water containing 60 ml of saturated $NaHSO_3$ solution. The entire dilution was extracted with four 250-ml portions of ether and the combined ether extracts in turn were extracted with two 150-ml portions of 10% $NaHCO_3$. The dark alkaline solution was boiled with Norit, filtered, cooled, and acidified with 6 *N* HCl. The tan precipitate was collected and dried to yield 17.5 g (88%) of product which melted at 241–243°. After two recrystallizations from 95% ethanol, white crystals were obtained and melted at 254–255° dec; λ_{max}^{KBr} 3.0 (OH), 3.4–4.1 (OH of CO_2H), 6.05 μ (C=O).

Anal. Calcd for $C_{10}H_8O_3S$: C, 57.68; H, 3.90; S, 15.39. Found: C, 57.41; H, 3.96; S, 15.11.

3-Methyl-5-hydroxybenzo[*b*]thiophene.—3-Methyl-5-hydroxybenzo[*b*]thiophene-2-carboxylic acid (4 g, 0.019 mole) was slowly heated during 1 hr to 210° in 40 ml of redistilled quinoline containing 2 g of Cu powder. The temperature was maintained at 210° for a further hour and then the reaction mixture was cooled, diluted with 150 ml of ether, and filtered. The etheral solution was extracted with 6 *N* HCl until acidic to congo red paper. The ether layer was then extracted with 20% NaOH, decolorized with Norit, and acidified with 6 *N* HCl. The acidic solution was extracted with three 75-ml portions of ether and dried (Na_2SO_4), and the ether was removed to yield a brown oil. The oil was dissolved in boiling cyclohexane and upon cooling gave 1.8 g (57%) of product. Analytical material was obtained after three recrystallizations from cyclohexane, mp 93–94°;[4] λ_{max}^{KBr} 2.96 (OH), 3.25 (=CH), 3.41 (CH_3), 8.22, 8.59, 7.20 μ (phenolic OH). The ultraviolet spectrum indicated $\lambda_{max}^{95\% \text{ ethanol}}$ in mμ (ϵ): 238 (21,800), 265 (5270), 270 sh (4660), 308 (3060), and 317 (2880); nmr ($CDCl_3$), δ 2.22 (3 H, doublet), 5.72 (1 H, singlet), 6.7–7.2 (3 H, multiplet), 7.5–7.67 (1 H, doublet).

Anal. Calcd for C_9H_8OS: S, 19.45. Found: S, 19.41.

The picric acid charge-transfer complex was prepared in the usual manner,[12] as tiny orange needles which melted at 150–151° after recrystallization from ethanol.

Anal. Calcd for $C_{15}H_{11}N_3O_8S$: N, 10.68; S, 8.14. Found: N, 10.90; S, 8.46.

3-Methyl-5-benzoyloxybenzo[*b*]thiophene.—A solution of 2.76 g (0.017 mole) of 3-methyl-5-hydroxybenzo[*b*]thiophene, 20 ml of dry pyridine, and 2.36 g (0.017 mole) of benzoyl chloride was heated to gentle reflux for 3 hr. The reaction mixture was cooled to room temperature and poured into 125 ml of ice water. The solid which separated was collected and washed with 5% $NaHCO_3$ prior to recrystallization from ethanol to yield 3.85 g (85%) of white needles: mp 67–68.5°; λ_{max}^{KBr} 3.28 (=CH), 3.45 (CH_3), 5.79 (C=O), 6.27 μ (C=C aromatic); nmr ($CDCl_3$), δ 2.33 (3 H, doublet), 7.0–8.5 (9 H, multiplet).

Anal. Calcd for $C_{16}H_{12}O_2S$: C, 71.62; H, 4.51; S, 11.95. Found: C, 71.87; H, 4.88; S, 11.82.

3-Bromomethyl-5-benzoyloxybenzo[*b*]thiophene.—A solution containing 0.5 g (1.87×10^{-3} mole) of 3-methyl-5-benzoyloxybenzo[*b*]thiophene and 0.019 g of benzoyl peroxide dissolved in 20 ml of reagent CCl_4 was heated to a gentle reflux whereupon 0.33 g (1.87×10^{-3} mole) of recrystallized N-bromosuccinimide was added and two 200-w lights focused on the reaction flask. The reaction was allowed to reflux for 2 hr, allowed to cool to room temperature, and filtered to remove succinimide. The CCl_4 was removed under a stream of N_2 to yield a yellow solid. The crude product was recrystallized from cyclohexane to give 0.51 g (80%) of white plates: mp 115–116°; λ_{max}^{KBr} 3.28 (=CH), 5.79 (C=O), 6.26 μ (C=C aromatic); nmr ($CDCl_3$), δ 4.62 (2 H, singlet), 7.0–8.4 (9 H, multiplet).

