Central Nervous System Depressants. III.[1] 2-Aminoalkyl-3,3a,4,5-tetrahydroimidazo[1,5-*a*]quinolin-1(2H)-ones

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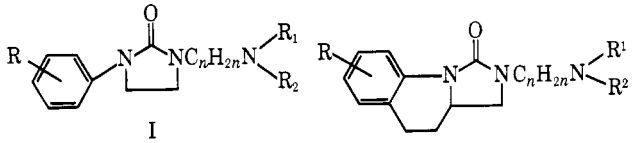
2-Aminoalkyl-3,3a,4,5-tetrahydroimidazo[1,5-*a*]quinolin-1(2H)-ones have been prepared by treating 2-aminomethyl-1,2,3,4-tetrahydroquinolines with N,N′-carbonyldiimidazole, followed by aminoalkylation. These compounds exhibit potent CNS depressant activity when tested in laboratory animals.

In the first paper of this series,[2] we reported that 1-aminoalkyl-3-aryl-2-imidazolidinones (I) were highly active as CNS depressants when tested in laboratory animals. We have now investigated a series of 2-aminoalkyl-3,3a,4,5-tetrahydroimidazo[1,5-*a*]quinolin-1(2H)-ones (II), which may be considered as cyclic analogs of I.



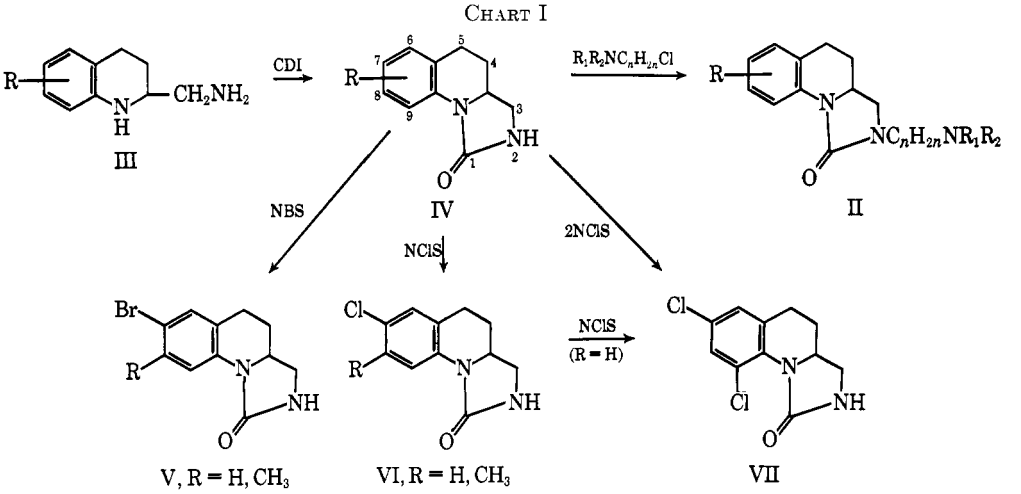
I II

The 3,3a,4,5-tetrahydroimidazo[1,5-*a*]quinolin-1-(2H)-ones (IV) and the aminoalkylated derivatives (II) were prepared as described in Chart I. 2-Aminomethyl-1,2,3,4-tetrahydroquinoline derivatives (III) were prepared by Raney nickel catalyzed reduction of Reissert compounds[3] followed by acid hydrolysis of the benzoyl group. III was then converted to IV by reaction with N,N′-carbonyldiimidazole (CDI) in tetrahydrofuran. When IV (R = H or 8-CH_3) was treated with N-chlorosuccinimide (or N-bromosuccinimide) in DMF, halogenation occurred in the 7 position to give VI (or V), and when 2 moles of N-chlorosuccinimide were used (R = H) halogenation occurred in both the 7 and 9 positions (VII). Nearly quantitative yields of the bromo derivatives were obtained, while the yields of the chloro derivatives were somewhat lower. The desired 2-aminoalkyl-3,3a,4,5-tetrahydroimidazo[1,5-*a*]quinolin-1(2H)-ones (II) were obtained by treating IV with NaH and an aminoalkyl chloride in diglyme. The yields in this last step varied widely, and some of the lower reported yields can be explained by difficulty in purification.

