antihistaminic activity (guinea pig ileum) of I was greater than 40 μg/l., whereas the standard drug had an ED_{50} of 14 μg/l.[6]

Experimental Section[7]

4,4′-Diamino-3,3′-dipicolyl Diphosphate (II).—The diamino compound (10 g), mp 245–250°,[2] was dissolved in ethanol and 85% H_3PO_4 was added dropwise until no further precipitation occurred. The crude product was filtered, air dried, and used directly in the next step; yield 14.8 g.

2,8-Diaza-10,11-dihydro-5H-dibenzo[*b,f*]azepine (III).—The diphosphate (II, 32.0 g) was heated at 295–305° for 4 hr. After cooling, the black solid was suspended in water and the mixture was made strongly basic with NaOH (50%) solution. The crude product was filtered and air dried; yield 12.2 g (75%). A small sample was sublimed at a bath temperature of 280–285° and the light yellow sublimate was recrystallized from dilute ethanol; mp 200–202°.

Anal. Calcd for $C_{12}H_{11}N_3 \cdot 0.5H_2O$: C, 69.88; H, 5.87; N, 20.38. Found: C, 69.50; H, 5.54; N, 20.58.

5-Dimethylaminopropyl-2,8-diaza-10,11-dihydro-5H-dibenzo-[*b,f*]azepine (I).—A mixture of 10 g (0.05 mole) of the amine III, 2.6 g of NaH (50% in mineral oil) and 150 ml of xylene was heated under reflux with stirring for 2 hr. A solution of 6.6 g of dimethylaminopropyl chloride in 50 ml of xylene was added, and the mixture was refluxed with stirring for 15 hr. Dilute (10%) HCl was added, and the organic layer was separated and discarded. The acid solution was made basic with NH_4OH and extracted with $CHCl_3$. The solvent was removed and the product was distilled, bp 206–210° (0.2 mm), yield 7.0 g (48%).

Anal. Calcd for $C_{17}H_{22}N_4$: C, 72.30; H, 7.85; N, 19.84. Found: C, 71.98; H, 8.12; N, 19.36.

The **dimaleate** salt was prepared and recrystallized from ethanol–ether; mp 156–157°.

Anal. Calcd for $C_{17}H_{22}N_4 \cdot 2(C_4H_4O_4)$: C, 58.36; H, 5.88; N, 10.89. Found: C, 57.98; H, 5.94; N, 10.98.

The **tetrahydrochloride** was recrystallized from absolute ethanol–ether; mp 223–224° dec.

Anal. Calcd for $C_{17}H_{22}N_4 \cdot 4HCl$: C, 47.67; H, 6.12; N, 13.08. Found: C, 47.60; H, 6.37; N, 13.07.

(6) Biological data reported herein was obtained by Drs. F. E. Roth and R. Taber of the Biological Research Division of Schering Corp.

(7) Microanalysis by Mr. E. Connor of these laboratories. All melting points are uncorrected. Conditions for maximum yield were not studied.

2-Phenylindolizines

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As a part of a continuing investigation of aminoalkyl derivatives of heterocyclic compounds, we have prepared for pharmacological study the 2-phenylindolizines and their 5,6,7,8-tetrahydro derivatives listed in Table I. The indolizines were obtained by treating the quaternary salts formed from 2-bromoacetophenone and the appropriately substituted pyridines with sodium bicarbonate.[1] To avoid difficulty at the quaternization step, the compounds with an aminoalkyl group were made by reducing an alkyl carbamate group with lithium aluminum hydride after the indolizine ring had been formed. Most of the indolizines were unstable to light and air and darkened rapidly. However, the quaternary salts of the tertiary alkyl bases were relatively stable. No bisquaternary salt was formed, even with excess alkyl halide.

The indolizines were not hydrogenated with palladium or platinum catalysts but were reduced easily to the 5,6,7,8-tetrahydro compounds with Raney nickel at room temperature. The tetrahydro derivatives were somewhat more stable than the parent compounds, and salts of the aminoalkyl compounds were obtained.

