analyses are indicated only by symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values.

(+)-3-Methoxy-6α-hydroxy-4,5α-epoxy-Δ⁷-N-methylisomorphinan (*trans*-**Codeine**) (II).—A mixture of I (2.8 g), AcOK (7 g), H_2O (2 ml), and DMF (40 ml) was refluxed for 23 hr and evaporated *in vacuo*. The residue was dissolved in H_2O, basified with NH_4OH, extracted with $CHCl_3$, dried, and evaporated. Conversion of the residue into the picrate in EtOH gave II·picrate (1.26 g, 53.2%), mp 244–245° dec (from Me_2CO–EtOH). This was identical with an authentic sample.

3-Methoxy-6-oxo-4,5α-epoxy-N-methylisomorphinan (*trans*-**Dihydrocodeinone**) (**IV**) **Picrate**.—A mixture of III (from 0.35 g of the hydrochloride), $Al(O\text{-}t\text{-}Bu)_3$ (0.35 g), benzophenone (1.7 g), and C_6H_6 (5 ml) was refluxed for 20 hr under N_2. The mixture was acidified with dil H_2SO_4, the H_2O layer was separated, basified with 10% NaOH, extracted with $CHCl_3$, dried, and evaporated. The residue was chromatographed on Al_2O_3 and eluted with C_6H_6–Et_2O (9:1). The eluate was converted into the picrate and recrystallized from EtOH–Me_2CO to give IV·picrate (0.06 g, 11%), mp 220–230° dec, ir, 1723 cm^{-1}. *Anal.* ($C_{24}H_{24}N_4O_{10}$) C, H, N. The free base was crystallized from Et_2O, mp 98–99°, identical with an authentic specimen. (mp, nmr, and tlc).

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Analeptics. 1-Formimidoylindolines

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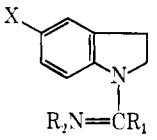
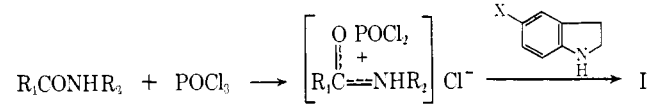
Although the value of analeptics in the treatment of CNS depression is uncertain,[2] bemegride has been generally recognized as useful in treating patients with severe barbiturate intoxication. In the course of investigation of amidines as medicinals, we discovered that certain 1-formimidoylindolines (I) have analeptic effects comparing favorably with bemegride. We wish to report the results of analeptic screening on these compounds. In I, X represents H, Ac, and NO_2 groups;



(I)

and R_1, R_2 represent H, alkyl, and alkylamino groups. R_1 and R_2 may join together to form a cyclic moiety.

These compounds were synthesized by the action of an amide–$POCl_3$ adduct[3] on an appropriate indoline. Their physical constants are tabulated in Table I.



Biological Data and Correlations. Analeptic Activity.—With few exceptions, the compounds listed in this report were screened for analeptic activity by both: (1) the antagonism of pentobarbital in cats and (2) the antagonism of chloral hydrate in mice.

Pentobarbital Antagonism.—Cats of either sex, previously equipped with chronically indwelling iv cannulas, were individually placed into an observation cubicle (60 × 60 × 60 cm) and allowed to move about freely at the end of a leash. A dose of 12 mg/kg of aq pentobarbital sodium was infused at the rate of approximately 2 mg/kg per min *via* tubing contained in the leash. One-half hour after the start of this infusion the animals were in a stage of light anesthesia characterized by unconsciousness, immobility, relaxed nictitating membranes, and irresponsiveness to handling, but active pinnal, palpebral, and paw-pinch withdrawal reflexes. At this time the test compound in aq solution was infused in a concentration of 10 mg/ml and at a rate of 0.2 ml/min until (a) consciousness was restored, (b) a total of 25 mg/kg of test compound was administered, or (c) mounting toxicity interfered. Recovery of consciousness was recognized by the presence of alertness to surroundings, including the ability of the eyes to follow the movement of a nearby object, and attempts to change to an upright position. Results are presented in Table I. All compounds were tested in two cats.