The ir spectrum of 3,3a,4,5-tetrahydroimidazo[1,5-*a*]quinolin-1(2H)-one (IV, R = H) has a C=O band at 5.87 and an N–H band at 3.07 μ. The spectra of the aminoalkylated derivatives have a C=O band at about 5.87–5.90 μ and, as expected, lack the N–H band.

The nmr characteristics of the aromatic protons of the halogenated compounds are described in Table I and were the basis of structure assignments. It is also significant that samples of 7-chloro-3,3a,4,5-tetrahydroimidazo[1,5-*a*]quinolin-1(2H)-one (VI, R = H) prepared by halogenation of IV (R = H) or by cyclization of 2-aminomethyl-6-chloro-1,2,3,4-tetrahydroquinoline (III, R = 6-Cl) were identical by nmr and infrared spectra.

Chart I



III IV II V, R = H, CH_3 VI, R = H, CH_3 VII

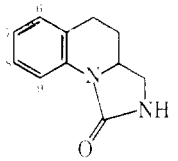
Pharmacological Results.—The 2-aminoalkyl-3,3a,4,5-tetrahydroimidazo[1,5-*a*]quinolin-1(2H)-ones (II) were screened for CNS depressant activity by methods previously described.[2] When judged by reduction of locomotor activity (MDD_{50}) these compounds had the same order of activity as the imidazolidinones (I).[2] Among the more interesting compounds, the 8-chloro derivatives (Table IV, **39**, **40**, **41**), analogous to the *m*-chlorophenylimidazolidinones, were active at about 1–2 mg/kg, while 8-methyl derivatives (**36**–**38**, **43**, **44**) were almost as active. The 7-halogen

(1) Previous paper in this series: W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Med. Chem.*, **9**, 858 (1966).

(2) W. B. Wright, Jr., H. J. Brabander, R. A. Hardy, Jr., and A. C. Osterberg, *ibid.*, **9**, 852 (1966).

(3) (a) A. Reissert, *Ber.*, **38**, 1610 (1905); (b) H. Rupe, R. Paltzer, and K. Engel, *Helv. Chim. Acta*, **20**, 209 (1937); (c) A. Gassmann and H. Rupe, *ibid.*, **22**, 1241 (1939); (d) H. v. Bidder and H. Rupe, *ibid.*, **22**, 1268 (1939); (e) F. D. Popp, W. Blount, and P. Melvin, *J. Org. Chem.*, **26**, 4930 (1961).

TABLE I: NMR CHARACTERISTICS OF AROMATIC PROTONS[a]



Nmr, δ (J, cps)			
Proton			
6	7	8	9
6.67–7.25 m	6.67–7.25 m	6.67–7.25 m	8.15 m
7.17 s	Cl	*Ca.* 7.12[b]	8.16 d (9)
7.30 s	Br	*Ca.* 7.25[b]	8.16 d (9)
7.23 d (2)	Cl	7.40 d (2)	Cl
7.08 d (8)	6.87 q (2,8)	Cl	8.27 d (2)
7.23 s	Br	CH_3	8.15 s
7.08 s	Cl	CH_3	8.15 s

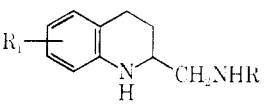
[a] Nmr spectra were determined in DMSO-d_6 on a Varian A-60 spectrophotometer. Chemical shifts (δ) are reported relative to tetramethylsilane (δ = 0.00) internal standard. Signals are designated as follows: s, singlet; d, doublet; q, quartet; m, complex multiplet. [b] Chemical shifts overlap and pattern is diffused.

heated on a steam bath for 20–44 hr and cooled. The mixture was diluted with C_6H_6 and a little H_2O, and NaOH pellets were carefully added, with cooling, until the mixture was strongly basic. The C_6H_6 layer was separated and the aqueous layer was again extracted with C_6H_6. The organic layers were combined, washed (saturated NaCl), dried ($MgSO_4$), and concentrated. The residual oil was used in the next step without further purification. In some cases, the compounds were further characterized by formation of HCl salts.