Pharmacology.[2]—The compounds were screened for their effects on the central nervous system in mice[3] and in some instances in cats. In mice (orally) the tertiary aminoalkylindolizines (**2**, **8**, Table I), were stimulants at 1–5 mg/kg, depressants at higher doses, and lethal (convulsions) at 100 mg/kg. Compound **6** produced a locomotor depression at 1 mg/kg which was pronounced at 30 mg/kg, and it was lethal at 100 mg/kg. The secondary amine **4** was less active, exhibiting slight to marked ataxia at 10–100 mg/kg, and it was lethal at 300 mg/kg. The 5,6,7,8-tetrahydro derivatives **12** and **13** had an action similar to that of the parent compounds but were less active and less toxic. The carbamate **3** and its tetrahydro derivative **11** produced a slight depression only, at 30–100 mg/kg, and were nonlethal at 1000 mg/kg. The dimethylamide **7** was a stimulant at 10–30 mg/kg, a depressant at higher doses, and lethal at 1000 mg/kg.

In cats (orally) **6** produced stimulation at 1–10 mg/kg, while **7** and **8** at 4–30 mg/kg caused stimulation followed by emesis.

Experimental Section[4]

Pyridylalkylamine Carbamates.—A solution of 0.5 mole of the aminoalkylpyridine and 10 g of pyridine in 300 ml of $CHCl_3$ was stirred and kept below 40° while 0.6 mole of ethyl chloroformate was added. After several hours 50 ml of water was added and the mixture was kept overnight. Strong NaOH solution was added with cooling until the mixture was strongly basic, and the $CHCl_3$ was separated, dried briefly (K_2CO_3), filtered, and distilled.

2-(3-Aminopropyl)pyridine.—3-(2-Pyridyl)propionitrile (52 g) in 400 ml of ethanol saturated with NH_3 was hydrogenated at 70–75° with 10 g of Raney nickel under 100 kg/cm² of hydrogen. The product was distilled.

2-(3-Methylaminopropyl)pyridine.—2-(3-*N*-Carbethoxyaminopropyl)pyridine (27.5 g) added dropwise to 10 g of $LiAlH_4$ in 500 ml of ether was stirred and refluxed for 6 hr. The cooled mixture was decomposed by the successive addition of 9 ml of water, 9 ml of 15% NaOH, and 27 ml of water, and after 1 hr the precipitate was filtered and washed by shirrying it with more ether. The solution was dried (K_2CO_3), filtered, and distilled.

N,N-Dimethyl-4-(2-pyridyl)butyramide.—4-(2-Pyridyl)butyric acid was heated in a metal bath at 210–220° (air condenser) and dimethylamine was passed through the molten mixture until the acid carbonyl had disappeared from the infrared spectrum of the melt (1.5–2 hr). The residue was dissolved in benzene, filtered, and distilled, bp 119–121 (1 mm),[5] yield 70%.

N-Phenacylpyridinium Bromides.—Molar equivalents of the pyridine and 2-bromoacetophenone were refluxed in benzene for 14–20 hr. The benzene was decanted from the quaternary salt

(1)(a) D. E. Ames, T. F. Grey, and W. A. Jones, *J. Chem. Soc.*, 920 (1950); (b) O. Westphal, K. Jann, and W. Heffe, *Arch. Pharm.*, **294**, 37 (1961); (c) V. S. Venturella, *J. Pharm. Sci.*, **52**, 868 (1963); **53**, 107 (1964); **53**, 1166 (1964).

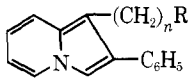
(2) We are indebted to Dr. S. Irwin (Department of Psychiatry, The University of Oregon Medical School, Portland, Ore.) and the Biological Division of the Schering Corp. for this data.