Chloral Hydrate Antagonism.—Groups of 20 fasted, male, albino mice were administered an oral dose of 20 mg/kg of the test compound followed immediately by an ip dose of 300 mg/kg of chloral hydrate. If the duration of the ensuing hypnosis was 50% or less of that produced in saline-treated controls additional doses were administered and the dose which would reduce sleeping time by 50% was determined graphically from a dose–response curve. Results appear in Table I. Three compounds (**8**, **13**, and **17**) approximated the analeptic potency of bemegride in this test.

Discrepancies between the results of these two tests may result from the chemical difference in the hypnotics themselves as well as the species in which they are employed. In addition, the infusion technique used in cats requires that the test compound be prompt in exerting its analeptic effect before its toxic actions intervene. Indeed, convulsant stimulation is a common toxic manifestation in this series and in some cases analepsis may actually have been a result of it.

Extended testing with the more active compounds demonstrated that motor stimulation is not a necessary concomitant of analeptic action. According to an activity cage technique using rats,[4] **2** and **8** were inactive, **6** and **13** were depressant, and **17** was mildly stimulant. Bemegride is mildly depressant to motor activity, although amphetamine is markedly stimulant.

Other Tests. Analgesia.—Thirteen compounds were screened for analgetic properties in mice by means of the phenylquinone writhing test.[5] Compounds **6**, **9**, **13**,

(1) To whom inquiries should be addressed.
(2) F. Hahn, *Pharmacol. Rev.*, **12**, 447 (1960).
(3) H. Brederick and K. Brederick, *Chem. Ber.*, **94**, 2278 (1961).
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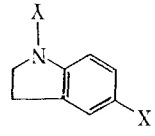
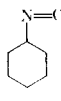
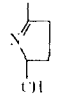
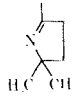
TABLE I
1-FORMIMIDOYLINDOLINES



No.	X	Y	% yield	Recrystn solvent	Mp, °C	Formula	Analyses	Pento-barbital antagonism, cat, iv	Chloral hydrate antagonism, mouse ED_{50} (mg/kg) ip
1	H	$-CH=NCH_3$	11.3	EtOH	282–283	$C_{10}H_{12}N_2 \cdot HCl$	C, H, Cl, N	A[b]	Inactive at 20
2	H	$-CH=NCH(CH_3)_2$	23.6	EtOH–Et_2O	213.5–215	$C_{12}H_{16}N_2 \cdot HCl \cdot 0.5H_2O$	C[c] H, Cl, N	A	>20
3	H	$-C(=CH_2)-N-CH_3$	35.6	EtOH–Et_2O	228.5–230.5	$C_{11}H_{14}N_2 \cdot HCl$	C, H, Cl, N	A	>20
4	H	$-CNHCH_2$ (=) NCH_3	30.2	Heptane	142–143	$C_{11}H_{12}N_2$	C, H, N	A	>20
5	H		28.0	EtOH–Et_2O	221–222	$C_{15}H_{20}N_2 \cdot HCl$	C, H, Cl, N	W[c]	Inactive at 20
6	H		21.5	EtOH–Et_2O	265–266.5	$C_{12}H_{14}N_2 \cdot HCl$	C, H, Cl, N	A	>50
7	H		31.2	EtOH–Et_2O	212–214	$C_{12}H_{16}N_2 \cdot HCl$	C, H, Cl, N	A	>20
8	H		41.0	EtOH–Et_2O	250–251	$C_{13}H_{16}N_2 \cdot HCl$	C, H, Cl, N	A	15
9	H		26.4	EtOH–Et_2O	233.5–235.5	$C_{14}H_{16}N_2 \cdot HCl$	C, H, Cl, N	A	Inactive at 20
10	H		16.0	EtOH–Et_2O	224–226	$C_{14}H_{18}N_2 \cdot HCl$	C, H, Cl, N	W	Inactive at 20
11	H		38.0	EtOH–Et_2O	199–201.5	$C_{12}H_{14}N_2S \cdot HCl$	C, H, Cl, N	A	Inactive at 20
12	H		5.5	EtOH	325–327.5	$C_{11}H_{13}N_3 \cdot HCl$	C, H, Cl, N	A	Inactive at 20
13	CH_3CO		17.6	(i-$Pr)_2O$	124.5–126	$C_{14}H_{16}N_2O$	C, H, N	A	10

