22.6 g (85%) of **6** as an off-white powder. High-performance LC analysis indicated that the product was 95% pure, containing 5% of a mixture of **3** and **11**. Samples of 3.01 and 2.87 g were separately further purified on a column of Sephadex LH-20 (2.8 L) eluted with 7:1:1 hexane–toluene–MeOH to provide 99% pure **6**: IR 3600–3200 (OH), 1715 (C=O); UV (1.89×10^{-5} M) λ_{max} 238 nm (ϵ 27 100), 245 (30 100), 254 sh (19 300); $[\alpha]_D$ +71.5 ± 0.3° (*c* 0.755, $CHCl_3$), −18.1 ± 0.3° (*c* 0.785, CH_3OH). Anal. ($C_{48}H_{74}O_{14}\cdot 0.5H_2O$) C, H.

3,4,22,23-Tetrahydroavermectin B_1 (11). The aforementioned Sephadex LH-20 chromatography of **6** also provided impure **11**, which was purified using preparative TLC (1000 μm of silica gel developed twice with 9:1 toluene–*i*-PrOH). The product was eluted with EtOAc, lyophilized, and dried to provide 231 mg (4%) of **11** as a white powder, 98% pure by high-performance LC: IR 3600–3200 (OH), 1705 (C=O); UV (3.06×10^{-5} M) λ_{max} 238 nm (ϵ 25 800), 244 (29 300), 252 sh (18 900); $[\alpha]_D$ +87.5 ± 1.1° (*c* 0.570, $CHCl_3$), +39.6 ± 0.4° (*c* 0.790, CH_3OH). Anal. ($C_{48}H_{76}O_{14}$) C, H.

22,23-Dihydroavermectin B_1 Monosaccharide (9). To a stirred solution of 99:1 *i*-PrOH–concentrated H_2SO_4 (65 mL) at 25 °C was added solid **6** (500 mg, 0.571 mmol). After stirring for 18 h, the solution was diluted with CH_2Cl_2 (200 mL), neutralized with saturated aqueous $NaHCO_3$ solution, and diluted with enough H_2O to dissolve precipitated salts. The organic layer was separated, washed with brine (100 mL), dried over anhydrous $MgSO_4$, and evaporated. The product was purified using preparative TLC (1000 μm of silica gel developed twice with 19:1 $CHCl_3$–THF). The product was eluted with EtOAc, evaporated, lyophilized, and dried to provide 355 mg (85%) of **7** as a white powder. An analytical sample was prepared by chromatographing 131 mg of **7** on Sephadex LH-20 (150 mL) eluted with 7:1:1 hexane–toluene–MeOH. Evaporation, lyophilization, and drying provided 82 mg of white powder, >99% pure by high-performance LC: IR 3600–3200 (OH), 1720 (C=O); UV (3.29×10^{-5} M) λ_{max} 238 nm (ϵ 26 800), 245 (29 900), 253 sh (19 100); $[\alpha]_D$ +46.6 ± 0.6° (*c* 0.680, $CHCl_3$), −4.3 ± 0.2° (*c* 0.775, CH_3OH). Anal. ($C_{41}H_{62}O_{11}\cdot 0.5H_2O$) C, H.

22,23-Dihydroavermectin B_1 Aglycon (10). To a stirred solution of 99:1 MeOH–concentrated H_2SO_4 (20 mL) at 25 °C was added 2.03 g (2.32 mmol) of **6**. After the solution was stirred for 18 h, the reaction was neutralized by the addition saturated aqueous $NaHCO_3$ solution (20 mL), diluted with Et_2O (20 mL), and enough water was added to dissolve precipitated salts. The layers were separated and the aqueous phase was washed with Et_2O (3 × 10 mL). The combined organic phases were washed with H_2O (25 mL) and brine (25 mL), dried over anhydrous $MgSO_4$, and evaporated. Crude **10** was chromatographed on a column of silica gel (200 g), eluted with 3:1 CH_2Cl_2–EtOAc. Evaporation, lyophilization, and drying afforded 1.03 g (76%) of **10** as a white powder. An analytical sample was prepared using preparative TLC (1000 μm of silica gel developed with 90:10:1 CH_2Cl_2–EtOAc–EtOH). Elution with EtOAc, evaporation, lyophilization, and drying provided pure **10**: IR 3600–3200 (OH), 1712 (C=O); UV (4.03×10^{-5} M) λ_{max} 238 nm (ϵ 25 600), 244 (27 800), 252 sh (18 300); $[\alpha]_D$ +112.1 ± 1.0° (*c* 0.800, $CHCl_3$), +39.7 ± 0.4° (*c* 0.795, CH_3OH). Anal. ($C_{34}H_{50}O_8$) C, H.

