71 g, 0.56 mol) was added during 1 hr to a stirred suspension of **1** (135 g, 0.56 mol) in 1 l. of dry C_6H_6 while maintaining a constant temperature of 10°. The mixture was stirred at room temperature overnight, filtered through glass wool, and diluted to exactly 2 l. with dry C_6H_6. To a 1-l. aliquot of the acid chloride (*ca.* 61.2 g, 0.28 mol) was added 250 ml of absolute EtOH and the solution refluxed for 8 hr. Evaporation of the solvents, *in vacuo*, and distillation yielded **3**, 58 g, 85.3%. A mixture melting point with **3** from method A or B showed no depression.

3-Carbethoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (12) (III, R = C_2H_5; R′ = CH_3). Method A.—Compound **3** (12 g, 0.05 mol), dissolved in a minimum amount of DMF, was added dropwise to a stirred suspension of NaH (3 g of a 51% preparation, freed from mineral oil) in 10 ml of DMF. After the reaction subsided, MeI (7.1 g, 0.05 mol) was slowly added maintaining constant temperature. The mixture was stirred at room temperature overnight, after which it was warmed for 1 hr at 70°, cooled, poured into ice, and worked up in the usual manner. The product, a golden yellow oil [bp 157–163° (0.03 mm)], weighed 8.5 g (70.6%). Compound **14** in Table I was also prepared by this procedure. *Anal.* ($C_{15}H_{17}NO_2$) C, H, N.

Method B.—4-Carbethoxycyclohexanone (34 g, 0.20 mol) in 175 g of glacial AcOH was heated to reflux and 1-Me-1-PhNNH$_2$ (24.4 g, 0.20 mol) was added over 1 hr. The mixture was refluxed an additional hour and 75 ml of glacial AcOH, previously saturated with dry HCl, was slowly added. After 1 hr the solution developed a precipitate which did not redissolve on refluxing for 12 hr. The ppt was removed by filtration of the cooled mixture, and the filtrate poured into 500 ml of H_2O and extracted with Et_2O. The product, after the usual work-up, was distilled as in method A; yield, 37.4 g, 72.7%. Compounds **13** and **14** in Table I were also prepared by this procedure.

3-Carbethoxy-9-(3-dimethylaminopropyl)-1,2,3,4-tetrahydrocarbazole (16) (IV, R′ = $(CH_2)_3N(CH_3)_2$).—To 3 g of NaH (51%) in 10 ml of DMF was added **3** (12 g, 0.05 mol) dissolved in

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