Preparation of 7-Substituted Pyrrolo[2,3-*d*]pyrimidines and 9-Substituted Purines as Potential Antiparasitic Agents

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Received October 4, 1982

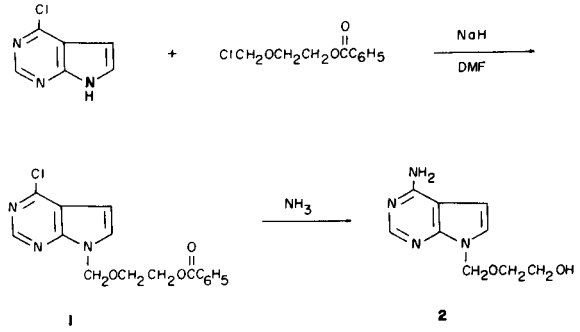
A series of six 7-substituted pyrrolo[2,3-*d*]pyrimidines and two 9-substituted purines were prepared and evaluated for potential antiparasitic activity. All were inactive against *P. berghei* in mice. Six of the target compounds were also evaluated for antitrypanosomal activity against *T. rhodesiense* in mice. All six compounds were also inactive in this screen.

J. Heterocyclic Chem., **20**, 295 (1983).

In 1975 Jaffe (1) published a review article in which he indicated that several nucleoside analogs possessed antiparasitic activity. Among the more active examples were puromycin, aminopuromycin, tubercidin and cordycepin. It has also been noted (2) that *(S)*-9-(2,3-dihydroxypropyl)-adenine was inhibitory to a number of DNA and RNA viruses and that 9-(2-hydroxyethoxymethyl)guanine was specifically effective against Herpes simplex virus. It was therefore concluded that an intact sugar moiety was not necessary for biological activity. The purpose of the present work was to prepare a series of acyclic nucleoside and nucleotide analogs of tubercidin, 2-fluoroadenosine and aminopuromycin in an attempt to develop a new series of effective antiparasitic agents.

Chemistry.

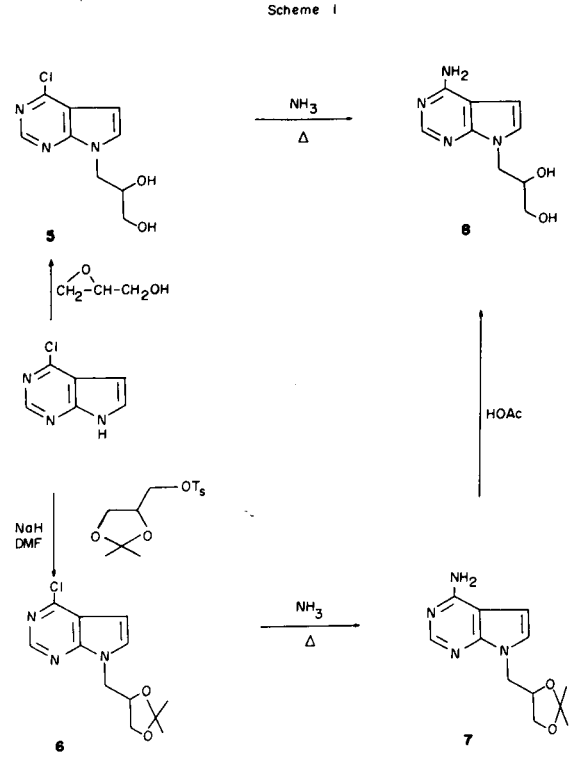
The first example 7-(2-hydroxyethoxymethyl)-4-aminopyrrolo[2,3-*d*]pyrimidine (**2**) was prepared as shown below. 4-Chloropyrrolo[2,3-*d*]pyrimidine (3) was condensed with 2-benzoyloxyethoxymethyl chloride (4) to afford intermediate **1** which upon treatment with methanolic ammonia



