cone and associates for the microanalyses, Mr. C. Pidacks and staff for the partition chromatography, and Mr. W. Fulmor and associates for the infrared and nmr spectra. In particular, we gratefully acknowledge the assistance given by Mr. G. O. Morton in his interpretation of the nmr spectra. We also thank Dr. P. J. Kohlbrenner and coworkers for preparation of some of the intermediates and Dr. A. C. Osterberg, Dr. E. Greenblatt, and associates for the pharmacological testing results.

Central Nervous System Depressants. IV. 2-Aminoalkyl-1,2-dihydro-3H-imidazo[1,5-*a*]indol-3-ones[1]

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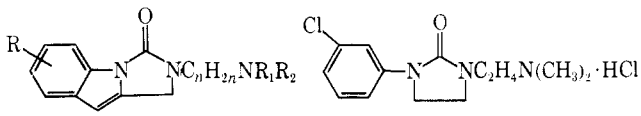
The synthesis of 2-aminoalkyl-1,2-dihydro-3H-imidazo[1,5-*a*]indol-3-ones is described. A number of these compounds have moderate CNS depressant activity.

The present publication describes the preparation and properties of a series of 2-aminoalkyl-1,2-dihydro-3H-imidazo[1,5-*a*]indol-3-ones (I). These compounds may be considered cyclic analogs of imidoline, 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinone hydrochloride (II), previously described as a potent CNS depressant agent in laboratory animals.[2]

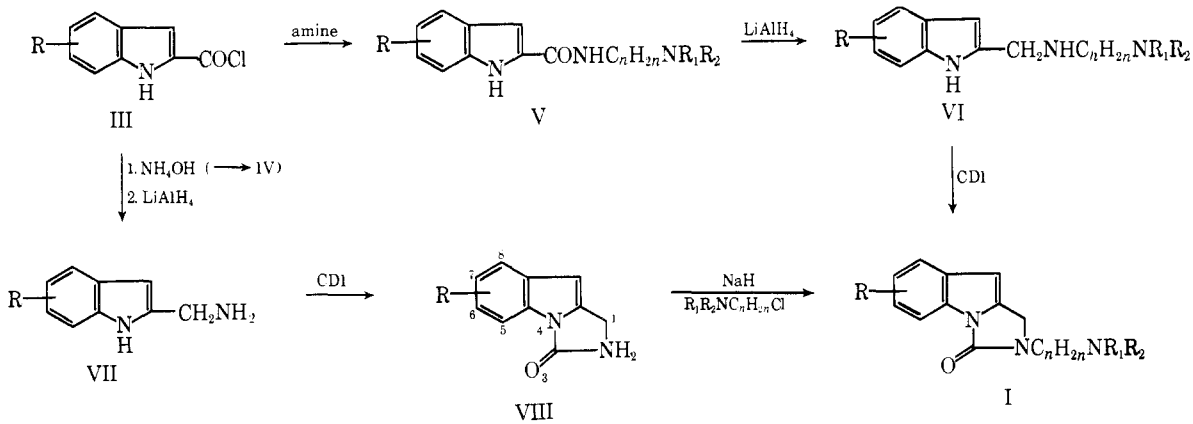


I II

The compounds were prepared as illustrated in Chart I. The 2-indolecarbonyl chlorides (III) were prepared by treating the appropriate acid with thionyl chloride in ether. They were converted to the amides (IV and V), which were reduced with $LiAlH_4$ to the 2-aminomethylindoles (VI and VII). In most experiments, a nearly quantitative yield of the crude aminomethyl derivative was obtained. A portion was removed for characterization (Table III), and the remainder was treated with N,N′-carbonyldiimidazole (CDI) in order to cyclize to the 1,2-dihydro-3H-imidazo[1,5-*a*]indol-3-ones (I and VIII). The 2-aminoalkyl-1,2-dihydro-3H-imidazo[1,5-*a*]indol-3-ones (I) were also prepared by alkylation of VIII. The yields in the cyclization step (VI → I and VII → VIII) showed considerable variation and products were often difficult to purify. The failure to give high yields may be attributed to the low nucleophilicity of the indole nitrogen. Later studies indicated that better yields (than those reported) can probably be obtained by heating the crude reaction products in ethanol or dimethyl sulfoxide for a short period of time before work-up.