Acknowledgment. We thank Drs. G. Albers-Schönberg, B. H. Arison, and A. W. Douglas for providing spectral data.

Supplementary Material Available: 300-MHz ^1H NMR and mass spectral data (2 pages). Ordering information is given on any current masthead page.

Synthesis of Potential Inhibitors of Hypoxanthine–Guanine Phosphoribosyltransferase for Testing as Antiprotozoal Agents. 2. 1-Substituted Hypoxanthines

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Evidence indicating that effective in vivo inhibition of hypoxanthine guanine phosphoribosyltransferase (HGPRT, EC 2.4.2.8) should produce antiprotozoal activity without significant toxic effects on mammalian hosts prompted syntheses of 1-substituted hypoxanthines bearing functionalized side chains whose groupings might interact with appropriate groupings of HGPRT to form covalent bonds or strong hydrophobic bonds. 3-(Fluorosulfonyl)benzoyl, 4-(fluorosulfonyl)benzoyl, 4-chlorobenzoyl, and bromoacetyl derivatives of two parent amines, 1-(2-aminoethyl)-hypoxanthine and 1-(4-aminobenzyl)hypoxanthine, were synthesized for evaluation in this connection. None of these compounds extended the life span of *Plasmodium berghei* infected mice or showed significant in vitro inhibition of HGPRT from H.Ep.-2 cells, but 1-[2-(bromoacetamido)ethyl]hypoxanthine displayed in vivo activity against *Trypanosoma rhodesiense*.

In the first paper in this series,[1] we reviewed the sizable body of biochemical evidence indicating that the intracellular phosphoribosylation of hypoxanthine, a conversion promoted by hypoxanthine–guanine phosphoribosyltransferase (HGPRT, EC 2.4.2.8), is a vital event in the purine metabolism of protozoal parasites. The parasites are apparently devoid of an alternative biosynthetic route to purine nucleotides, but the cells of their mammalian hosts possess the enzymes of the de novo pathway to purine nucleotides and use the purine phosphoribosyltransferases in secondary ways. The evidence indicates that effective in vivo inhibition of HGPRT should prevent proliferation of protozoal parasites without significant toxic effects on mammalian hosts.

In recent developments in this connection, Kidder and Nolan observed severe inhibition of growth when culture media of *Crithidia fasciulata* and four species of *Leishmania* containing adenine as the purine source were treated with deoxycoformycin, a potent inhibitor of adenine aminohydrolase (EC 3.5.4.2). Deoxycoformycin did not affect growth when hypoxanthine was the purine source.[2] The conclusion that hypoxanthine is the obligatory base for nucleotide synthesis in the organisms studied is the same as that reached by Van Dyke following studies of the relative amounts of incorporation of hypoxanthine, adenine, and adenosine in the nucleic acids of *Plasmodium berghei*.[3] In another recent development, Wang and co-workers found evidence suggesting that the anticoccidial action of 9-(2-chloro-6-fluorobenzyl)adenine is due to inhibition of hypoxanthine transport, possibly