2-Aminomethyl-1,2,3,4-tetrahydro-6-methoxyquinoline and 2-Aminomethyl-1,2,3,4-tetrahydro-6-hydroxyquinoline.—When N-[(1,2,3,4-tetrahydro-6-methoxy-2-quinolyl)methyl]benzamide was treated with three parts of 37% HCl for 20 hr as described above, a 55% yield of 2-aminomethyl-1,2,3,4-tetrahydro-6-methoxyquinoline was obtained.

In a second experiment, 100 g of the benzamide and 300 ml of 37% HCl were heated on the steam bath for 32 hr, cooled, and triturated with Et_2O. A precipitate separated and was filtered off and washed with EtOH and then Et_2O. The product, 71 g, was dissolved in 200 ml of H_2O, and 140 ml of 5 *N* NaOH was added. The solution was extracted four times with C_6H_6 and the C_6H_6 layer was concentrated. The resulting oil, 25 g (39%), was the desired 2-aminomethyl-1,2,3,4-tetrahydro-6-methoxyquinoline. The aqueous layer was treated with 10

TABLE II: DERIVATIVES OF 2-AMINOMETHYL-1,2,3,4-TETRAHYDROQUINOLINE



No.	R	R_1	Yield, %	Mp, °C	Cryst solvent	Formula	Analyses
1	H	H	55[a]			$C_{10}H_{14}N_2$	*b*
2	H	6-Cl	76[c]	288–290[d]	EtOH	$C_{10}H_{14}Cl_2N_2$[d]	C, H, Cl, N
3	H	7-Cl	100[e]			$C_{10}H_{13}ClN_2$	*b*
4	H	7-CH_3	94[c]	240–245[c]	95% EtOH	$C_{11}H_{18}Cl_2N_2$[c]	C, H, N; Cl[f]
5	H	6-CH_3O	55[g]	230–232[c,h]	EtOH	$C_{11}H_{18}Cl_2N_2O$[c]	C, H, Cl, N
6	H	6-OH	*i*	147–149	EtOH	$C_{10}H_{14}N_2O$	C, H, N
7	Benzoyl	H	44	137–139[j]	MeOH	$C_{17}H_{18}N_2O$	C, H, N
8	Benzoyl	6-Cl	48	166–168	EtOH	$C_{17}H_{17}ClN_2O$	C, H, Cl, N
9	Benzoyl	7-Cl	60	138–140	EtOAc	$C_{17}H_{17}ClN_2O$	C, H, Cl, N
10	Benzoyl	7-CH_3	63	132–134	EtOH	$C_{18}H_{20}N_2O$	C, H, N
11	Benzoyl	6-CH_3O	68	133–135[k]	EtOAc	$C_{18}H_{20}N_2O_2$	C, H, N

[a] Base, bp 125–130° (1.0 mm); lit.[3b] bp 168° (11 mm). [b] Used in next step without analysis. [c] Crude base. [d] Hydrochloride. [e] Dihydrochloride. [f] Cl: calcd, 28.5; found, 27.7. [g] 20-hr reflux. [h] Lit.[3c] mp 224–225°. [i] By-product, yield not determined. [j] Lit.[3b] mp 138–139°. [k] Lit.[3c] mp 131–132°.

compounds (**29**, **30**) were active at about 6–9 mg/kg, while 7-methoxy derivatives (**32**, **33**) and aryl-unsubstituted compounds (**23**–**27**) were somewhat less active. Much larger doses were generally required to cause ataxia (RWD_{50}), and the spread between MDD_{50} and RWD_{50} was similar to that of the imidazolidinones. None of these compounds were considered to be toxic at ten times the motor depressant dose.

Experimental Section

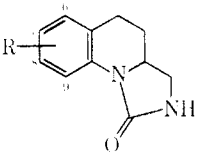
The preparation of the compounds is described below using general procedures when possible. Physical properties and important variations in these procedures are given in Tables II–IV. The ir spectra were determined on a Perkin-Elmer spectrophotometer (Model 21). Melting points were measured on a Mel-Temp 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.