The ir spectra of the 1,2-dihydro-3H-imidazo[1,5-*a*]-indol-3-ones have a characteristic C=O band at 5.75-5.78 μ, irrespective of substituents. Those compounds with a 2-H atom also have an N-H band at 3.1 μ.

CHART I



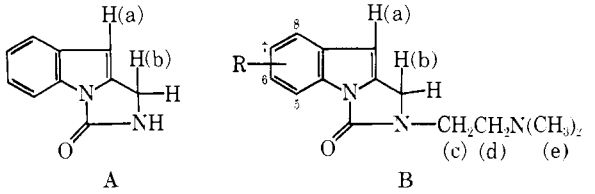
The important nmr characteristics of selected compounds are described in Table I. As would be expected, the protons (e) on the $N(CH_3)_2$ group are characterized by a singlet (6 H) at δ 2.25. The protons (d) of the CH_2 adjacent to the basic N atom are found as a triplet at δ 2.5, while those (c) of the CH_2 adjacent to the less basic N atom are further downfield at δ 3.50. The protons (b) of the remaining CH_2 group are at δ 4.42 for B. These are doublets (J = 2 cps) indicating long-range splitting by the single proton a. The CH_2 group (b) in A appears as a broad singlet. The fact that this does not appear as a doublet may be explained by use of a different solvent or by smearing caused by the N-H. The position of the signal for the single proton a is at

(1) Previous paper in this series: W. B. Wright, Jr., *J. Med. Chem.*, **11**, 1161 (1968).

(2) (a) W. B. Wright, Jr., H. J. Brabander, B. A. Hardy, Jr., and A. C. Osterberg, *ibid.*, **9**, 852 (1966); (b) W. B. Wright, Jr., and H. J. Brabander, U. S. Patent 3,196,152 (July 20, 1965).

Table I

Nmr Characteristics of the 1,2-Dihydro-3H-imidazo[1,5-*a*]indol-3-ones[a]



	Nmr, δ — Proton				
Compd	a	b	c	d	e
A	6.47 s	4.55 s			
B, R = H	6.27 s	4.42 d	3.50 t	2.50 t	2.25 s
B, R = 6-Cl	6.20 s	4.42 d	3.50 t	2.50 t	2.25 s
B, R = 7-Cl	6.20 s	4.42 d	3.50 t	2.50 t	2.25 s

[a] Sample A was dissolved in DMSO-d_6 and samples B were in $CDCl_3$. Chemical shifts are given in ppm (δ) relative to TMS (internal standard). Signals are designated as follows: s, singlet; d, doublet; t, triplet.

δ 6.47 in A and varies from δ 6.20–6.27 depending upon the substituent in the aromatic ring in B. This appears as a broadened single peak, which is presumably a triplet because of its splitting by b.

Pharmacological Results.—The 2-aminoalkyl-1,2-dihydro-3H-imidazo[1,5-*a*]indol-3-ones (I) were screened for CNS depressant activity by previously described methods.[2] The most interesting compounds (Table IV, **38**, **41**, **42**, **45**, **47**) contained a Cl atom in the aromatic ring and a two-carbon alkylene chain. These compounds were less active as motor depressants than the analogous 1-aminoethyl-3-(*m*-chlorophenyl)-2-imidazolidinones[2] and 2-aminoethyl-3,3a,4,5-tetrahydroimidazo[1,5-*a*]quinolin-1(2H)-ones.[1] However, the spread between the motor depressant dose (MDD_{50}) and the rod-walking dose (RWD_{50}) was narrow and these compounds were generally more active than the above in their ability to reduce rod-walking ability (RWD_{50}).