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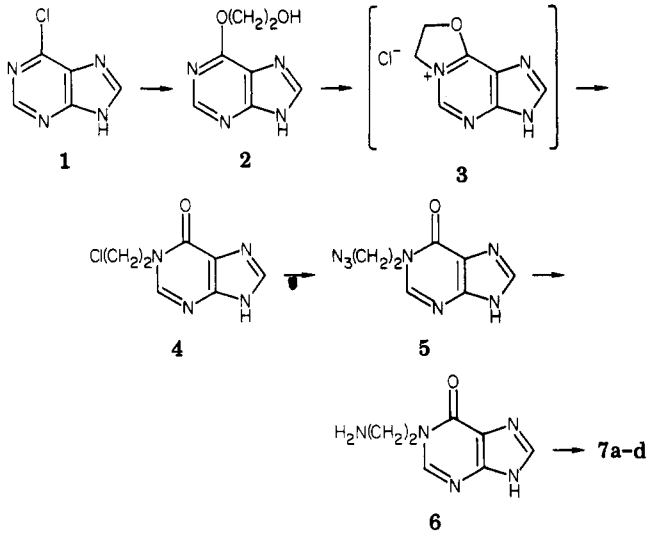
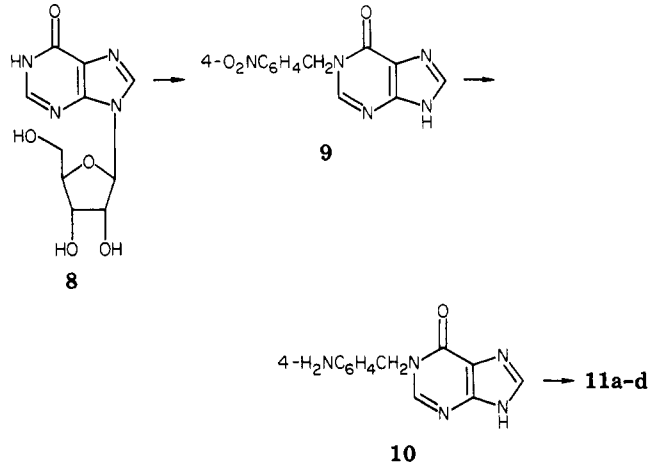
(3) Van Dyke, K. *Tropenmed. Parasitol.* **1975**, *26*, 232. Manandhar, M. S. P.; Van Dyke, K. *Exp. Parasitol.* **1975**, *37*, 138.

0022-2623/80/1823-1136$01.00/0

Scheme I. 1-(2-Aminoethyl)hypoxanthine and Derivatives

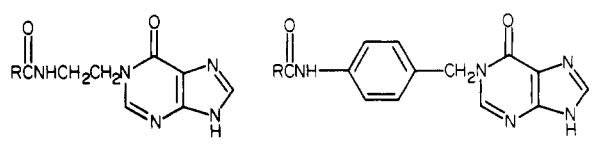


Scheme II. 1-(4-Aminobenzyl)hypoxanthine and Derivatives



through high affinity binding between the drug and the hypoxanthine–guanine carrier in cell membranes.[4]

Our efforts to prepare inhibitors of HGPRT began with studies of 7-substituted derivatives of guanine and hypoxanthine.[1] The general synthetic approach involved the introduction of both aliphatic and aromatic side chains bearing amino groups, which were then converted to *N*-acyl or *N*-aroyl derivatives bearing reactive groupings such as 3- and 4-(fluorosulfonyl)benzoyl or bromoacetyl and hydrophobic groupings such as 4-chlorobenzoyl. In the work described in this report, we studied analogous compounds derived from 1-(2-aminoethyl)hypoxanthine (**6**, Scheme I) and 1-(4-aminobenzyl)hypoxanthine (**10**, Scheme II). Preparations of the derivatives **7a–d** and **11a–d** were less involved than those of the 7-substituted guanine analogues described earlier because of favorable solubility of **6** and **10** in appropriate solvents.



7a, R = 3-$FSO_2C_6H_4$
b, R = 4-$FSO_2C_6H_4$
c, R = 4-ClC_6H_4
d, R = $BrCH_2$

11a, R = 3-$FSO_2C_6H_4$
b, R = 4-$FSO_2C_6H_4$
c, R = 4-ClC_6H_4
d, R = $BrCH_2$

1-Substituted hypoxanthines have been prepared by alkylation of inosine in the presence of an appropriate base in dimethylformamide (DMF), followed by removal of the ribosyl grouping by acidic hydrolysis.[5-7] An adaptation of that method was used in the synthesis of the 4-aminobenzyl compound **10** (Scheme II), but the key step in the synthesis of the 2-aminoethyl analogue **6** was the formation of 1-(2-chloroethyl)hypoxanthine (**4**) as a rearrangement product from the treatment of 6-(2-hydroxyethoxy)purine (**2**) with $SOCl_2$ in refluxing $CHCl_3$. Replacement of the hydroxyl grouping of **2** is apparently followed by ring closure at the 1 position[8] to give the intermediate **3**, whose oxazoline ring is then cleaved to produce **4**. The pure product, obtained in 70% yield, gave UV absorption maxima at pH 1, 7, and 13 identical with those reported for 1-ethyl-[6] and 1-butylhypoxanthine.[7] Treatment of **4** with NaN_3 in DMF gave the azido compound **5**, which was reduced catalytically to the amine **6**. The aroyl types **7a–c** were prepared from **6** and the substituted benzoyl chlorides in DMF containing $(i\text{-Pr})_2NEt$, and the bromoacetyl derivative **7d** was obtained using 4-nitrophenyl bromoacetate in Me_2CO–H_2O.