14	CH_3CO		13.1	EtOH	250.5–252.5	$C_{16}H_{20}N_2O \cdot HCl$	C, H, Cl, N	A	>20
15	NO_2	$-CH{=}NCH_3$	30.7	EtOH	244–246.5	$C_{10}H_{11}N_3O_2 \cdot HCl$	C, H, Cl, N	A	Inactive at 20
16	NO_2		42.5	EtOH	281–282	$C_{12}H_{13}N_3O_2 \cdot HCl$	C, H, Cl, N	A	Inactive at 20
17	NO_2		22.2	EtOH	268.5–270.5	$C_{14}H_{17}N_3O_2 \cdot HCl$	C, H, Cl, N	W	20
dl-Amphetamine sulfate								A	1.3
Bemegride								A	14.4

[a] Based on analytically pure sample. Many of these experiments were conducted only once and the optimal conditions were not established. [b] A = active. [c] W = weakly active. [d] C: calcd, 61.66; found, 62.21.

15, and bemegride had ED_{50}'s of 10 mg/kg sc or less, **1, 3, 7, 10, 11, 12, 14,** and **16** had ED_{50}'s of 11 to 35 mg/kg sc, and **4** was inactive. Further testing in the rat of the 4 most active compounds by the tail flick method[6] and the $AgNO_3$ inflamed joint test[7] indicated that none of these compounds possessed significant analgetic properties.

The results of analeptic screening show that **8** and **13** compare favorably with bemegride as analeptics, and warrant further evaluation in the CNS area.

Experimental Section

1-Formimidoylindolines.—A solution of equimolar amounts of indoline and appropriate amide in 1,2-dichloroethane [250 ml (0.1 m)] was treated dropwise with an equimolar solution of $POCl_3$ in 1,2-dichloroethane [50 ml (0.1 m)] over a period of 0.5–1 hr. The mixture, after being stirred for 15 hr, was poured onto crushed ice, and made strongly basic with 20% NaOH with stirring. The organic layer was separated and extracted with dilute HCl. The acid solution was made basic with 20% NaOH and extracted again (Et_2O). The extract was concentrated to obtain the crude product. The HCl salt was prepared in the usual manner and recrystallized from appropriate solvent as shown in Table I.

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Synthesis of Some Local Anesthetics

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It has been found by many workers[1,2] that the essential structure requirements for a local anesthetic are a lipolytic end containing an aromatic nucleus, a hydropilic end consisting of a tertiary amino group, and an intermediate alkyl or substituted alkyl chain. Compounds having a dialkylamino alkylamino group connected to an aromatic or heterocyclic nucleus as a lipolytic moiety confer greater activity and less toxicity. Therefore, it was thought worthwhile to synthesize some pyridine-2-aminoacetyl-2-aminobenzothiazole and *N*,*N*-diethylanilino-*p*-aminoacetyl-2-aminobenzothiazole derivatives, by condensation of chloroacetyl chloride with different 2-aminobenzothiazoles followed by treatment with 2-aminopyridine and *p*-amino-*N*,*N*-diethylaniline, respectively.

Experimental Section

Different 2-aminobenzothiazoles were prepared according to Hugershoff.[3] Chloroacetyl-2-aminobenzothiazoles were prepared by known methods.[4]

Pyridine-2-aminoacetyl-2-aminobenzothiazole.—2-Chloroacetylaminobenzothiazole (5 g) dissolved in EtOH (30 ml) was added to 2-aminopyridine (3 g) dissolved in EtOH (20 ml) and the reac-

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