1 2

in a sealed vessel afforded the target compound **2**. The 4-dimethylamino analog **3** was prepared similarly by substituting dimethylamine for ammonia. Treatment of **2** with trimethylphosphate (TMP) and phosphorous oxychloride afforded the phosphate ester **4**. 4-Amino-7-(2,3-dihydropyrrolo[2,3-*d*]pyrimidine (**8**) was prepared as shown in Scheme 1. 4-Chloropyrrolo[2,3-*d*]pyrimidine (3) could be condensed with glycidol under standard conditions to yield **5** which upon treatment with ammonia afforded **8**. A higher yield route to **8** involved the use of the sequence developed by Holy (5). Treatment of 4-chloropyrrolo[2,3-*d*]-pyrimidine with 1-*O*-*p*-toluenesulfonyl-2,3-*O*-isopropylidine-sn-glycerol (5) afforded intermediate **6**. Treatment of **6** with ammonia afforded **7** and finally cleavage of the isopropylidene with acetic acid yielded **8**. The 4-dimethylamino analog **9** was prepared similarly.

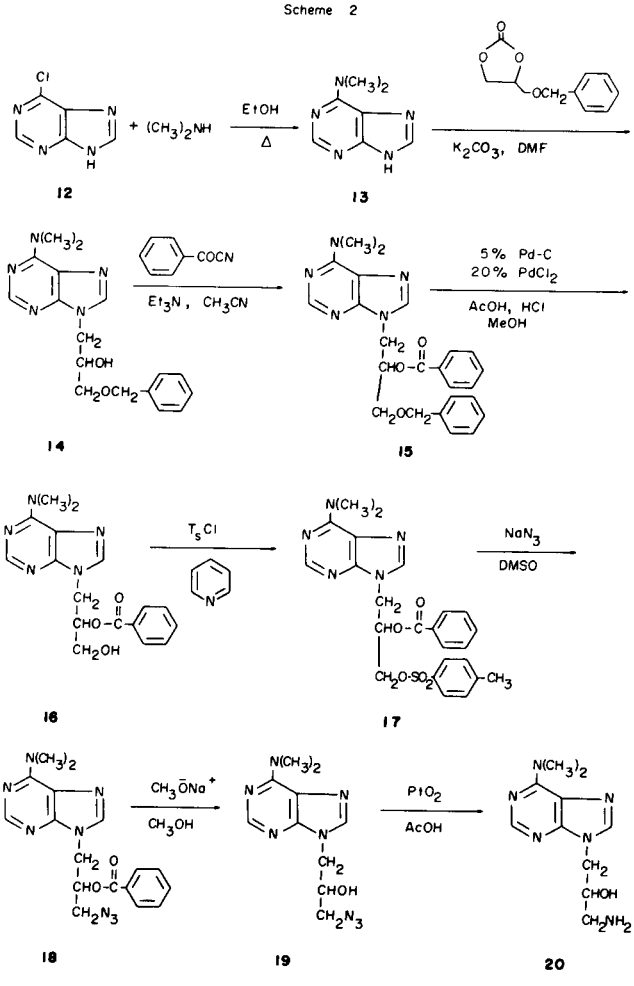
Scheme I



Treatment of **8** with TMP and phosphorous oxychloride afforded the phosphate ester **10**. 9-(2,3-Dihydroxypropyl)-2-fluoroadenine (**11**) was prepared from 2-fluoroadenine (6) and glycidol as described earlier for the preparation of **5**. Finally the aminopuromycin analog **20** was prepared *via* the lengthy sequence shown in Scheme 2. This is essentially the sequence developed by Holy (7) to prepare 9-(3-amino-2-hydroxypropyl)adenine. 6-Chloropurine (**12**) was

prepared following the procedure of Bendich, *et al.* (8). Treatment with dimethylamine in a sealed tube afforded 6-dimethylaminopurine (**13**). Condensation with 4-benzyloxymethyl-2-oxo-1,3-dioxalane afforded intermediate **14**. Treatment of **14** with benzoyl cyanide afforded the benzoate ester **15** which was debenzylated with palladium-carbon/palladium chloride to afford the 3'-hydroxy-2'-benzoate **16**. Treatment with tosyl chloride afforded tosylate **17**. Substitution of the tosylate with sodium azide afforded **18** which upon treatment with sodium methoxide resulted in cleavage of the ester to yield **19**. Reduction of azide **19** with PtO_2 afforded the target puromycin aminonucleoside analog **20**.

