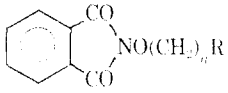
TABLE I
N-(ω-AMINOALKOXY)PHTHALIMIDE HYDROCHLORIDES



No.	R	n	Mp, °C	Yield, %	Formula	% nitrogen Calcd	% nitrogen 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	$C_{17}H_{18}N_2O_3 \cdot HCl$	7.81	7.74
7	$N(CH_2C_6H_5)_2$	2	190–195	37	$C_{24}H_{22}N_2O_3 \cdot HCl$	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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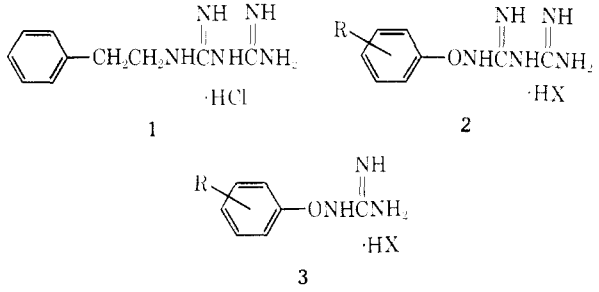
Phenethylbiguanide hydrochloride (**1**) is a clinically effective drug for the control of selected cases of diabetes.[1] The availability of aryloxyamine hydrochlorides by a recently developed procedure[2] has prompted us to synthesize for hypoglycemic testing several examples of the novel aryloxybiguanide 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. Lilly, *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).

TABLE I

ARYLOXYBIGUANIDE AND ARYLOXYGUANIDINE SALTS

Compound	Mp, °C	Yield, %	Recrystn solvent	Formula	Calcd, % C	Calcd, % H	Calcd, % Cl	Calcd, % N	Found, % C	Found, % H	Found, % Cl	Found, % N
Phenoxybiguanide hydrochloride (**2a**)	158–159	12	2-Propanol	$C_8H_{12}ClN_5O$	41.83	5.23	15.47	30.50	41.91	5.15	15.48	30.78
p-Tolyloxybiguanide nitrate (**2b**)	150–151	14	Methanol	$C_9H_{14}N_6O_4$	40.00	5.22		31.10	39.94	5.39		30.95
m-Chlorophenoxybiguanide nitrate (**2c**)	192–193	22	Ethanol	$C_8H_{11}ClN_6O_4$	33.05	3.79	12.22	28.92	32.65	4.08	12.49	29.22
Phenoxyguanidine hydrochloride (**3a**)	156–158	96	2-Propanol, ether	$C_7H_{10}ClN_3O$	44.80	5.33	18.93	22.40	45.01	5.45	18.90	22.50
m-Chlorophenoxyguanidine nitrate (**3b**)	149–150	24	2-Propanol, ether	$C_7H_9ClN_4O$	33.80	3.62	14.29	22.54	33.63	3.94	13.81	22.43

estimated as "reducing sugar" content by the method of Hoffman as modified for the Technicon Auto-Analyzer,[4] were not depressed significantly below controls when determined at 2 hr after dosing. For comparison, phenethylbiguanide hydrochloride effected a 50% lowering of blood sugar levels when administered at a dose of 50 mg/kg.[5]

Experimental Section[6]

Aryloxybiguanide Salts.—A solution of 0.02 mole of an aryloxyamine hydrochloride,[2,3] 0.02 mole of cyanoguanidine, and 40 ml of methanol was allowed to stand at room temperature for 4 days, and then concentrated under reduced pressure to an oily solid. For **2a**, the solid was recrystallized. For **2b** and **2c**, the crude solid was added to saturated aqueous sodium nitrate. The solid which then precipitated was recrystallized. Details are listed in Table I.

Aryloxyguanidine Salts.—A solution of 0.05 mole of an aryloxyamine hydrochloride[2,3] and 10 ml of 50% aqueous cyanamide[7] was allowed to stand overnight at room temperature. The solvent was distilled under reduced pressure, and the brown liquid residue was dissolved in warm 2-propanol. Addition of ether to the solution effected the separation of a solid (for **3a**) or a liquid (for **3b**). Addition of the liquid to saturated aqueous sodium nitrate gave a solid. Recrystallization gave the products; details are included in Table I.

(4) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937).

(5) The animal testing was carried out by Drs. S. Riggi and D. Blickens of the Experimental Therapeutics Research Section of these laboratories.

(6) Melting points were determined in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff.

(7) Aero® Cyanamide-50, American Cyanamid Co.

Reactions of Phenacyl Sulfides with Ammonia, Amines, and Hydrazines

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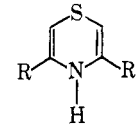
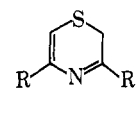
Our interest in 1,4-thiazines is derived from the parental relationship of these monocycles to the well-known and psychopharmacologically active phenothiazines and from the fundamental chemical nature of these little studied materials. Out attention was turned to 1,5-diketo sulfides with the thought that they would be easily accessible starting materials for convenient routes into the 1,4-thiazine system.

(1) Alfred P. Sloan Research Fellow.

Few attempts to accomplish condensation between 1,5-diketo sulfides and ammonia or amino compounds have been recorded and results, whether successful or unsuccessful, often appear ambiguous. In this paper we wish to report some structural clarifications and extensions of previous studies employing phenacyl sulfide and phenacyl sulfone as starting materials in the synthesis of 1,4-thiazines and related compounds.



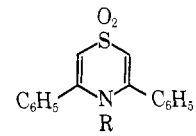
I



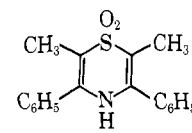
II

a, R = C_6H_5
b, R = H

Fujii[2] reported the synthesis of 3,5-diphenyl-1,4-thiazine by the condensation of phenacyl sulfide with ammonia; structure Ia was suggested for the product. We have repeated this preparation and found compelling evidence for the alternate structure IIa. The infrared spectrum is devoid of N–H absorption and the nmr spectrum shows, in addition to ten aromatic protons, a one-proton singlet at δ 6.28 (vinyl) and a two-proton singlet at δ 3.27. Such a structure has been previously proposed for the parent 1,4-thiazine (IIb).[3] This proposal, which was based on the failure of the compound to give a sulfonamide, has yet to be confirmed.



IIIa, R = H
b, R = CH_3
c, R = C_2H_5
d, R = $C_6H_5CH_2$
e, R = *n*-C_4H_9
f, R = CH_3OOCCH_2



IV

Baliah and Rangarajan[4] reported the formation of 3,5-diphenyl-4H-1,4-thiazine 1,1-dioxide (IIIa) by the condensation of phenacyl sulfone with ammonia in glacial acetic acid. The structure assignment was based on the observation that this compound underwent what was believed to be N-methylation by methyl

(2) K. Fujii, *J. Pharm. Soc. Japan*, **77**, 359 (1957); *Chem Abstr.*, **51**, 12103 (1957).

(3) C. Barkenbus and P. S. Landis, *J. Am. Chem. Soc.*, **70**, 684 (1948).

(4) V. Baliah and T. Rangarajan, *J. Org. Chem.*, **26**, 970 (1961).