Experimental Section

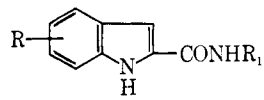
The preparation of the compounds is described below using general procedures when possible. Physical properties and important variations in these procedures are given in Tables II–IV. The ir spectra were determined on a Perkin-Elmer spectrophotometer (Model 21). Melting points were measured on a Mel-Temp apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

2-Indolecarboxamide Derivatives (Table II). General Procedure A.—A solution or suspension of 0.1 mole of the indolecarboxylic acid derivative in 200 ml of Et_2O was cooled and a solution of 30 ml of $SOCl_2$ in 100 ml of Et_2O was added. The mixture was stirred for 1 hr with cooling and then for 5–18 hr without cooling. The Et_2O was removed using a rotating evaporator. Et_2O was added and the mixture was again concentrated. This was repeated once more. The crystalline residue was stirred with about 300 ml of Et_2O and any insoluble material was filtered off and discarded. Aliquots of the Et_2O layer were added dropwise with cooling to a solution of 2 molar equiv of the amine (or excess aqueous NH_3) in about 10 parts of Et_2O. The mixture was left at room temperature overnight and then treated with 1 *N* NaOH. The product was filtered off (if insoluble) or extracted into Et_2O and recovered. It was recrystallized from a suitable solvent.

2-(Aminomethyl)indole Derivatives (Table III). General Procedure B.—A solution or suspension of 0.03 mole of the 2-indolecarboxamide derivative in dry THF was added with stirring and cooling to a mixture of 2.28 g (0.06 mole) of $LiAlH_4$ and 30 ml of THF. The reaction mixture was heated at reflux temperature for 6 hr, cooled, and treated with 16 ml of 6.5% NaOH. The precipitate was filtered off and washed with THF. The mother liquor was concentrated and the residue was re-

Table II

Indolecarboxamide Derivatives[a]



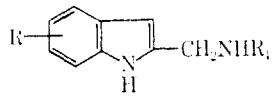
No.	R	R_1	Yield, %	Crystn solvent	Mp, °C	Formula	Analyses
1	H	H	37	50% EtOH	236–238[b]	$C_9H_8N_2O$	C, H, N
2	4-Cl	H	52	50% EtOH	181–183	$C_9H_7ClN_2O$	C, H, Cl, N
3	5-Cl	H	70	50% EtOH	236–238	$C_9H_7ClN_2O$	C, H, Cl, N
4	6-Cl	H	57	50% EtOH	210–212	$C_9H_7ClN_2O$	C, H, Cl, N
5	H	$(CH_3)_2NC_2H_4$	40	EtOH	142–144	$C_{13}H_{17}N_3O$	C, H, N
6	H		87	EtOAc	163–165	$C_{15}H_{19}N_3O$	C, H, N
7	4-Cl		66	EtOAc	177–179	$C_{15}H_{18}ClN_3O$	C, H, Cl, N
8	5-Cl	$(CH_3)_2NC_2H_4$	63	C_6H_6	209–210	$C_{13}H_{16}ClN_3O$	C, H, Cl, N
9	5-Cl		40	EtOAc	219–221	$C_{16}H_{20}ClN_3O$	C, H, Cl, N
10	5-CH_3O	$(CH_3)_2NC_2H_4$	43	C_6H_6	168–169	$C_{14}H_{19}N_3O_2$	C, H, N
11	6-Cl	$(CH_3)_2NC_2H_4$	68	Me_2CO	185–187	$C_{13}H_{16}ClN_3O$	C, H, Cl, N
12	6-Cl		70	EtOH	220–222	$C_{15}H_{18}ClN_3O$	C, H, Cl, N
13	6-Cl		74	EtOH	203–205	$C_{16}H_{20}ClN_3O$	C, H, Cl, N
14	6-Cl		75	EtOH	229–231	$C_{15}H_{18}ClN_3O_2$	C, H, Cl, N
15	6-Cl	$(CH_3)_2NC_3H_6$	69	Me_2CO	171–173	$C_{14}H_{18}ClN_3O$	C, H, Cl, N

[a] Prepared by Procedure A. [b] Lit.[3] mp 234.5–235.5°.

(3) E. Leete, L. Marion, and I. D. Spenser, *Can. J. Chem.*, **33**, 405 (1955).

