TABLE II

Compd	Yield, %	Mp, °C	Kugelrohr distn,[a] °C (mm)	n_D (°C)	Formula	Analyses
6	72	86.0–87.5			$C_{17}H_{22}FNO_2$	C, H, N
6	67	Two forms: 58–61, 81.5–83.0			$C_{17}H_{22}FNO_2$	C, H, N
8	55		110–120 (1×10^{-3})	1.5366 (20)	$C_{19}H_{24}FNO_3$	C, H, N
9	51		117 (7×10^{-5})	1.5345 (23.5)	$C_{15}H_{22}FNO_2$	C, H, N

[a] Temperatures given are those of the air bath, at which the materials were collected.

same conditions. A small syrupy fraction was collected at 140°, which solidified upon standing. It was recrystallized from C_6H_6–petroleum ether (bp 30–60°) as white, fine prismatic needles, mp 58–61°. The second fraction was collected at 155° and recrystallized twice from C_6H_6–petroleum ether as prismatic granules, mp 81.5–83.0°. The ir spectra of the two substances in solid state (Nujol mull) were markedly different, but were superimposable in solution ($CHCl_3$): 2.9 (broad), 3.4, 5.95, 11.98 μ.

3,3-Ethylenedioxytropane (15).—A mixture of tropinone hydrobromide (**14**, 30 g, 0.136 mol), ethylene glycol (17.5 g), and PhMe (150 ml) was stirred and refluxed for 47 hr, while water plus the glycol (7 ml) was collected in a Barrett trap. After cooling, the organic layer was decanted, and the black tarry substance was dissolved in 2 *N* KOH (100 ml) and continuously extracted with Et_2O (250 ml) for 6 hr. The Et_2O extract and the PhMe layer were combined, dried, and evaporated *in vacuo*, giving the crude product as a dark liquid (31 g). Two kugelrohr distillations afforded the pure product as a colorless liquid, collected at 45–50° (air-bath temperature) and 0.02 mm, $n^{20}D$ 1.4936. *Anal.* ($C_{10}H_{17}NO_2$) C, H, N.

3,3-Ethylenedioxynortropane (16).—To a mixture of **15** (9.2 g, 50 mmol), NaOH (20 g), and H_2O (80 ml), which was cooled to −10°, was added a warm aqueous solution of $K_3Fe(CN)_6$ [98.8 g, 0.3 mol, in H_2O (170 ml)] at a rate to maintain the reaction mixture at ±3° with efficient stirring. The addition required 60 min. After stirring at room temperature for 43 hr, the mixture was continuously extracted with Et_2O (250 ml) for 72 hr. The Et_2O extract was stirred with KOH pellets for 2 hr, filtered through Celite, and evaporated *in vacuo*. Kugelrohr distillation of the red liquid residue (8 g) gave the product (7 g, 83% yield), collected at 35–40° (0.002 mm). An analytical sample was obtained by redistillation on kugelrohr, as a colorless liquid, collected at 105–110° (5 mm), $n^{19.8}D$ 1.5033. *Anal.* ($C_9H_{15}NO_2$) C, H, N.

Acknowledgments.—The authors are indebted to the Pharmacology Department of the Bristol Research Laboratories, Syracuse, N. Y., for the biological tests.

Synthesis of Compounds with Potential Central Nervous System Stimulant Activity. I. 2-Amino-2-oxazolin-4-one-5-spirocycloalkanes and 2-Amino-2-oxazolin-4-one-5-spiro(4′-piperidines)

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The known activity of many 2-amino-2-oxazolines[1,2] and 2-amino-2-oxazolin-4-ones[3–5] as CNS stimulants

(1) G. I. Poos, J. R. Carson, J. D. Rosenau, A. P. Roszkowski, N. M. Kelley, and J. McGowin, *J. Med. Chem.*, **6**, 266 (1963).
(2) Lab. Dansse, French Patent 1,426,080 (1966).
(3) L. Schmidt, *Arzneimittel-Forsch.*, **6**, 423 (1956).
(4) H. Najer and R. Giudicelli, *Bull. Soc. Chim. France*, 1231 (1961).
(5) C. F. Howell, N. Q. Quinones, and R. A. Hardy, Jr., *J. Org. Chem.*, **27**, 1679 (1962).