The 1-benzoyl-2-cyano-1,2-dihydroquinoline derivatives, Reissert compounds,[3] were prepared by the CH_2Cl_2–H_2O method of Popp[3c] and hydrogenated (Raney Ni) to the N-[(1,2,3,4-tetrahydro-2-quinolyl)methyl]benzamides (Table II) following the procedure of Rupe.[3b]

2-Aminomethyl-1,2,3,4-tetrahydroquinolines (Table II). Procedure A.—A mixture of 100 g of the N-[(1,2,3,4-tetrahydro-2-quinolyl)methyl]benzamide and 300–500 ml of 37% HCl was

TABLE III

3,3a,4,5-TETRAHYDROIMIDAZO[1,5-*a*]QUINOLIN-1(2H)-ONES

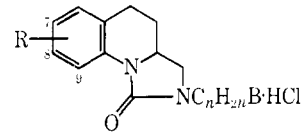


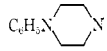
No.	R	Yield, %[a]	Mp, °C	Formula	Analyses
12	H	80[b]	192–194[c]	$C_{11}H_{12}N_2O$	C, H, N
13	8-CH_3	56[b]	165–167	$C_{12}H_{14}N_2O$	C, H, N
14	7-Br	91[d]	210–212	$C_{11}H_{11}BrN_2O$	C, H, Br, N
15	7-Cl	72[b,e]	206–207	$C_{11}H_{11}ClN_2O$	C, H, Cl, N
16	8-Cl	65[b]	193–195	$C_{11}H_{11}ClN_2O$	C, H, Cl, N
17	7,9-Cl_2	*d*, *f*	263–266[f]	$C_{11}H_{10}Cl_2N_2O$	C, H, Cl, N
18	7-Cl-8-CH_3	47[d,g]	210–212	$C_{12}H_{13}ClN_2O$	C, H, Cl, N
19	7-Br-8-CH_3	97[d,g]	219–221	$C_{12}H_{13}BrN_2O$	C, H, Br, N
20	7-CH_3O	68[b]	182–184	$C_{12}H_{14}N_2O_2$	C, H, N
21	7-OH	43[b,h]	229–231	$C_{11}H_{12}N_2O_2$	C, H, N

[a] Recrystallized from EtOH. [b] Procedure B. [c] Lit.[3d] mp 197°. [d] Procedure C. [e] 72% by procedure B. Purified by partition chromatography (heptane–methanol). [f] 79%, mp 250–258° from R = H; 94%, mp 250–258° from R = 7-Cl. Analytical sample by partition chromatography. [g] From 8-methyl analog. [h] Purified by partition chromatography (heptane–EtOAc–MeOH–H_2O).

Table IV

2-Aminoalkyl-3,3a,4,5-tetrahydroimidazo[1,5-*a*]quinolin-1(2H)-one Hydrochlorides[a]



