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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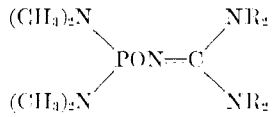
Received November 9, 1966

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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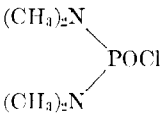

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novel system in which one of the carbon atoms of a biguanide skeleton has been replaced with a P=O unit.

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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Received August 3, 1966

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.

TABLE I

SALTS OF α-AMINO-*p*-TOLUENESULFONAMIDE

No.	Salt	Acid added to base in EtOH: Acid	Solvent	Molar ratio base:acid	Yield, %	Mp, °C	Formula	Calcd, %: Acid[a]	Base[b]	Other	Found, %: Acid	Base	Other
1	Acetate	Acetic	None	1:1	91	169.0–172.0	$C_7H_{10}N_2O_2S \cdot C_2H_4O_2$	24.4		N, 11.38	24.1		N, 11.40
2	Carbamate	CO_2	None	1:0.7[d]	95	153.4–154.5	$(C_7H_{10}N_2O_2S)_2 \cdot CO_2$		89.4	CO_2, 10.6		89.5	CO_2, 10.0
3	Citrate	Citric·H_2O	2-Propanol	1:0.33	75	158.6–161.0	$(C_7H_{10}N_2O_2S)_3 \cdot C_6H_8O_7$	25.6	74.4		25.1	71.9	H_2O, 0.4[c]
4	Fumarate	Fumaric	DMF	1:0.5	99	208.0–209.5	$(C_7H_{10}N_2O_2S)_2 \cdot C_4H_4O_4$	23.8	76.2		23.4	75.7	
5	Succinate	Succinic	DMF	1:0.5	100	211.5–212.2	$(C_7H_{10}N_2O_2S)_2 \cdot C_4H_6O_4$	24.1	75.9		24.1	75.7	

[a] Lithium methoxide titration. [b] Acetous perchlorate titration. [c] Karl Fischer titration. [d] Excess CO_2 used; theoretical ratio 1:0.5.

while the acetate caused little or no change in the same parameters.

The same authors reported that the acute intravenous toxicity of the acetate was significantly less than that of the hydrochloride salt, in both mouse and rat. The 24 hr intravenous LD_{50} values are 900 ± 52 and 1580 ± 101 mg/kg, respectively, in the mouse; and 1170 ± 74 and 2040 ± 139 mg/kg, respectively, in the rat, for HCl and HOAc salts of α-amino-*p*-toluenesulfonamide.

Experimental Section

To a stirred solution of 1 mole of α-amino-*p*-toluenesulfonamide in 2 l. of boiling ethanol, the equivalent amount of the acid, dissolved in a suitable solvent, was added over a period of 15–20 min. The resulting thick slurry was cooled to 10° and the solid was filtered. The filter cake, after having been pressed hard under a rubber dam, was washed with alcohol and dried at 60° *in vacuo*. No recrystallization was carried out. The yields ranged from 75 to 100%.

The carbamate salt was prepared directly by saturation of a warm (50°) solution of the base with excess CO_2. The data are summarized in Table I.

Bisoxime Sulfonates and Bisquaternary Hydrazones

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Received August 18, 1966

The important class of antineoplastic compounds known as alkylating agents includes the nitrogen mustards, bis- and trisethylenimine derivatives, bisepoxides, and bismethanesulfonate esters. Common to all of these alkylating agents is their possession of at least two functional groups which can interact readily with biological nucleophiles, in some cases by way of carbonium ions and in others by way of nucleophilic displacement, affording cross-linking and inactivation of the nucleic acids and possibly other cell constituents.[1] The distance between the alkylating centers is important, and this variable was particularly suitable for study in the case of the bismethanesulfonate esters.[2]

Consideration of the structure and reactivity of bisoxime sulfonates [$RSO_2ON{=}CR'(CH_2)_nCR'{=}NOSO_2R$] led us to hope that this type of compound might also have the cross-linking properties of the established alkylating agents. Oxime sulfonates are highly reactive, undergoing facile solvolysis (Beckmann rearrangement) and incorporating a variety of nucleophiles such as amines, alcohols, and phosphate anions.[3] A second type of compound which offered similar theoretical possibilities was the bisquaternary hydrazones [$(CH_3)_3N^+N{=}CR(CH_2)_nCR{=}NN^+(CH_3)_3$].[4] Another interesting feature for this type is that, although we are not aware of any literature examples, a direct nucleophilic displacement on nitrogen is at least a theoretical possibility. This possibility affords a distinction to the classical alkylating agents wherein nucleophilic attack must take place on carbon. Of further interest in this type was the possibility of preparing compounds in which appropriate separation of the two positively charged nitrogen atoms would afford pertinent analogs of the well-known hypotensive bisquaternary amines.[5]

We therefore undertook the preparation of a series of simple bisoxime sulfonates and bisquaternary hydrazones,[6] with emphasis on variation of the distance between the two reactive groups. The bissulfonates of diketoximes were prepared conveniently by treatment with methane- or *p*-toluenesulfonyl chloride in pyridine. Bismethanesulfonates were prepared from 1,2-cyclohexanone dioxime and 1,4-cyclohexanone dioxime, and bis-*p*-toluenesulfonates were prepared from dimethylglyoxime and 2,5-hexanedione dioxime (Table I). The last-mentioned compound was prepared by addition of the sulfonyl halide to a suspension, in benzene, of the disodium salt of the dioxime. Not surprisingly, no bissulfonates of dialdoximes could be obtained by these techniques.[8] Condensation with excess 1,1-dimethyl-

(1) D. F. Gamble, H. W. Bond, and A. Burger in "Medicinal Chemistry," A. Burger, Ed., 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1960, p 1083.

(2) G. R. Greenberg, *Federation Proc.*, **12**, 651 (1953).

(3) W. Z. Heldt, *J. Am. Chem. Soc.*, **80**, 5880 (1958), and references cited therein.

(4) P. A. S. Smith and E. E. Most, Jr., *J. Org. Chem.*, **22**, 358 (1957).

(5) A. Burger in "Medicinal Chemistry," A. Burger, Ed., 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1960, p 509.

(6) Prior to this investigation reports on only two bisoxime *p*-toluenesulfonates[7] and no bisquaternary hydrazones could be found in the literature.

(7) I. L. Knunyants and B. P. Fabrichnyi, *Dokl. Akad. Nauk SSSR*, **68**, 701 (1949); G. I. Glover and H. Rapoport, *J. Am. Chem. Soc.*, **86**, 3397 (1964).

(8) The elimination of substituents from aldoxime derivatives constitutes a general method of nitrile synthesis (R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, p 598). In several attempted preparations of aldoxime *p*-toluenesulfonates, we detected, by infrared absorption spectra, the formation of nitrile groups.