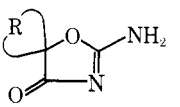
TABLE I

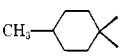
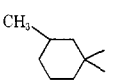
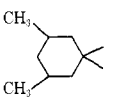
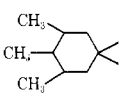
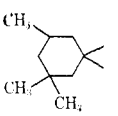
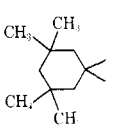
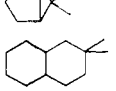
Compd[a]	Min dose causing signif inc in spont motor act., mg/kg Ip	mg/kg Oral	Approx LD_{50}, mg/kg Ip	Oral
Pemoline	10	10	500	500
1h	50	50	300	300
1j	50	100	750	750
3a	100	200	>1000	>1000

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

TABLE II

2-AMINO-2-OXAZOLIN-4-ONE-5-SPIROCYCLOALKANES

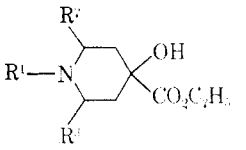


No.	R	Formula	Mp, °C[a]	Yield, %
1a		$C_6H_8N_2O_2$	188–193	15.0
b		$C_7H_{10}N_2O_2$	215–220	16.2
c		$C_8H_{12}N_2O_2$	220–225	16.0
d		$C_9H_{14}N_2O_2$	248–253	21.3
e		$C_{10}H_{16}N_2O_2$	262–266	31.2
f		$C_9H_{14}N_2O_2$	272–277	11.3
g		$C_9H_{14}N_2O_2$	249–252	30.7
h		$C_{10}H_{16}N_2O_2$	278–282	30.5
i		$C_{11}H_{18}N_2O_2$	296–302	36.4
j		$C_{11}H_{18}N_2O_2$	261–266	25.8
k		$C_{12}H_{20}N_2O_2$	318–321	27.8
l		$C_9H_{12}N_2O_2$	284–289	31.4
m		$C_{12}H_{18}N_2O_2$	248–268	13.3

[a] All compounds melted with decomposition.

TABLE III

ETHYL 4-HYDROXYPIPERIDINE-4-CARBOXYLATES

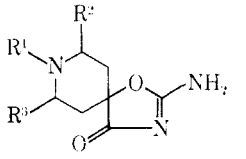


No.	R^1	R^2	R^3	Formula	Bp, °C (torr)	Mp, °C	Yield,[a] %
2a	Me	H	H	$C_9H_{17}NO_3$	86–92 (0.8)	46–47	35.3
b	Et	H	H	$C_{10}H_{19}NO_3$	77–80 (0.5)		53.2
c	*i*-Pr	H	H	$C_{11}H_{21}NO_3$	97–103 (1.0)		30.2
d	$PhCH_2$	H	H	$C_{15}H_{21}NO_3$	142–148 (0.2)		66.4
e	$Ph(CH_2)_2$	H	H	$C_{16}H_{23}NO_3$	160–164 (0.8)	56–58	58.3
f	Me	Me	Me	$C_{11}H_{21}NO_3$	111–115 (4.0)	69–73	62.1

[a] Over-all from ketone.