TABLE III

2-(AMINOMETHYL)INDOLE DERIVATIVES[a]

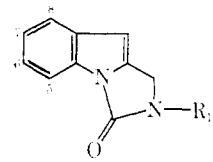


No.	R	R_1	Yield, %	Salt	Mp, °C	Formula	Analyses
16	H	H	66		70–72[b]	$C_9H_{10}N_2$	C, H, N
17	4-Cl	H	90		180–183[c]	$C_9H_9ClN_2$	C, H, Cl, N
18	5-Cl	H	52		86–87[d]	$C_9H_9ClN_2$	C, H, Cl, N
19	6-Cl	H	79		100–102[d]	$C_9H_9ClN_2$	C, H, Cl, N
20	H	$(CH_3)_2NC_2H_4$	50	2HCl	204–205[c]	$C_{13}H_{21}Cl_2N_3$	C, H, Cl, N
21	H		71	2HCl	218–220[c]	$C_{15}H_{23}Cl_2N_3$	C, H, Cl, N
22	4-Cl		55[e]	2HCl	213–215[c]	$C_{15}H_{22}Cl_3N_3$	C, H, Cl, N
23	5-Cl	$(CH_3)_2NC_2H_4$	58		[f]	$C_{13}H_{18}ClN_3$	C, H, Cl, N
24	5-Cl		69	2HCl	234–236[c]	$C_{16}H_{24}Cl_3N_3$	C, H, Cl, N
25	5-CH_3O	$(CH_3)_2NC_2H_4$	40		[g]	$C_{14}H_{21}N_3O$	
26	6-Cl	$(CH_3)_2NC_2H_4$	56		[h]	$C_{13}H_{18}ClN_3$	C, H, Cl, N
27	6-Cl		65		[i]	$C_{15}H_{20}ClN_3$	
28	6-Cl		95	2HCl	235–237[c]	$C_{16}H_{24}Cl_3N_3$	C, H, Cl, N
29	6-Cl		95	2HCl	217–219[c]	$C_{15}H_{22}Cl_3N_3O$	C, H, Cl, N
30	6-Cl	$(CH_3)_2NC_3H_6$	49[e]	2HCl	205–207[c]	$C_{14}H_{22}Cl_3N_3$	C, H, Cl, N

[a] Compounds prepared by procedure B. [b] Recrystallized from C_6H_6–C_6H_{12}. [c] Recrystallized from EtOH. [d] Recrystallized from C_6H_6. [e] Reduction was incomplete at 6 hr and crude product was again reduced for 20 hr. [f] Bp 170–180° (0.05 mm). [g] Bp 180° (0.08 mm) dec. Used in next step without analysis. [h] Bp 162–168° (0.08 mm). [i] Used in next step without purification.

TABLE IV

1,2-DIHYDRO-3H-IMIDAZO[1,5-*a*]INDOL-3-ONES[a]



No.	R	R_1	Yield, %	Salt	Mp, °C	Cryst solvent	Formula	Analyses
31	H	H	81[b]		226–228[c]	EtOAc	$C_{10}H_8N_2O$	C, H, N
32	6-Cl	H	62		215–217	EtOAc	$C_{10}H_7ClN_2O$	C, H, Cl, N
33	7-Cl	H	36		227–229[d]	EtOAc	$C_{10}H_7ClN_2O$	C, H, Cl, N
34	8-Cl	H	85		234–236	EtOAc	$C_{10}H_7ClN_2O$	C, H, Cl, N
35	7-Cl		43[e]	HCl	200–203	MeOH	$C_{16}H_{19}Cl_2N_3O$	C, H, Cl, N
36	H	$(CH_3)_2NC_2H_4$	43[f]	Maleate	182–184	EtOH	$C_{18}H_{21}N_3O_5$	C, H, N
37	H		15	HCl	240–242	EtOH	$C_{16}H_{20}ClN_3O$	C, H, Cl, N
38	6-Cl	$(CH_3)_2NC_2H_4$	45	HCl	246–249	EtOH	$C_{14}H_{17}Cl_2N_3O$	C, H, Cl, N
39	6-Cl	$C_2H_5(CH_3)NC_2H_4$	20[g]	HCl	214–216	EtOH	$C_{15}H_{19}Cl_2N_3O$	C, H, Cl, N
40	6-Cl	$(C_2H_5)_2NC_2H_4$	35[g]	HCl	194–196	EtOH-Et_2O	$C_{16}H_{21}Cl_2N_3O$	C, H, Cl, N
41	6-Cl		68	HCl	243–245	EtOH	$C_{16}H_{19}Cl_2N_3O$	C, H, Cl, N
42	6-Cl		58	HCl	269–272	EtOH	$C_{15}H_{27}Cl_2N_3O$	C, H, Cl, N
43	6-Cl		37	HCl	183–185	EtOH	$C_{16}H_{19}Cl_2N_3O_2$	C, H, Cl, N
44	7-Cl	$(CH_3)_2NC_2H_4$	41		80–81	EtOAc	$C_{14}H_{16}ClN_3O$	C, H, Cl, N
45	7-Cl		19	HCl	278–280	EtOH	$C_{17}H_{21}Cl_2N_3O$	C, H, Cl, N
46	7-CH_3O	$(CH_3)_2NC_2H_4$	35[d]	HCl	226–228	EtOH	$C_{15}H_{20}ClN_3O_2$	C, H, Cl, N
47	8-Cl	$(C_2H_5)_2NC_2H_4$	40[d,g]	HCl	166–168	EtOH-Et_2O	$C_{16}H_{21}Cl_2N_3O$	C, H, Cl, N
48	8-Cl		80		102–104	EtOH	$C_{16}H_{18}ClN_3O$	C, H, Cl, N
49	6-Cl	$(CH_3)_2NC_3H_6$	29	HCl	250–252	EtOH	$C_{15}H_{19}Cl_2N_3O$	C, H, Cl, N