Alkylation of inosine with 4-nitrobenzyl bromide in DMF containing K_2CO_3 was followed by deribosylation of the resulting 1-(4-nitrobenzyl)inosine to give 1-(4-nitrobenzyl)hypoxanthine (**9**) in 83% overall yield. Catalytic reduction gave the amine **10**. Aroylation of **10** in glacial AcOH containing $(i\text{-Pr})_2NEt$ then gave the derivatives **11a–c**, which precipitated from the reaction solutions. Bromoacetic anhydride and **10** in glacial AcOH gave **11d**.

Biological Data.[9] None of these compounds proved effective against *P. berghei* in mice[10] nor did any inhibit HGPRT (from H.Ep.-2 cells) in vitro.[11,12] The similarities of the substrate specificities of HGPRT from *P. chabaudi* to those of the enzyme from a mammalian source[13] make it reasonable to conclude that the *P. berghei* enzyme is probably not inhibited in the in vivo tests. The bromoacetamido compound **7d**, however, was found to have activity against *Trypanosoma rhodesiense* in mice. In a described test system,[14] **7d** gave the following results: at a dose level of 106 mg/kg of body weight, one of five treated mice survived; at 212 mg/kg, one of five survived; and at 424 mg/kg, two of five survived, with two deaths attributed to toxicity. Since **7d** did not exert inhibitory action against HGPRT in the in vitro assay, we cannot account for its in vivo activity against *T. rhodesiense* in

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(8) A related ring closure at the 1 position was observed in earlier studies on 6-[(2-chloroethyl)thio]purine.[6]

(9) The antimalarial and antitrypanosomal test results were provided by the Walter Reed Army Institute of Research. The test methods are described in ref 10 (antimalarial) and 14 (antitrypanosomal).

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Table I. Data on Compounds Shown in Schemes I and II

no.	yield, %	mp, °C dec[a]	molecular formula[b]
2	76	>260	$C_7H_5N_4O_2$
4	70	>300	$C_7H_7ClN_4O$
5	65	138-140	$C_7H_7N_7O \cdot 0.5H_2O$
6	98	224-226	$C_7H_9N_5O$
7a	84	>180	$C_{14}H_{12}FN_5O_4S \cdot 0.75H_2O$
7b	94	260	$C_{14}H_{12}FN_5O_4S$[c]
7c	81	281-283	$C_{14}H_{12}ClN_5O_2$
7d	73	>280	$C_9H_{10}BrN_5O_2$
9	83	253-255	$C_{12}H_9N_5O_3$
10	90	250-251	$C_{12}H_{11}N_5O$
11a	62	224-226	$C_{19}H_{14}FN_5O_4S \cdot 0.5H_2O$
11b	66	218-220	$C_{19}H_{14}FN_5O_4S \cdot 0.5H_2O$
11c	85	350-352	$C_{19}H_{14}ClN_5O_2 \cdot 0.5H_2O$
11d	89	>325	$C_{14}H_{12}BrN_5O_2$

[a] Several compounds lack definite melting points, and the figures given represent onset of visible decomposition (Mel-Temp apparatus). [b] Anal. C, H, N on all compounds except 7b. [c] Anal. C, H; N: calcd, 19.17; found, 19.61.

terms of our hypothesis on the consequences of inhibition of HGPRT. Although it is possible that **7d** may specifically inhibit HGPRT from *T. rhodesiense*, it seems more likely that it may interfere with hypoxanthine–guanine transport in the organism.