Anal. Calcd for $C_{16}H_{11}BrO_2S$: C, 55.34; H, 3.19; Br, 23.02. Found: C, 55.03; H, 3.25; Br, 23.59.

5-Benzoyloxybenzo[*b*]thiophene-3-carboxaldehyde.—A solution of 2.87 g (8.27×10^{-3} mole) of 3-bromomethyl-5-benzoyloxybenzo[*b*]thiophene and 1.18 g (8.40×10^{-3} mole) of hexamethylenetetramine in 25 ml of $CHCl_3$ was refluxed for 6 hr, after which time it was cooled to room temperature and the $CHCl_3$ was removed under reduced pressure leaving a light tan crude hexamine salt. This salt was treated with 30 ml of 50% aqueous acetic acid and the resulting solution was heated to reflux for 3 hr. At the completion of the heating period, 40 ml of water and 7 ml of concentrated HCl was added and the mixture refluxed for an additional 5 min. The reaction mixture was allowed to stand overnight, then diluted with 200 ml of water and extracted with three 75-ml portions of ethyl acetate. The combined extracts were dried (Na_2SO_4), and the solvent was removed to yield a tan solid. Recrystallization from ethanol gave 0.94 g (40%) of white needles: mp 96–97°; λ_{max}^{KBr} 3.26 (=CH), 3.59 (CH), 5.79 and 6.0 (C=O), 6.25 μ (C=C).

Anal. Calcd for $C_{16}H_{10}O_3S$: C, 68.06; H, 3.57; S, 11.36. Found: C, 67.87; H, 3.55; S, 11.06.

The semicarbazone was prepared by the usual procedure[12] as white plates, mp 224–225°, following recrystallization from ethanol.

Anal. Calcd for $C_{17}H_{13}N_3O_3S$: C, 60.16; H, 3.86; N, 12.38. Found: C, 59.99; H, 3.82; N, 12.59.

5-Benzoyloxy-3-(2-nitrovinyl)benzo[*b*]thiophene.—A solution of 0.3 g (1.1×10^{-3} mole) of 5-benzoyloxybenzo[*b*]thiophene-3-carboxaldehyde and 0.12 g of ammonium acetate in 6 ml of nitromethane was brought to a gentle reflux and maintained for 1 hr, after which time the excess nitromethane was removed under a stream of N_2 to leave a yellow solid. The crude solid was dissolved in boiling benzene, filtered, and upon cooling gave 0.275 g (80%) of yellow needles: mp 179–180°; λ_{max}^{KBr} 3.27 (=CH), 5.79 (C=O), 6.14 (C=C olefin), 6.64 and 7.5 μ (NO_2).

Anal. Calcd for $C_{17}H_{11}NO_4S$: C, 62.76; H, 3.41; N, 4.31. Found: C, 63.20; H, 3.60; N, 4.23.

5-Hydroxy-3-(2-nitrovinyl)benzo[*b*]thiophene.—This benzene-insoluble material can be isolated from the condensation reaction between nitromethane and 5-benzoyloxybenzo[*b*]thiophene-3-carboxaldehyde, and composes 5% of the crude reaction mixture. Recrystallization from chloroform gave gold needles: mp 227–228° dec; λ_{max}^{KBr} 3.0 (OH), 3.28 (=CH), 6.18 (C=C olefin), 6.70 and 7.6 μ (NO_2).

Anal. Calcd for $C_{10}H_7NO_3S$: C, 54.29; H, 3.19; N, 6.33. Found: C, 54.41; H, 3.32; N, 6.48.