TABLE IV

2-AMINO-2-OXAZOLIN-4-ONE-5-SPIRO(4′-PIPERIDINES)



No.	R^1	R^2	R^3	Formula	Mp, °C[a]	Yield, %
3a	Me	H	H	$C_8H_{13}N_3O_2$	257–261	38.2
b	Et	H	H	$C_9H_{15}N_3O_2$	246–250	37.1
c	*i*-Pr	H	H	$C_{10}H_{17}N_3O_2$	239–244	35.5
d	$PhCH_2$	H	H	$C_{14}H_{17}N_3O_2$	225–229	50.3
e	$Ph(CH_2)_2$	H	H	$C_{15}H_{19}N_3O_2$	253–258	47.7
f	Me	Me	Me	$C_{10}H_{17}N_3O_2$	293–298	4.5

[a] All compounds melted with decomposition.

and anorectic agents led us to synthesize a series of 5-spiro-substituted 2-amino-2-oxazolin-4-ones.

With the exception of 2-amino-3,8-diazaspiro[4.5]-dec-2-en-4-one (**3g**) which was obtained by hydrogenolysis of the N-benzyl derivative **3d**, the spiro compounds were prepared by reaction of guanidine with the ethyl ester of the appropriate hydroxy acid.[6,7]

Those hydroxy acids which were not commercially available were prepared from the corresponding ketones by acid hydrolysis of the cyanohydrins.

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. Evidence of CNS stimulation was seen with compounds **1h**, **1j**, and **3a**. In Table I the potency and toxicity of these three compounds are compared with similar data obtained for 2-amino-5-phenyl-2-oxazolin-4-one (pemoline). The remaining compounds were weak CNS depressants and generally nontoxic at doses below 1 g/kg. None of the compounds showed significant anorectic activity in rats.

Experimental Section

All melting points were determined with a Thomas–Hoover capillary apparatus and are corrected. 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. Ir spectra were determined by Mr. A. J. Kammer with a Perkin-Elmer 521 grating spectrometer. Where ν_{max} values are given for groups of compounds, the absorptions in the region 1600–1800 cm^{-1} for each compound within the group were within ±5 cm^{-1} of the given value. At higher frequencies ν_{max} for each compound was within ±20 cm^{-1} of the given value.

2-Amino-2-oxazolin-4-one-5-spiroalkanes (1a–m).—A solution of the appropriate 1-hydroxycycloalkanecarboxylic acid[8] (10.0 g) and *p*-toluenesulfonic acid (0.05 g) in EtOH (100 ml) was refluxed for 8 hr. The solution was cooled and concentrated at reduced pressure, and the residue was dissolved in ether (100 ml). The Et_2O solution was washed [10% aqueous Na_2CO_3 (20 ml), H_2O (two 20-ml portions)], dried (Na_2SO_4), and concentrated at reduced pressure. The hydroxy esters were obtained in 70–90% yield and had ν_{max} 3520 (OH) and 1720 (C=O) cm^{-1} (7% solutions in $CHCl_3$).

The ethyl 1-hydroxycycloalkanecarboxylate (0.1 mole) was refluxed with guanidine hydrochloride (9.56 g, 0.1 mole), KOH (5.61 g, 0.1 mole), and EtOH (100 ml) for 1 hr. The mixture was cooled, diluted with H_2O (400 ml), and adjusted to pH 7 with AcOH. The white crystals which deposited were collected, washed [H_2O (two 40-ml portions), Et_2O (three 40-ml portions)], and recrystallized (EtOH). The 2-amino-2-oxazolin-4-ones thus obtained (Table II) had ν_{max} 3250, 3050 (NH), 1720 (sharp C=N), and 1660 (C=O) cm^{-1} (Nujol), and analyzed correctly (C, H, N).

Ethyl 4-Hydroxypiperidine-4-carboxylates (2a–f).—The appropriately substituted 4-piperidone (50.0 g) and acetone cyanohydrin (200 ml) were allowed to remain at 25° for 2 days, during which time white crystals of the piperidone cyanohydrin were deposited. The crystals were collected and dried at 25° and 1 mm for 6 hr. The cyanohydrins had ν_{max} 3570, 3415 (OH), and 2230 (C≡N) cm^{-1} (7% in $CHCl_3$).