Experimental Section

Additional data on the synthetic procedures are listed in Table I. Analytical results indicated by element symbols were within ±0.4% of the theoretical values. Microanalyses were performed for the most part by Galbraith Laboratories, Knoxville, Tenn. Spectral determinations and some of the elemental analyses were performed at Southern Research Institute (Molecular Spectroscopy Section) under the direction of Dr. William C. Coburn, Jr. ^1H NMR spectra (Varian XL-100-15) were obtained on most of the compounds, and UV (Cary Model 17) and IR (Perkin-Elmer Models 521 and 621) spectra were obtained on each compound. The spectra produced by each compound were consistent with those to be expected. Only the spectral data that aided in establishing the structure of the parent amine **6** are listed. Thin-layer chromatographic analyses [Analtech precoated (250 μm) silica gel G(F) plates] were used to follow the courses of the reactions and to examine products for purity; each compound moved as a single spot. Most of the chromatograms were run in $CHCl_3$–MeOH (5:1, v/v). The red spot produced by **6** and **10** on ninhydrin-treated chromatograms allowed sensitive monitoring of the courses of the reactions used to prepare the derivatives **7a–d** and **11a–d**. Compounds **7a,b,d** and **11a,b,d** gave bluish-purple spots on chromatograms treated with 4-(4-nitrobenzyl)pyridine as described by Baker and co-workers.[15] Unless other conditions are specified, evaporations were performed at about 25 °C with a rotary evaporator and a water aspirator. Products were dried in vacuo (oil pump) over P_2O_5 at room temperature.

6-(2-Hydroxyethoxy)purine (2). NaH (22.6 g of 50% in oil dispersion, 0.470 mol) was added in portions over a 5-h period to stirred, freshly distilled ethylene glycol (550 mL). After the last portion had dissolved, 6-chloropurine (36.3 g, 0.235 mol) was added, and the mixture was heated at 100–120 °C (mainly at 110 °C) for 4 h, then cooled, and treated dropwise with concentrated HCl to produce pH 5. Refrigeration for several hours gave a white precipitate, which was collected and recrystallized from H_2O (2.5 L) to give pure **2**.

1-(2-Chloroethyl)hypoxanthine (4). A stirred suspension of **2** (10.5 g, 58.3 mmol) in $CHCl_3$ (200 mL) at 0–5 °C was treated dropwise during 30 min with a solution of freshly distilled $SOCl_2$ (27.6 g, 0.232 mol) in $CHCl_3$ (40 mL). The continuously stirred mixture was kept at 0–5 °C for 30 min before the cooling bath was removed. After 30 min at ~25 °C, the mixture was gradually heated to boiling and was refluxed for 2.5 h. The solid filtered from the cooled mixture was stirred with H_2O (50 mL), and the mixture was treated with sufficient 5% $NaHCO_3$ solution to produce pH 6. The collected and dried crude product (9.92 g) was recrystallized from MeCN (1 L) to give pure **4**: UV λ_{max} ($\epsilon \times 10^{-3}$), 0.1 N HCl, 249 nm (9.60); pH 7, 251 (9.05); 0.1 N NaOH, 261 (9.84); ^1H NMR (Me_2SO-d_6) δ 3.9, 4.2 (2 m, CH_2CH_2), 8.1, 8.3 (2 s, C_2 H, C_8 H), 13.3 (br s, imidazole NH).

1-(2-Azidoethyl)hypoxanthine (5). A mixture of **4** (2.0 g, 10 mmol) and NaN_3 (1.3 g, 20 mmol) in DMF (75 mL) was stirred at 100 °C for 3 h. The cooled mixture was filtered, and the DMF was removed from the clear filtrate by evaporation in vacuo (<1 mm). The solid residue was dissolved in H_2O (10 mL), and the solution was treated under N_2 in the hood with 6 N HCl to produce pH 5. The solid that formed was collected and purified by recrystallization from H_2O (10 mL).

1-(2-Aminoethyl)hypoxanthine (6). A solution of $5 \cdot 0.5H_2O$ (7.50 g, 35 mmol) in EtOH–H_2O (85:15, v/v; 750 mL) containing PtO_2 (750 mg) as catalyst was hydrogenated at room temperature and atmospheric pressure for 24 h. The system was purged and recharged with H_2 after 2, 4, and 7 h. The catalyst was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. Solid **6** that remained was stirred with EtOH (75 mL) and then collected: UV λ_{max} ($\epsilon \times 10^{-3}$), 0.1 N HCl, 249 nm (9.16); pH 7, 250 (8.82); 0.1 N NaOH, 261 (9.58).