3-(β-Aminoethyl)-5-hydroxybenzo[*b*]thiophene Hydrochloride.—Lithium aluminum hydride (4.0 g, 0.105 mole) was added to 100 ml of dry tetrahydrofuran (THF), followed by the dropwise addition of 2.25 g (6.9×10^{-3} mole) of 5-benzoyloxy-3-(2-nitrovinyl)benzo[*b*]thiophene which was dissolved in 50 ml of dry THF. The reaction mixture was gently refluxed for 6 hr before the excess $LiAlH_4$ was decomposed by the careful addition of water, 200 ml of 2 *N* NaOH was added, and the entire reaction mixture was filtered. The THF was removed by distillation, and the basic solution was saturated with CO_2 (pH 8.3) and extracted continuously with ether for 48 hr. Dry HCl was passed into the ether solution, yielding a yellow oil which solidified under vacuum. Recrystallization from methanol–ethyl acetate gave 0.19 g (12%) of white plates: mp 195–196.5°; λ_{max}^{KBr} 3.00 (OH), 3.23–3.40 (NH_3^+), and strong absorptions at 6.84, 6.96, 7.25, 8.03, and 8.19 μ. The ultraviolet spectrum indicated $\lambda_{max}^{95\% \text{ ethanol}}$ in mμ (ϵ): 237 (18,630), 264 (5520), 270 sh (4820), 309 (3310), and 316 (3200).

Anal. Calcd for $C_{10}H_{12}ClNOS$: C, 52.28; H, 5.27; N, 6.09. Found: C, 52.38; H, 5.45; N, 6.10.

Acknowledgments.—We wish to acknowledge support of the U. S. Public Health Service by research grant GM 10366 and fellowship GM-24, 364-02. We are also grateful to Dr. Carl Pfeiffer and colleagues at the New Jersey Neuro-Psychiatric Institute for biological screening data.

(12) R. Shriner, R. Fuson, and D. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948.

Some *p*-Hydroxyphenoxyacetic Acid Derivatives

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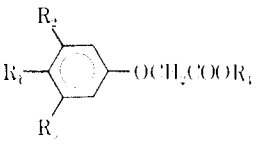
The antithyroid activity of α-methyl-β-(3,5-diiodo-4-hydroxyphenyl)propionic acid[3] and of esters of 3,5-

(1) To whom inquiries should be addressed.

(2) This investigation was supported by Grant AM-06480, National Institutes of Health.

(3) S. B. Barker, H. B. Dirks, Jr., W. R. Garlick, and H. M. Klitgaard, *Proc. Soc. Expil. Biol. Med.*, **78**, 840 (1951).

TABLE I



No.	R_1	R_2	R_3	R_4	Mp, °C	Formula	%C Calcd	%C Found	%H Calcd	%H Found
I	H	H	H	C_2H_5	121–122	$C_{10}H_{12}O_4$	61.22	61.14	6.17	6.44
II	CH_3CO	H	H	H	161–163	$C_{10}H_{10}O_5$	56.61	56.17	5.6	4.95
III	CH_3CO	H	H	C_2H_5	51–53	$C_{12}H_{14}O_5$	60.2	60.32	5.86	5.74
IVa	CH_3CO	$HgOCOCH_3$	$HgOCOCH_3$	H	>300	$C_{14}H_{14}Hg_2O_8$	23.12	23.32	1.94	2.23
V	H	Br	Br	H	166–168[a]	$C_8H_6Br_2O_4$	29.48	29.66	1.86	2.03
VI	H	I	H	H	194–198	$C_8H_7IO_4$	32.50	32.73	2.38	2.32
VII	H	I	I	H	215–220	$C_8H_6I_2O_4$	22.89	23.71	1.44	1.36

[a] Lit.[8] mp 160–162°.

diiodo-4-hydroxybenzoic acid[4] suggests a 2,6-diiodophenol moiety as necessary for antithyroid activity in this series. In view of the antithyroid activity of halogenated phenoxyacetic acids,[5] it seemed of interest to prepare compounds retaining a 2,6-diiodophenol as well as a phenoxyacetic acid moiety and to screen such compounds for their thyroid activity.

Attempts to prepare 3-iodo- and 3,5-diiodo-4-hydroxyphenoxyacetic acid (VII) by iodinating 4-hydroxyphenoxyacetic acid in basic solution or with iodine monochloride in acetic acid[6] failed. Side reactions could not be prevented by acetylation and/or esterification of 4-hydroxyphenoxyacetic acid before iodination.

The preparation of 3,5-acetoxymercuri-4-hydroxyphenoxyacetic acid (IV)[7] proceeded smoothly; 3,5-diacetoxymercuri-4-acetoxyphenoxyacetic acid (IVa) was prepared to characterize IV, the purification of which proved inconvenient. Bromination of IV yielded 3,5-dibromo-4-hydroxyphenoxyacetic acid (V), a compound which had been obtained by Gallo and co-workers[8] by direct bromination in dioxane–pyridine. Iodination of IV yielded only 3-iodo-4-hydroxyphenoxyacetic acid (VI); 3,5-diiodo-4-hydroxyphenoxyacetic acid (VII) was obtained by direct iodination in dioxane in the presence of a small amount of pyridine. The analysis of all compounds except IV is presented in Table I.