(3) S. Irwin in "Clinical Pharmacological Techniques," J. H. Nodine and P. S. Siegler, Ed., Yearbook Medical Publishers, Inc., Chicago, Ill., 1964, Chapter 4.

(4) Melting points were taken in capillary tubes in a Hershberg apparatus and are uncorrected. The physical constants of pyridine intermediates are in Table II.

(5) I. Ernest and J. Pliml, *Chem. Listy*, **51**, 543 (1957), give bp 106° (0.5 mm).

TABLE I
2-PHENYLINDOLIZINES



No.	n	R	Mp, °C[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	1	$NCH_3(COOC_2H_5)$	Gum	$C_{19}H_{20}N_2O_2$	74.00	6.54	9.09	73.65	6.78	8.78
2	1	$N(CH_3)_2$	67–69	$C_{17}H_{18}N_2$	81.55	7.24		81.35	7.26	
3	2	$NHCOOC_2H_5$	82–83	$C_{19}H_{20}N_2O_2$	74.00	6.54		74.23	6.49	
4	2	$NHCH_3$	Oil	$C_{17}H_{18}N_2$	81.56	7.25	11.19	81.30	7.48	10.82
5	2	$NCH_3(COOC_2H_5)$	Gum	$C_{20}H_{22}N_2O_2$	74.51	6.88	8.69	74.32	7.01	8.34
6	2	$N(CH_3)_2$	Oil	$C_{18}H_{20}N_2$	81.79	7.63	10.68	81.70	7.78	10.41
7	2	$CON(CH_3)_2$	93–95	$C_{19}H_{20}N_2O$	78.00	6.88		77.67	6.75	
8	3	$N(CH_3)_2$	Oil	$C_{19}H_{22}N_2$	81.97	7.97	10.06	81.77	8.20	9.91
9	2	$N(CH_3)_3 \cdot Br$	254–257	$C_{19}H_{23}BrN_2$	64.39	6.24		64.33	6.39	
10	2	$N(CH_3)_3 \cdot I$	243–246	$C_{19}H_{23}IN_2$	57.42	5.54		57.30	5.55	
11[b]	2	$NHCOOC_2H_5$	77–81	$C_{19}H_{24}N_2O_2$	73.04	7.79		73.00	7.62	
12[b]	2	$NHCH_3 \cdot HCl$	189–191	$C_{17}H_{23}ClN_2$	70.20	7.97		69.89	8.05	
13[b,c]	2	$N(CH_3)_2 \cdot HCl$	211–214	$C_{18}H_{25}ClN_2$	70.18	6.96		69.98	7.87	

[a] Compounds 1 and **7** were crystallized from isopropyl acetate, **3** from isopropyl ether, **9** and **10** from ethanol, 11 from ether, **12** from 2-propanol, and **13** from acetonitrile. [b] 5,6,7,8-Tetrahydro compound. [c] Base prepared by hydrogenating **6** as described for 11.

TABLE II
2-SUBSTITUTED PYRIDINES
$C_5H_4N(R)$

R	Bp, °C (mm)	Yield, %	d_{25}	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
$(CH_2)_3NH_2$[a]	114–117 (4)	70	1.5135	$C_8H_{12}N_2$	70.55	8.88	70.60	8.84
$(CH_2)_3NH(CH_3)$	65–69 (1)	72	1.5122	$C_9H_{14}N_2$	71.95	9.39	71.63	9.54
$(CH_2)_2NCH_3(COOC_2H_5)$	99–102 (1)	95	1.5027	$C_{11}H_{16}N_2O_2$	63.44	7.74	63.43	7.74
$(CH_2)_3NH(COOC_2H_5)$	137–141 (3)	95	1.5091	$C_{11}H_{16}N_2O_2$	63.44	7.74	63.24	7.57
$(CH_2)_3NCH_3(COOC_2H_5)$	132–134 (3)	95	1.4983	$C_{12}H_{18}N_2O_2$	64.84	8.16	64.57	8.26

[a] Dihydrochloride, mp 175–176°, from ethanol. *Anal.* Calcd for $C_8H_{14}Cl_2N_2$: N, 13.39. Found: N, 13.24.

which was refluxed briefly with fresh benzene and again decanted. The product, except in two instances, was a dark, viscous gum which could not be crystallized and the yields varied from 40–80%. With 10 g or less of reactants warming on the steam bath without any solvent gave better yields, but with larger quantities the temperature rose too high once the reaction started. The crystalline products obtained were as follows.