Aroyl Derivatives 7a–c. The procedure described below for the preparation of 1-[2-[4-(fluorosulfonyl)benzamido]ethyl]-hypoxanthine (**7b**) was also used to prepare **7a** and **7c**. A solution of 4-(fluorosulfonyl)benzoyl chloride (2.78 g, 12.5 mmol) in DMF (25 mL) was added during 10 min with ice-bath cooling to a stirred suspension of **6** (1.79 g, 10 mmol) in DMF (50 mL) containing $(i\text{-Pr})_2NEt$ (1.72 g, 13 mmol). The ice bath was then removed, and the mixture was stirred for 1 h at 20–25 °C. DMF was removed from the resulting solution by evaporation in vacuo. The residue was stirred with Et_2O (100 mL), and the white solid was collected and washed with Et_2O followed by H_2O to give **7b**.

1-[2-(Bromoacetamido)ethyl]hypoxanthine (7d). A solution of 4-nitrophenyl bromoacetate[15] (3.25 g, 12.5 mmol) in Me_2CO (150 mL) was added to a solution of **6** (1.79 g, 10 mmol) in H_2O (50 mL). More 4-nitrophenyl bromoacetate (650 mg, 2.5 mmol) was added after 2 h. After a total reaction time of 4 h, the solvents were removed by evaporation under reduced pressure. The residue was stirred with H_2O (5 mL), collected, and washed with EtOH followed by Et_2O to give pure **7d**.

1-(4-Nitrobenzyl)hypoxanthine (9). A mixture of inosine (10.7 g, 40.0 mmol), anhydrous K_2CO_3 (8.0 g, 60 mmol; dried in vacuo at 110 °C over P_2O_5), 4-nitrobenzyl bromide (9.1 g, 42 mmol), and DMF (600 mL) was stirred at ~25 °C for 18 h. The DMF was removed by evaporation in vacuo (<1 mm), and the residue was stirred with Et_2O and collected. The air-dried solid was then stirred with 1 N HCl (60 mL), and the mixture was heated at 100 °C for 1 h. Solid that separated when the solution was allowed to cool was collected, stirred with 5% $NaHCO_3$, and then combined with the precipitate obtained when the acidic filtrate from the first solid was neutralized to pH 6 by treatment with NaOH solution. The crude product (11.2 g) was then recrystallized from H_2O (1.75 L) to give pure **9**.

1-(4-Aminobenzyl)hypoxanthine (10). A suspension of **9** (6.78 g, 25.0 mmol) and 5% Pd on C (700 mg) in 0.3 N HCl (675 mL) was hydrogenated at ambient conditions (26 °C and 746 mmHg pressure). The calculated volume of H_2 (1.94 L) was consumed in 5 h. The catalyst was removed by filtration, and the filtrate was concentrated to 200 mL by evaporation in vacuo before it was treated with concentrated NH_4OH solution (to pH 6) to give **10**.

Aroyl Derivatives 11a–c. The procedure used to prepare 1-[4-[3-(fluorosulfonyl)benzamido]benzyl]hypoxanthine (**11a**) also sufficed for **11b** and **11c**. A solution of 3-(fluorosulfonyl)benzoyl chloride (1.85 g, 8.30 mmol) in AcOH (25 mL) was added during 10 min to a stirred solution of **10** (1.93 g, 8.00 mmol) in AcOH (75 mL) containing $(i\text{-Pr})_2NEt$ (1.15 g, 8.60 mmol). Stirring at ~25 °C was continued for 1 h while **11a** separated. The collected product was washed with Et_2O followed by H_2O.

1-[4-(Bromoacetamido)benzyl]hypoxanthine (11d). A solution of freshly distilled bromoacetic anhydride (3.12 g, 12.0 mmol) in AcOH (25 mL) was added to a stirred solution of **10**

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(1.93 g, 8.00 mmol) in AcOH (75 mL). After 15 min at ~25 °C, the solution was poured into Et_2O (500 mL). The solid that formed was collected and washed with Et_2O followed by H_2O to give pure **11d**.

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Studies on Antimicrobial Agents. 1. Synthesis and Relation between the Antimicrobial Activities and Certain Physicochemical Properties of Some *N'*-(Pyridinioacetyl) Fatty Acid Hydrazides[1]