Screening of V, VI, and VII failed to reveal any thyromimetic or antithyroid activity in an antigoiter test performed by a variation of the method of Cortell[9] (Table II).

TABLE II

Group	No. of animals	Diet	Injections	Thyroid wt ± SD, mg/100 g
1	6	Control	None	8.6 ± 1.7
2	5	Thiouracil	None	17.8 ± 3.6
3	6	Thiouracil	T_4	9.5 ± 2.0
4	6	Thiouracil	VII	19.3 ± 2.8
5	6	Thiouracil	VII, T_4	8.3 ± 2.9
6	6	Thiouracil	V	19.2 ± 3.6
7	6	Thiouracil	V, T_4	7.8 ± 1.2

(4) M. M. Sheahan, J. H. Wilkinson, and N. F. Naclagan, *Biochem. J.*, **48**, 188 (1951).

(5) H. M. Klitgaard, H. B. Dirks, S. B. Barker, S. C. Wang, and S. Wawzonek, *Endocrinology*, **48**, 525 (1951).

(6) N. Zenker and E. C. Jorgensen, *J. Am. Chem. Soc.*, **81**, 4643 (1959).

(7) S. Wawzonek and S. C. Wang, *J. Org. Chem.*, **16**, 1271 (1951).

(8) G. G. Gallo, C. R. Pasqualucci, and P. Sensi, *Ann. Chim.* (Rome), **52**, 902 (1960); *Chem. Abstr.*, **58**, 10185 (1963).

Experimental Section

4-Hydroxyphenoxyacetic Acid Ethyl Ester (I).—To 4-hydroxyphenoxyacetic acid (5.1 g, 30 mmoles), dissolved in ethanol (100 ml), 3 ml of concentrated H_2SO_4 was added and the mixture refluxed for several hours. The solution, concentrated *in vacuo*, yielded a crystalline product (5.6 g, 95%) which was subsequently recrystallized from 50% ethanol.

4-Acetoxyphenoxyacetic Acid (II).—4-Hydroxyphenoxyacetic acid (1.68 g, 10 mmoles) was allowed to stand at room temperature in the presence of acetic anhydride (20 ml, 0.27 mole) and a few drops of concentrated H_2SO_4. After a few hours the mixture was poured onto ice and the product (2.1 g, 93%) was easily recrystallized from 95% ethanol.

4-Acetoxyphenoxyacetic Acid Ethyl Ester (III).—Ester I (1.0 g, 5 mmoles) was dissolved in acetyl chloride (5 ml) and a few drops of concentrated H_2SO_4 acid was added. After a few hours in the dark at room temperature the mixture was poured onto ice and kept in the refrigerator overnight. The white solid (0.8 g, 66%) was recrystallized from 50% ethanol; it easily decomposed to the original acid.

3,5-Diacetoxymercuri-4-hydroxyphenoxyacetic Acid (IV).—4-Hydroxyphenoxyacetic acid (1.68 g, 10 mmoles) and NaOH (0.5 g, 12.5 mmoles) were dissolved in 50 ml of water under nitrogen. Mercuric acetate (6.4 g, 20 mmoles), dissolved in water (50 ml) and acetic acid (4 ml), was added; the mixture was heated to 100° for 30 min and stirred vigorously for another hour while cooling. The buff-colored crude product (*Anal.* Calcd for $C_{12}H_{12}Hg_2O_8$: C, 21.52; H, 1.76. Found: C, 20.11; H, 1.76) could not be conveniently purified and was characterized as the 4-acetoxy derivative (IVa).

3,5-Dibromo-4-hydroxyphenoxyacetic Acid (V).—To a stirred suspension of IV (1.7 g, 2.5 mmoles) in water (20 ml), bromine (1.1 g, 6.9 mmoles) was added dropwise and stirring was continued for 15 min after the addition was complete. The yellow-brown solid formed (0.73 g, 89%) was recrystallized from 50% ethanol or precipitated from acetic acid by water.