[a] Prepared by procedure C unless otherwise noted. [b] Yield of crude product, mp 198–200°. This was after heating original crude product, only partly cyclized, in DMSO for 30 min before first work-up. [c] Purified by partition chromatography (heptane–methyl Cellosolve–Celite). [d] Purified by partition chromatography (heptane–MeOH–Celite). [e] Procedure E. [f] Purified by partition chromatography (heptane–EtOAc–MeOH–H_2O–Celite). [g] Procedure D.

crystallized from a suitable solvent or distilled. The hydrochloride salts were prepared by dissolving the base in EtOH or Et_2O and adding ethanolic HCl.

1,2-Dihydro-3H-imidazo[1,5-*a*]indol-3-ones (Table IV). Procedure C. Reaction of the 2-(Aminomethyl)indole with N,N'-Carbonyldiimidazole.—A solution or suspension of 0.02 mole of the dry 2-(aminomethyl)indole in 40 ml of dry THF or C_6H_6 was cooled and a solution of 3.87 g (0.022 mole) of 92% N,N'-carbonyldiimidazole in 40 ml of THF was added. The mixture was allowed to stand at room temperature for 18–20 hr and then heated on the steam bath for 1–4 hr. The solvent was distilled using a rotating evaporator and the residue was warmed with about 50 ml of H_2O. The product was filtered off and washed with H_2O (if solid) or extracted into C_6H_6. The C_6H_6 layer was washed with H_2O and concentrated. Cyclization was usually incomplete, and further purification was obtained by crystallization of the base or salt from a suitable solvent or by partition chromatography. The salts were obtained by dissolving the base in Et_2O or EtOH and adding ethanolic HCl or excess maleic acid.

Procedure D. By Aminoalkylation of the 1,2-Dihydro-3H-imidazo[1,5-*a*]indol-3-one.—A solution or suspension of 0.01 mole of the 1,2-dihydro-3H-imidazo[1,5-*a*]indol-3-one in 30 ml of diglyme was added dropwise to a suspension of 0.011 mole of 50% NaH (in mineral oil) in 20 ml of diglyme. The mixture was stirred for 30–60 min and a solution of 0.012 mole of the dialkylaminoethyl chloride in 20 ml of diglyme was added. The reaction mixture was heated at reflux temperature for 5 hr, filtered while hot, and concentrated. The residue was dissolved in dilute HCl and extracted with C_6H_6 to remove nonbasic impurities. The aqueous layer was treated with excess 5 *N* NaOH and extracted with C_6H_6. The C_6H_6 layer was washed (H_2O), dried ($MgSO_4$), and concentrated. The residue was converted to the hydrochloride salt and recrystallized from a suitable solvent.

