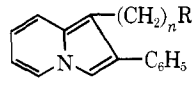
TABLE I
2-PHENYLINDOLIZINES



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	$N(CH_3)_3 \cdot I$	245–246	$C_{19}H_{23}IN_2$	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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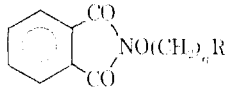
In an earlier paper,[2] the preparation of a series of N-(ω-aminoalkoxy)phthalimides was described. Several new compounds have now been synthesized by the re-

(1) This investigation was supported by Grant GB-3331 from the National Science Foundation.

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

TABLE I
N-(ω-AMINOALKOXY)PHTHALIMIDE HYDROCHLORIDES



No.	R	n	Mp, °C	Yield, %	Formula	% nitrogen— Calcd	Found
1	$N(CH_2C_6H_5)_2$	1	270–272	...	$C_{23}H_{20}N_2O_3 \cdot HCl$	6.85	6.71
2	$N(C_2H_5)_2$	2	245–246	14	$C_{14}H_{18}N_2O_3 \cdot HCl$	9.38	9.48
3	$N(CH_2CH_2CH_3)_2$	2	235–236	3	$C_{16}H_{22}N_2O_3 \cdot HCl$	8.57	8.44
4		2	235–237.5	18	$C_{17}H_{22}N_2O_3 \cdot HCl$	8.27	7.97
5	$N[CH_2CH(CH_3)_2]_2$	2	196–200	26	$C_{18}H_{26}N_2O_3 \cdot HCl$	7.89	8.04
6		2	241–241.5	4	$C_{19}H_{18}N_2O_4 \cdot HCl$	7.81	7.74
7	$N(CH_2C_6H_5)_2$	2	190–195	37	$C_{25}H_{26}N_2O_3 \cdot HCl$	6.62	6.85

action of N-(β-bromoethoxy)phthalimide with for the most part acyclic secondary amines. Since N-hydroxyphthalimide is a weak acid ($pK_a = 7$),[3] its aminomethylation was attempted in order to obtain compounds containing a phthalimidooxy group separated from an amino group by a single carbon atom. Treatment of N-hydroxyphthalimide with formaldehyde and dibenzylamine resulted in the desired product. With other amines, however, aminomethylated products could not be realized. Attempts to isolate the products by distillation at reduced pressure resulted in decomposition and all efforts to isolate aminomethylation products as their hydrochloride or picrate derivatives were unsuccessful.

N-(ω-Aminoalkoxy)phthalimides bear structural resemblances to isofebrifugine and febrifugine and for this reason several of the compounds described here and in the previous paper[2] were screened for antimalarial activity against *Plasmodium berghei*. None of the compounds showed interesting activity.[4]

Experimental Section[5]

N-(Dibenzylaminomethoxy)phthalimide.—N-Hydroxyphthalimide (3.32 g, 0.0204 mole) was suspended in 35 ml of boiling 95% ethanol followed by 2 ml of 37% formaldehyde. Next, dibenzylamine (4.53 g, 0.023 mole) was added to the refluxing mixture. The reaction mixture changed to a deep red color upon addition of the amine and the color faded to light orange after refluxing for 0.5 hr. The reaction mixture was placed in the refrigerator overnight, whereupon colorless needles were deposited. After filtration and recrystallization from absolute ethanol there was obtained 2.06 g (27.2%) of product, mp 146–148°.

Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.16; H, 5.51; N, 7.43.

A hydrochloride derivative was prepared by dissolving the base in absolute methanol and acidifying with methanolic HCl. Recrystallization from absolute ethanol–ethyl acetate afforded the pure salt, mp 270–272°.

Anal. Calcd for $C_{23}H_{20}N_2O_3 \cdot HCl$: N, 6.85. Found: N, 6.71.

N-(β-Aminoethoxy)phthalimide Hydrochlorides.—A typical reaction is described: that for the preparation of N-(β-diethylaminoethoxy)phthalimide hydrochloride. For specific data see Table I. A mixture of N-(β-bromoethoxy)phthalimide (6.75 g, 0.025 mole), diethylamine (3.84 g, 0.0525 mole), and 50 ml of dry benzene was heated in a 100-ml bomb at 125° for 4 hr. After cooling, the reaction mixture was filtered and the precipitate of diethylamine hydrobromide (3.33 g, 86.5%) was washed with a small amount of benzene. The filtrate was evaporated *in vacuo* and the residue was dissolved in 25 ml of absolute ethanol and acidified with methanolic HCl. All solvents were removed *in vacuo* and the remaining solid was recrystallized from absolute ethanol and gave 1.0 g (14%) of product, mp 245–246°.

(3) D. E. Ames and T. F. Grey, *J. Chem. Soc.*, 3518 (1955).

(4) Test results supplied by the Walter Reed Army Institute of Research, Washington, D. C.

(5) Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Dr. Kurt Eder, Geneva, Switzerland.

The Synthesis of Aryloxybiguanide and Aryloxyguanidine Salts

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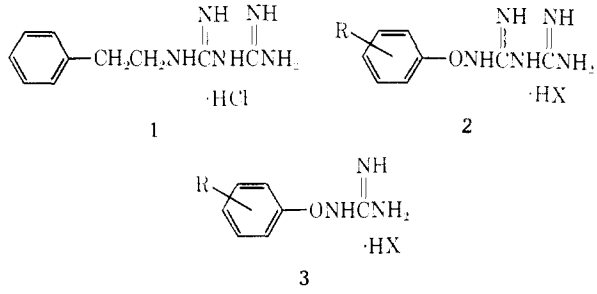
Phenethylbiguanide hydrochloride (**1**) is a clinically effective drug for the control of selected cases of diabetes.[1] The availability of aryloxyamine hydrochlorides by a recently developed procedure[2] has prompted us to synthesize for hypoglycemic testing several examples of the novel aryloxybiguanide salts. Also described are the syntheses of two aryloxyguanidine salts. Under mild conditions, the appropriate aryloxyamine hydrochloride[3] was allowed to react with cyanoguanidine to provide the aryloxybiguanide salts (**2a**, R = H, X = Cl; **b**, R = *p*-CH_3, X = NO_3; **c**, R = *m*-Cl, X = NO_3) and with cyanamide to provide the aryloxyguanidine salts (**3a**, R = H, X = Cl; **b**, R = *m*-Cl, X = NO_3).



These compounds were administered as solutions in aqueous 0.5% sodium carboxymethylcellulose orally at 250 mg/kg to normal chicks. Blood glucose levels,

(1) J. Pomeranze, H. Fujii, and G. T. Muratoff, *Proc. Soc. Exptl. Biol. Med.*, **95**, 193 (1957).

(2) C. L. Bumgardner and R. L. Lidy, *Chem. Ind.* (London), 559 (1962); J. S. Nicholson and D. A. Peak, *ibid.*, 1244 (1962).

(3) V. J. Bauer and H. P. Dalalian, *J. Med. Chem.*, **8**, 886 (1965).