3-Iodo-4-hydroxyphenoxyacetic Acid (VI).—To a stirred suspension of IV (4.3 g, 6.3 mmoles) in KI (50 ml, 10%) a solution of iodine (11.8 mmoles) in 10% KI was added dropwise over a period of 1.5 hr and stirring was continued for 2 hr after the addition was complete. At the end of this period excess iodine was removed (5% Na_2SO_3), the mixture was acidified (pH 2–3), and the green-yellow product (1.6 g, 53%) was filtered off.

3,5-Diiodo-4-hydroxyphenoxyacetic Acid (VII).—To a 4-hydroxyphenoxyacetic acid (0.85 g, 5 mmoles), dissolved in dioxane (20 ml), pyridine (1.2 ml, 14.9 moles) was added; to the stirred, cold mixture iodine (2.64 g, 10.4 mmoles) in dioxane (40 ml) was added dropwise over a period of 2 hr. After a further 30 min of stirring, freshly prepared sodium sulfite was added to remove excess iodine, the reaction mixture was reduced to half its volume *in vacuo* and the yellow crystals (0.84 g, 40%) were filtered and washed with cold water.

Antigoiter Assay.—The assay was performed by a variation of the method of Cortell.[9] Male Wistar rats, weighing 90 ± 15 g were fed a diet combining 0.3% powdered thiouracil for a period of 10 days. Thyroxine-receiving groups were injected daily with a dose of 7 mμmoles of thyroxine dissolved in alkaline saline.

(9) R. E. Cortell, *J. Clin. Endocrinol.*, **9**, 955 (1949).

Compounds V and VII were similarly injected daily in doses of 1.4 μmoles, *i.e.*, at 200 times the thyroxine level. The results of the assay, listed in Table II, fail to show any thyromimetic or antithyroid effect of compounds V and VII. Compound VI was found inactive at 1000 times the thyroxine dose in a previous experiment.

Phosphinylguanidines. Phosphorus Analogs of Biguanides

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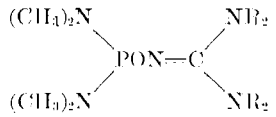
Many biguanides display the ability to lower the blood-sugar levels of animals.[1] In this communication we describe the synthesis of two phosphinylguanidines of type **1**. These compounds represent examples of a



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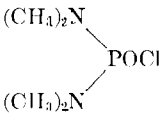

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novel system in which one of the carbon atoms of a biguanide skeleton has been replaced with a P=O unit.

The reactions of commercially available N,N′-bisdimethylphosphorodiamidic chloride (**2**) with guanidine[2] and 1,1,3,3-tetramethylguanidine gave 2-[bis(dimethylamino)phosphinyl]guanidine (**1**, R = H) and 2-[bis(dimethylamino)phosphinyl]-1,1,3,3-tetramethylguanidine (**1**, R = CH_3), respectively. The phosphinylguanidines **1** were administered as suspensions in 0.5% sodium carboxymethylcellulose solution orally at 250 mg/kg to normal chicks and intraperitoneally at 200 mg/kg to normal rats. Blood glucose levels, estimated as "reducing sugar" content by the method of Hoffman as modified for the Technicon Auto-Analyzer,[3] were not depressed significantly below controls when determined at 2 hr after dosing for chicks and 3 hr after dosing for rats.

Experimental Section[4]

2-[Bis(dimethylamino)phosphinyl]guanidine.—To 5.5 g (0.094 mole) of guanidine[2] was added dropwise with stirring and ice-bath cooling during 15 min 8.2 g (0.048 mole) of N,N′-bisdimethylphosphorodiamidic chloride. The mixture was allowed to stand for 16 hr at room temperature, taken up in hot acetonitrile, and filtered. Upon cooling, a solid, 1.6 g, mp 170–180°, separated from the filtrate and was collected. Recrystallization from acetonitrile gave 1.0 g (11%) of colorless needles: mp 179–182° dec; infrared (KBr disk), strong bands at 2.9 (NH), 8.8 (P=O), and 10.1 μ (PN).[5]

Anal. Calcd for $C_5H_{16}N_5OP$: C, 31.09; H, 8.29; N, 36.27. Found: C, 30.35; H, 8.07; N, 36.43.

The compound was converted to the picrate, yellow needles, mp 207–208° (from ethanol).

Anal. Calcd for $C_{11}H_{19}N_8O_8P$: C, 31.28; H, 4.50; N, 26.54; P, 7.35. Found: C, 31.43; H, 4.55; N, 25.99; P, 7.21.