No.	*n*	R	B	Yield, %	Salt	Mp, °C	Formula	Analyses
22	2	H	CH_3NH	88[b]	HCl	178–180	$C_{14}H_{20}ClN_3O$	C, H, Cl, N
23	2	H	$(CH_3)_2N$	50	Fumarate	151–152	$C_{19}H_{23}N_3O_5$	C, H, N
24	2	H	$C_2H_5(CH_3)N$	27	HCl	181–183	$C_{16}H_{24}ClN_3O$	C, H, Cl, N
25	2	H	$(C_2H_5)_2N$	78	Fumarate	134–135	$C_{21}H_{29}N_3O_5$	C, H, N
26	2	H		39	Fumarate	163–165	$C_{21}H_{27}N_3O_5$	C, H, N
27	2	H		41	HCl	251–252	$C_{23}H_{29}ClN_4O$	C, H, Cl, N
28	2	H	$C_6H_5CH_2(CH_3)N$	48	HCl	198–200	$C_{21}H_{26}ClN_3O$	C, H, Cl, N
29	2	7-Br		62	HCl	249–251	$C_{17}H_{23}BrClN_3O$	C, H, Cl, N
30	2	7-Cl		63	HCl	237–239	$C_{17}H_{23}Cl_2N_3O$	C, H, Cl, N
31	2	7-Cl	$C_6H_5CH_2(CH_3)N$	46	HCl	218–220	$C_{21}H_{25}Cl_2N_3O$	C, H, Cl, N
32	2	7-CH_3O	$C_2H_5(CH_3)N$	45	HCl	187–189	$C_{17}H_{26}ClN_3O_2$	H, Cl, N; C[c]
33	2	7-CH_3O		59	HCl	232–234	$C_{18}H_{26}ClN_3O_2$	C, H, Cl, N
34	2	7-CH_3O	$C_6H_5CH_2(CH_3)N$	45	HCl	202–204	$C_{22}H_{28}ClN_3O_2$	C, H, Cl, N
35	2	8-CH_3	CH_3NH	90[b]	HCl	195–197	$C_{15}H_{22}ClN_3O$	C, H, Cl, N
36	2	8-CH_3	$C_2H_5(CH_3)N$	41	HCl[d]	175–177	$C_{17}H_{26}ClN_3O$	C, H, Cl, N
37	2	8-CH_3		56	Fumarate	176–178	$C_{22}H_{29}N_3O_5$	C, H, N
38	2	8-CH_3	$C_6H_5CH_2(CH_3)N$	43	HCl	204–206	$C_{22}H_{28}ClN_3O$	C, H, Cl, N
39	2	8-Cl	$C_2H_5(CH_3)N$	43	HCl	165–167	$C_{16}H_{23}Cl_2N_3O$	C, H, Cl, N
40	2	8-Cl	$(C_2H_5)_2N$	63	HCl	157–159	$C_{17}H_{25}Cl_2N_3O$	C, H, Cl, N
41	2	8-Cl		60	HCl	214–215	$C_{17}H_{23}Cl_2N_3O$	C, H, Cl, N
42	2	7,9-Cl_2		38	HCl	266–268	$C_{17}H_{22}Cl_3N_3O$	C, H, Cl, N
43	2	7-Br-8-CH_3		40	HCl	276–278	$C_{18}H_{25}BrClN_3O$	C, H, Cl, N
44	2	7-Cl-8-CH_3		40	HCl	268–270	$C_{18}H_{25}Cl_2N_3O$	C, H, Cl, N
45	3	H	$(CH_3)_2N$	80	Fumarate	147–149	$C_{20}H_{27}N_3O_5$	C, H, N

[a] Prepared by procedure D unless otherwise noted. [b] Procedure E. [c] Recrystallized from EtOH and Et_2O. [d] C: calcd, 60.1; found, 59.6.

ml of AcOH and a gummy layer, which did not dissolve in C_6H_6, separated. The gum was removed and, upon trituration with H_2O, crystallized. It was filtered off and recrystallized from EtOH. Microanalysis indicated that this product was 2-aminomethyl-1,2,3,4-tetrahydro-6-hydroxyquinoline.

3,3a,4,5-Tetrahydroimidazo[1,5-*a*]quinolin-1(2H)-ones (Table III). Procedure B. From the 2-Aminomethyl-1,2,3,4-tetrahydroquinoline Derivative.—A solution of 0.1 mole of the 2-aminomethyl-1,2,3,4-tetrahydroquinoline derivative in about 50 ml of C_6H_6 or THF was cooled and 18.7 g (0.11 mole) of 95% N,N′-carbonyldiimidazole in 200 ml of THF was added. The solution was allowed to stand at room temperature for 20 hr and then heated on the steam bath for 2 hr. The reaction mixture was concentrated to remove solvents and the residue was warmed with 200 ml of H_2O and filtered. The product was washed with H_2O and a little cold EtOH and further purified by recrystallization from EtOH.

Procedure C. By Halogenation of a 3,3a,4,5-Tetrahydroimidazo[1,5-*a*]quinolin-1(2H)-one Derivative.—Halogenation was achieved by a modification of the method of Loev and Kormendy.[4] A solution of 0.01 mole of the N-halosuccinimide in 10 ml of DMF was added to a cooled suspension of 0.01 mole of the 3,3a,-4,5-tetrahydroimidazo[1,5-*a*]quinolin-1(2H)-one derivative in 10 ml of DMF. The mixture was allowed to stand at room temperature for 1–5 hr and was then diluted with 100 ml of H_2O. The precipitate was filtered off, washed with H_2O, and recrystallized from EtOH.