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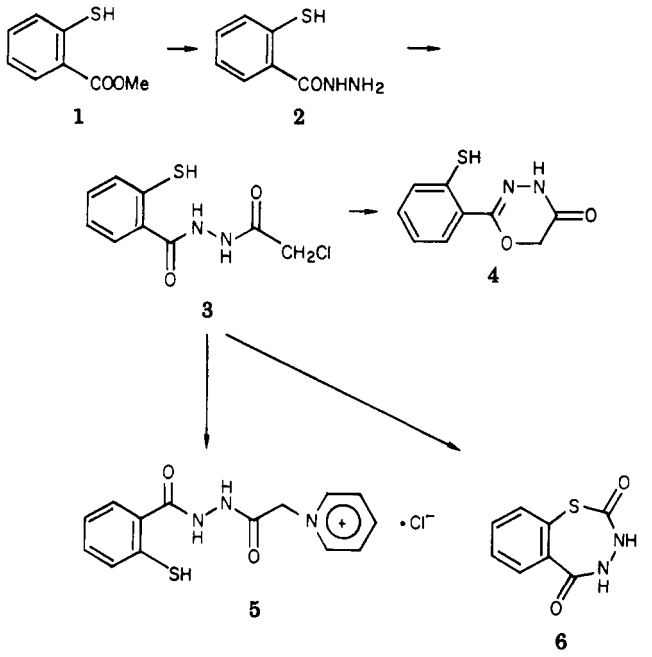
A new series of *N'*-(pyridinioacetyl)alkanoic and -benzoic acid hydrazides, as chloride salts, and some cyclic analogues produced by ring closure have been synthesized and tested in a search for more effective germicides. Physicochemical parameters, such as surface tension, critical micelle concentration, and thermodynamic activity (Ferguson values), were also determined. *Staphylococcus aureus* and *Streptococcus pyogenes* were the most susceptible of the organisms tested. *N'*-(Pyridinioacetyl)hexadecanoic acid hydrazide exhibited the highest toxicity to *Staph. aureus* and fungi. The mean surface tension of the equitoxic solutions is 59.8 ± 0.3 dyn/cm for bacteria and 51.65 ± 0.1 dyn/cm for fungi. *N'*-(Pyridinioacetyl)octadecanoic acid hydrazide and *N'*-(pyridinioacetyl)-9-octadecenoic acid hydrazide exhibit the highest toxicity to *S. pyogenes* (1.1×10^{-6} M). The surface tension of their equitoxic solutions and their Ferguson values indicate that these compounds may act through a different mechanism.

With the disclosure by Domagk[2] of the much improved germicidal activity obtained when a large aliphatic residue was attached to the quaternary nitrogen atom, the study of this type of compound was greatly stimulated. The chemotherapeutic applications of quaternary ammonium salts have gained importance since World War II; many members of this class with a potent bactericidal and antifungal activity have found general utility in skin disinfectants, as well as in the formulation of creams, ointments, lotions, etc. Although in the past 40 years many patents have been issued in the field, few improvements on benzalkonium chloride[2] were reached.

In a further exploration of the influence of chemical structure upon the antimicrobial activity of quaternary ammonium salts, some of the compounds described in an earlier paper[3a,b] were modified by the introduction of a bishydrazide residue into the pharmacophoric group. Hence, a series of 20 new *N'*-(pyridinioacetyl)alkanoic and -benzoic acid hydrazides as chloride salts has been prepared (Table I). These compounds and their cyclic analogues (Scheme I) produced by ring closure, 5,6-dihydro-2-(mercaptophenyl)-4*H*-1,3,4-oxadiazin-5-one (**4**) and 3,4,5,6-tetrahydro-2*H*-1,4,5-benzothiadiazocine-3,6-dione (**6**), previously reported,[4] were evaluated for in vitro antimicrobial activity against several strains of bacteria and fungi. Physicochemical parameters such as surface tension, critical micelle concentration, and thermodynamic activity (Ferguson values) were determined.

Scheme I



Chemistry. The *N'*-(pyridinioacetyl)alkanoic and -benzoic acid hydrazides, **1–20**, were prepared in a conventional manner[4,5] as shown in Scheme I. When **1** was

(1) This work forms part of a thesis submitted by one of us (S.M.S.) to the University of Buenos Aires for the Degree of Doctor in Experimental Pharmacology.
(2) G. Domagk, *Dtsh. Med. Wochenschr.*, **61**, 829 (1935).
(3) (a) A. G. Von Heyden, French Patent 812 360, May 8, 1937; *Chem. Abstr.*, **34**, 7068 (1940). (b) G. A. Knight and B. D. Shaw, *J. Chem. Soc.*, 682 (1938).
(4) S. M. Sicardi, S. Landam, and C. H. Gaozza, *J. Heterocycl. Chem.*, **10**, 1039 (1973).

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