2-[Bis(dimethylamino)phosphinyl]-1,1,3,3-tetramethylguanidine.—With stirring, 12.0 g (0.1 mole) of 1,1,3,3-tetramethylguanidine and 8.5 g (0.05 mole) of N,N′-bisdimethylphosphorodiamidic chloride were mixed. After the exothermic reaction subsided, the mixture was heated on a steam bath for 30 min under nitrogen. The mixture was taken up in ether and filtered, and the filtrate was concentrated under reduced pressure to a liquid containing some solid. After filtration, the material was distilled to give 5.8 g of colorless liquid, bp 130–135° (0.5 mm). Redistillation gave 3.9 g (31%) of colorless liquid: bp 123–126° (0.3 mm); infrared ($CHCl_3$), strong bands at 8.6 (P=O) and 10.1 μ (PN).[5]

Anal. Calcd for $C_9H_{24}N_5OP$: C, 43.37; H, 9.63; N, 28.11; P, 12.44. Found: C, 42.98; H, 9.75; N, 27.21; P, 12.48.

The compound was converted to the picrate, yellow prisms, mp 168–169° (from ethanol).

Anal. Calcd for $C_{15}H_{27}N_8O_8P$: C, 37.66; H, 5.65; N, 23.43; P, 6.49. Found: C, 38.00; H, 5.61; N, 23.37; P, 6.73.

(1) Salts of phenethylbiguanide, 1,1-dimethylbiguanide, and *n*-butylbiguanide are utilized in the clinical control of diabetes: L. J. P. Duncan and B. F. Clarke, *Ann. Rev. Pharmacol.*, **5**, 151 (1965).

(2) W. Marckwald and F. Struwe, *Ber.*, **55**, 458 (1922).

(3) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937). The animal testing was carried out by Drs. C. Boshart, S. Gordon, and E. Tocus of these laboratories.

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

(5) N. B. Colthup, L. H. Daly, and S. E. Wiberly, "Introduction to Infrared and Raman Spectroscopy," Academic Press Inc., New York, N. Y., 1964, p 405.

Salts of α-Amino-*p*-toluenesulfonamide

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α-Amino-*p*-toluenesulfonamide[1] has been in the armamentarium of the physician as a broad-spectrum antibacterial agent for almost a quarter century. It was synthesized and described by Klarer[2,3] and its outstanding therapeutic properties were first reported by Domagk[4] and summarized by Northey.[5]

Recently, it was found that this sulfonamide hydrochloride was a useful topical agent in burn wound sepsis.[6,7] However, some patients, particularly those who were treated with large quantities of this drug, developed metabolic acidosis. In order to overcome this side effect we have prepared a series of new organic salts (Table I).

The chemical isolation of the acetate, the salt of choice, now undergoing clinical trials, has not been reported in the literature, and it was only alluded to as a potentially useful compound.[8,9] Its use for the treatment of burns, in a hydrophillic ointment base, has successfully overcome the problem of metabolic acidosis.

Skulan and Hoppe[10] infused 0.5 *M* aqueous solutions of the hydrochloride and acetate salts in the marginal ear veins of unanesthetized nonfasted male rabbits. The hydrochloride produced a marked progressive fall in blood pH and plasma total CO_2 concentration,

(1) Also known as α-aminomethylbenzenesulfonamide, homosulfanilamide, Sulfamylon®, marfanil, mafenide, etc.

(2) J. Klarer, *Klin. Wochschr.*, **20**, 1250 (1941).

(3) J. Klarer, U. S. Patent 2,288,531 (1942).

(4) G. Domagk, *Klin. Wochschr.*, **21**, 448 (1942).

(5) E. H. Northey, "The Sulfonamides and Allied Compounds," Reinhold Publishing Corp., New York, N. Y., 1948, p 252.

(6) R. B. Lindberg, R. E. Brame, J. A. Moncrief, and A. D. Mason, *Federation Proc.*, **23**, 1725 (1964).

(7) R. B. Lindberg, J. A. Moncrief, W. E. Switzer, S. E. Order, and W. Miller, *J. Trauma*, **5**, 601 (1965).

(8) J. A. Mendelson and F. B. Brinkley, U. S. Patent 3,230,140 (1966).

(9) J. A. Moncrief, R. B. Lindberg, W. E. Switzer, and B. A. Pruitt, Jr., *Arch. Surg.*, **92**, 558 (1966).

(10) T. W. Skulan and J. O. Hoppe, *Life Sci.*, in press.