2-Aminoalkyl-3,3a,4,5-tetrahydroimidazo[1,5-*a*]quinolin-1(2H)-one Derivatives (Table IV). Procedure D. By Aminoalkylation.—A solution of 0.024 mole of the aminoalkyl chloride in 30–50 ml of diglyme or dry Et_2O was added to a mixture of 0.02 mole of the 3,3a,4,5-tetrahydroimidazo[1,5-*a*]quinolin-1(2H)-one, 0.022 mole of 50% NaH (in mineral oil), and 30 ml of diglyme, which had been stirred together for 10–30 min. The reaction mixture was heated to about 160°, boiling off the Et_2O if present, and held at this temperature for about 5 hr. The mixture was filtered hot to remove the salt and the mother liquor was concentrated to remove the diglyme. The residue was treated with excess 0.3 *N* HCl and C_6H_6 and the layers were separated. The aqueous layer was again extracted with C_6H_6, made basic with 5 *N* NaOH, and the crude product was extracted into C_6H_6. The C_6H_6 layer was washed with H_2O, dried ($MgSO_4$), and concentrated. The residue was dissolved in EtOH, and ethanolic HCl or a solution of fumaric acid in EtOH was added. The salt was filtered and recrystallized from EtOH.

Procedure E. By Debenzylation.—A mixture of 2.0 g of the 2-(2-benzylmethylaminoethyl)-3,3a,4,5-tetrahydroimidazo[1,5-*a*]-quinolin-1(2H)-one hydrochloride, 100 ml of 95% EtOH, and 1.0 g of 10% Pd–C was reduced in a Parr hydrogenator under about 3.16 kg/cm² of hydrogen pressure. When hydrogen absorption was complete, the catalyst was filtered off, the mother liquor was concentrated, and the residue was recrystallized from EtOH.

Acknowledgment.—We wish to thank Mr. L. Bran-

(4) B. Loev and M. F. Kormendy, *J. Org. Chem.*, **30**, 3163 (1965).

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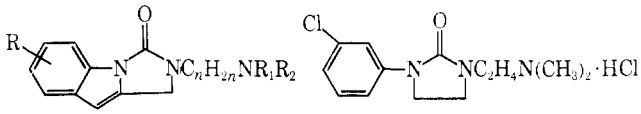
The synthesis of 2-aminoalkyl-1,2-dihydro-3H-imidazo[1,5-*a*]indol-3-ones is described. A number of these compounds have moderate CNS depressant activity.

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]

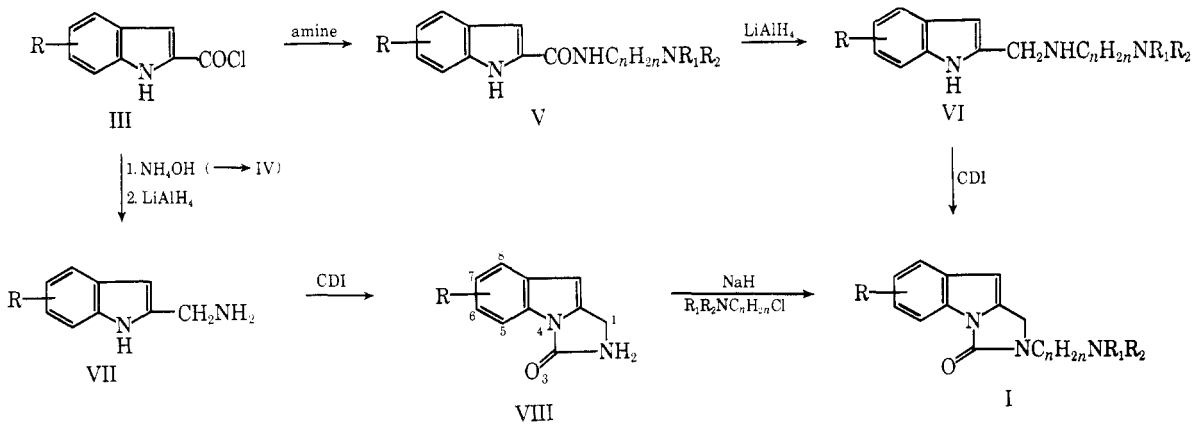


I II

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, R. 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).