N-Phenacyl-2-(2-cyanoethyl)pyridinium bromide, crystallized from alcohol, mp 191–193°. *Anal.* Calcd for $C_{16}H_{15}BrN_2O$: C, 58.17; H, 4.56. Found: C, 58.21; H, 4.76.

N,N-Dimethyl-4-[2-(N-phenacylpyridinium)]butyramide bromide, crystallized from 2-propanol by dilution with isopropyl acetate, mp 148–150°. *Anal.* Calcd for $C_{19}H_{23}BrN_2O_2$: C, 58.31; H, 5.92. Found: C, 58.27; H, 5.92.

1-Substituted 2-Phenylindolizines (See Table I).—The crude N-phenacylpyridinium bromide dissolved in ten parts of cold water was extracted twice with half-volumes of ether. The water solution was separated and heated on the steam bath with excess saturated $NaHCO_3$ solution for 30 min. The oil which separated was extracted with ether, washed with water, and dried (K_2CO_3), and the solvent was removed *in vacuo* under nitrogen. Most of the indolizines containing a carbamate group were viscous oils which could not be crystallized or purified, but they gave reasonably good analyses and infrared spectra which matched that of similar pure compounds. Those with a carbamate or amide group were reduced to amines ($LiAlH_4$) by the procedure given for 2-(3-methylaminopropyl)pyridine. With one exception the amines so obtained could not be crystallized or distilled and were purified by washing in ether solution with dilute NaOH and then water.

The indolizines were unstable to light and air but could be kept for several months in an inert atmosphere in a refrigerator. The 1-cyanomethyl derivative polymerized rapidly to a high-melting insoluble solid and HCN was evolved. They were decomposed by acids; even monoacid salts of compounds with aminoalkyl groups decomposed during their preparation or on attempted recrystallization. The methobromides and iodides of the tertiary amino compounds were prepared with excess alkyl halide in benzene at room temperature and were quite stable.

1-(2-Carbethoxyaminoethyl)-2-phenyl-5,6,7,8-tetrahydroindolizine.—Ten grams of the corresponding indolizine in 250 ml of alcohol was shaken with 5 g of Raney nickel and hydrogen at 4.2 kg/cm². The theoretical amount of hydrogen was absorbed in 4–5 hr and no further reduction took place. After filtering the catalyst, the solvent was removed *in vacuo* under N_2 and the residue was crystallized.

1-(2-Methylaminoethyl)-2-phenyl-5,6,7,8-tetrahydroindolizine Hydrochloride.—The 1-(2-carbethoxyaminoethyl)-2-phenyl-5,6,7,8-tetrahydroindolizine was reduced (excess $LiAlH_4$) by the procedure previously described. The desired base, a light yellow mobile oil, treated with slightly less than 1 equiv of dry HCl in 2-propanol gave cream-colored needles after two crystallizations from 2-propanol (N_2 atmosphere, minimum of heating). This base also was prepared by hydrogenating 1-(2-methylaminoethyl)-2-phenylindolizine with Raney nickel.

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N-(ω-Aminoalkoxy)phthalimides[1]

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In an earlier paper,[2] the preparation of a series of N-(ω-aminoalkoxy)phthalimides was described. Several new compounds have now been synthesized by the re-

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(2) M. J. Kornet, *J. Med. Chem.*, **9**, 269 (1966).