Procedure E. 7-Chloro-2-piperidinomethyl-1,2-dihydro-3H-imidazo[1,5-*a*]indol-3-one Hydrochloride.—A mixture of 1.03 g (0.005 mole) of 7-chloro-1,2-dihydro-3H-imidazo[1,5-*a*]indol-3-one, 0.50 ml (0.005 mole) of piperidine, 0.40 ml (0.005 mole) of 37% HCHO, and 40 ml of EtOH was heated on the steam bath for 2 hr. Some insoluble material was filtered off and the mother liquor was concentrated. The residual oil was dissolved in 5 ml of EtOH, and 1.5 ml of 3 *N* ethanolic HCl was added. The precipitate was filtered off and recrystallized from MeOH.

Acknowledgment.—We wish to thank Mr. L. Brancone and associates for the microanalyses, Mr. C. Pidacks and staff for the partition chromatography, and Mr. W. Fulmor and associates for the infrared and nmr spectra. In particular, we gratefully acknowledge the assistance given by Mr. G. O. Morton in his interpretation of the nmr spectra. We also thank Dr. P. J. Kohlbrenner and co-workers for preparation of some of the 2-indolecarboxylic acids used as intermediates and Dr. A. C. Osterberg, Dr. E. Greenblatt, and associates for the pharmacological testing results.

Synthesis and Diuretic Activity of 2-Amino-4-arylamino-6-mercapto-*s*-triazines and Related Derivatives

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Arylbiguanides and CS_2 reacted in the presence of KOH to give the title compounds along with isomeric 1-aryl-2-thioammelines. The 6-mercapto-*s*-triazines were further converted to the corresponding 6-alkylmercapto and 6-hydroxy derivatives. In general, these compounds showed mild diuretic activity when fed orally to rats, while 2-amino-4-*m*-fluoroanilino-*s*-triazine and a few others showed good diuresis and natriuresis.

We have reported[2] earlier the significant diuretic, saluretic, and antikaluretic activity of 2-amino-4-*m*-chloroanilino-*s*-triazine (III, R = *m*-Cl) in rats and dogs. Unfortunately, these results could not be extrapolated to humans except in some cases of Cor pulmonale where interesting diuretic activity was noted.[3] Accordingly, our attempts were directed at the modification of the parent molecule. Since several mercapto-*s*-triazoles exhibit significant diuretic activity,[4] and the SO_2NH_2 group is degraded to mercapto in the body,[5] it seemed worthwhile to incorporate mercapto and related groups in III, in search for better diuretics. The present paper deals with the synthesis and evaluation of several 2-amino-4-arylamino-6-mercapto-*s*-triazines and related compounds.

Chemistry.—N-Phenylthioammeline was prepared by Welcher and coworkers[6] by the extension of Rathke's method[7] for thioammeline involving the condensation of dicyandiamide with ammonium thiocyanate in the presence of HCl. Recently, Kurzer and Pitchfork[8] have shown that the product obtained from phenyldicyandiamide and ammonium thiocyanate was not the 2-amino-4-anilino-6-mercapto-*s*-triazine (II, R = H) but was hexahydro-4,6-diimino-1-phenyl-*s*-triazine-2-thione, *i.e.*, 1-phenyl-2-thioammeline (I, R = H), which they prepared by the condensation of biguanide and phenyl isothiocyanate. We have studied an alternate route, *viz.*, the extension of Rackmann's method[9] for thioammeline wherein biguanide is treated with CS_2 (Scheme I).

(1) To whom the inquiries should be addressed.

(2) (a) D. J. Mehta, U. K. Sheth, and C. V. Deliwala, *Nature*, **187**, 1034 (1960); (b) K. N. Modi, C. V. Deliwala, and U. K. Sheth, *Arch. Intern. Pharmacodyn.*, **151**, 13 (1964); (c) M. H. Shah, M. Y. Mhasalkar, and C. V. Deliwala, *J. Sci Ind. Res.* (India), **19C**, 282 (1960).

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(5) J. W. Clapp, *J. Biol. Chem.*, **223**, 207 (1956).

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(7) B. Rathke, *Ber.*, **20**, 1059 (1887).

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