The cyanohydrin (0.2 mole) was refluxed with concentrated HCl (100 ml) for 1 hr. The solution was concentrated at reduced pressure, the residue was extracted with boiling *i*-PrOH (500 ml), and the hot solution was filtered. The filtrate was cooled and concentrated at reduced pressure to give the hydroxy acid hydro-

(6) W. Traube and R. Ascher, *Ber.*, **46**, 2077 (1913).

(7) H. Najer, R. Giudicelli, E. Joannic-Voisinet, and M. Joannic, *Bull. Soc. Chim. France*, 1226 (1961).

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

chloride as a white solid, ν_{max} 3320 (OH), 1720 (C=O) cm^{-1} (Nujol).

The crude hydroxy acid hydrochloride was refluxed with *p*-toluenesulfonic acid (0.15 g) and EtOH (300 ml) for 16 hr. The solution was concentrated at reduced pressure and the residue was treated with 10% aqueous Na_2CO_3 (200 ml). The H_2O solution was extracted with $CHCl_3$ (three 250-ml portions), the combined extracts were washed with H_2O (100 ml), dried (Na_2SO_4), and concentrated at reduced pressure to a clear liquid. The ethyl 4-hydroxypiperidine-4-carboxylates (Table III) were purified by distillation and had ν_{max} 3520 (OH) and 1715 (C=O) cm^{-1} (7% in $CHCl_3$), and analyzed correctly (C, H, N).

2-Amino-2-oxazolin-4-one-5-spiro(4′-piperidines) (3a–f).—A solution of Na (2.30 g, 0.1 g-atom) in EtOH (145 ml) was added to a solution of guanidine hydrochloride (9.56 g, 0.1 mole) in EtOH (45 ml). The precipitated NaCl was removed by filtration and a solution of the ethyl 4-hydroxypiperidinecarboxylate (0.1 mole) in EtOH (50 ml) was added. The solution was refluxed for 1 hr and cooled. The white precipitate obtained was filtered, the filtrate was concentrated at reduced pressure, and the residue was treated with EtOH (20 ml). A further quantity of white solid was obtained. This material was combined with the precipitate and recrystallized from EtOH to give the required product (Table IV). All of the compounds (**3a–f**) had ν_{max} 3150 (NH), 1725 (sharp, C=N), and 1650 (C=O) cm^{-1} (Nujol) and analyzed correctly (C, H, N).

2-Amino-3,8-diazaspiro[4.5]dec-2-en-4-one (3g).—2-Amino-8-benzyl-3,8-diazaspiro[4.5]dec-2-en-4-one (**3d**, 5.20 g, 0.02 mole) was dissolved in ethylene glycol monomethyl ether (100 ml) and hydrogenated over 5% Pd–C (1.0 g) at 2 atm of pressure and 25°. Uptake of H_2 was complete after 0.25 hr but the reaction was continued for a further 0.5 hr. The catalyst was removed by filtration and the filtrate was concentrated at reduced pressure to *ca.* 25 ml. The product was obtained as a white crystalline precipitate, collected, washed (Et_2O, 25 ml), and dried; 3.30 g (97.2% yield); mp 313–317° (from EtOH); ν_{max} 3260, 3125, (NH), 1715 (sharp, C=N), and 1625 (C=O) cm^{-1}; analyzed correctly (C, H, N).

Acknowledgment.—We are grateful to Mrs. I. M. Cole for the biological data and to Dr. C. M. Lee and Mr. B. W. Horrom for helpful discussions.

N-Aminonormorphine[1a]

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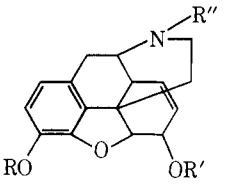
In the course of a study of centrally acting emetics, a sample of N-aminonormorphine (**1**) was required; a search of the literature did not reveal that this compound has been reported. Attempts to utilize a Raschig hydrazine synthesis[2] between chloramine and normorphine or norcodeine were unsuccessful. Schöpf and coworkers[3] had reduced N-nitrosopiperidine derivatives to N-amino systems with LAH, and Neurath and Duenger[4] had used this reagent to convert N-nitrosonor tobacco alkaloids to the hydrazine derivatives. However, treatment of N-nitrosonormorphine (**2**) and N-nitroso-O,O′-diacetylnormorphine (**3**) with LAH did not result in identifiable materials. Similar reduction of N-nitrosonorcodeine (**5**) gave a low yield of impure N-aminonorcodeine (**6**) which could be characterized



1, R = R′ = H; R″ = NH_2
2, R = R′ = H; R″ = NO
3, R = R′ = Ac; R″ = NO
4, R = R′ = Ac; R″ = NH_2
5, R = Me; R′ = H; R″ = NO
6, R = Me; R′ = H; R″ = NH_2
7, R = Me; R′ = H; R″ = N=$(CH_3)_2$

only as its acetone adduct **7**. Pure N-aminonorcodeine was prepared by a literature method:[5] Zn–AcOH reduction of N-nitrosonorcodeine (**5**). This method also permitted conversion of N-nitroso-O,O′-diacetylnormorphine (**3**) to its N-amino derivative (**4**). Zn–AcOH treatment of N-nitrosonormorphine (**2**) gave a complex mixture of unidentifiable products; however, acid-catalyzed hydrolysis of the ester links of N-amino-O,O′-diacetylnormorphine (**4**) permitted isolation of **1** in good yield. It appears that these N-aminomorphine derivatives undergo deep-seated decomposition in the presence of base.

Pharmacology.—N-Amino-O,O′-diacetylnormorphine (**4**), N-aminonormorphine hydrochloride (**1**), and N-aminonorcodeine hydrochloride (**6**) were dissolved in water and administered subcutaneously to Swiss–Webster male mice, weighing 17–20 or 30–35 g, and analgetic activity was tested by the hot plate method of Eddy and Leimbach.[6] Ten mice were used for each group and tested just prior to giving the drug and after 30 and/or 60 min. The reaction times of animals given the test drugs were compared with reaction times of mice given morphine sulfate, 7.5 mg/10 ml per kg.

Mice injected with **4** (28.4 mg/10 ml per kg, 60 mg/15 ml per kg, and 90 mg/20 ml per kg) showed prolongation of reaction times as compared with the control reaction times. The analgetic potency of **4** was estimated to be 0.1–0.067 times that of morphine. The mice injected with either **1** (15 mg/10 ml per kg, 30 mg/10 ml per kg, and 45 mg/10 ml per kg) or **6** (4.43 mg/1.65 ml per kg and 26.5 mg/10 ml per kg) showed no significant differences in reaction times between the control and the "after drug" periods.

Experimental Section[7]

N-Aminonorcodeine (6) was prepared in 40% yield by the method of von Braun,[5] mp 172.5–174°; lit.[5] mp 174°.

Acetone N-Aminonorcodeinyl Hydrazone (7)—Compound **6** (1.7 g, 0.0056 mole) was refluxed with 10 ml of Me_2CO for 0.25

(1) (a) This investigation was supported in part by Grant NB-04349, National Institute of Neurological Diseases and Blindness. (b) To whom all correspondence should be addressed.

(2) L. F. Audrieth and L. H. Diamond, *J. Amer. Chem. Soc.*, **76**, 4869 (1954); L. H. Diamond and L. F. Audrieth, *ibid.*, **77**, 3131 (1955).

(3) V. C. Schöpf, H. Arm, and H. Koop, *Justus Liebigs Ann. Chem.*, **712**, 168 (1968).

(4) G. Neurath and M. Duenger, *Beitr. Tabakforsch.*, **3**, 339 (1966).

(5) J. von Braun, *Ber.*, **49**, 761 (1916).

(6) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953).

(7) Melting points were determined on a Thomas–Hoover apparatus in open capillaries and are corrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated by the symbols of the elements, the analytical results obtained for those elements were within ±0.4% of the theoretical values.