Scheme 2



Biological Activity.

Target compounds **2, 3, 4, 8, 9, 10, 11** and **20** were evaluated for blood schizonticidal (suppressive) antimalarial activity against *P. berghei* in mice (9). All were inactive at the highest dose level tested (640 mg/kg) and all with the exception of **20** were non-toxic at this level. Compound **20** showed 1/5 toxic deaths. Also compounds **2, 3, 4, 9, 10** and **11** were evaluated for antitrypanosomal activity against *T. rhodesiense* in mice (10). All examples were also inactive in this screen. Although, based on Jaffe's review, the subject compounds may be expected to possess *in vitro* antiparasitic activity they obviously are not active *in vivo*. This may be attributable to membrane transport phenomena.

EXPERIMENTAL

All melting points and boiling points are uncorrected. Elemental analyses were peformed by Midwest Microlab Ltd., Indianapolis, Indiana. The nmr spectra were determined on a Varian Model T60A Spectrometer. Ethanol used in this work was specially denatured Grade 3A Alcohol (90%, ethanol, 5% 2-propanol and 5% methanol by volume).

7-(Benzoyloxyethoxymethyl)-4-chloropyrrolo[2,3-*d*]pyrimidine (**1**).

To a solution of 4-chloropyrrolo[2,3-*d*]pyrimidine (23 g, 0.15 mole) in dry *N,N*-dimethylformamide (250 ml) was added with stirring sodium hydride (60% oil dispersion, 7.0 g, 0.17 mole), followed by 2-benzoyloxyethoxymethyl chloride (**4**) (32 g, 0.15 mole). The reaction mixture was stirred at room temperature 30 minutes, diluted with water (500 ml), neutralized with acetic acid and extracted with chloroform (500 ml). The chloroform layer was washed with water (2 ×) dried over potassium carbonate and concentrated to dryness. The residual oil was chromatographed over silica gel (EM Labs) and eluted with chloroform. The product-containing fractions were combined and concentrated. The residual oil was crystallized from methanol to afford the title product, (18.2 g, 37%), mp 62.5-64°.

Anal. Calcd. for $C_{16}H_{14}ClN_3O_3$: C, 57.93; H, 4.25; N, 12.67. Found: C, 57.89; H, 4.26; N, 12.49.

7-(2-Hydroxyethoxymethyl)-4-aminopyrrolo[2,3-*d*]pyrimidine (**2**).

A solution of the above 4-chloropyrrolo[2,3-*d*]pyrimidine (4 g, 12 mmoles) in methanol saturated with ammonia at 0° (200 ml) was heated in a steel bomb at 130° for 8 hours. The solution was concentrated to dryness and the solid residue was crystallized from acetonitrile (25 ml) to afford the title compound (1.18 g, 47%), mp 127-129°.

Anal. Calcd. for $C_9H_{12}H_4O_2$: C, 51.91; H, 5.81; N, 26.91. Found: C, 51.61; H, 5.83; N, 26.87.

7-(2-Hydroxyethoxymethyl)-4-dimethylaminopyrrolo[2,3-*d*]pyrimidine (**3**).

2'-Benzoate **1** (9 g, 0.027 mole) was suspended in alcohol (170 ml) and cooled in an ice bath. Dimethylamine (15 g, 0.33 mole) was added with stirring. The mixture was heated in a steel bomb at *ca.* 120° for 12 hours, concentrated *in vacuo*, extracted with boiling benzene (100 ml) and filtered. After cooling in an ice bath the crystals were collected and air dried to give crude product, 6 g, mp 112-115°. Recrystallization from benzene (90 ml, Norit A) afforded the title compound, 4.8 g in two crops, (68%) mp 117-119°.

Anal. Calcd. for $C_{11}H_{16}N_4O_2$: C, 55.92; H, 6.83; N, 23.71. Found: C, 55.78; H, 6.73; N, 23.78.

7-(2-Hydroxyethoxymethyl)-4-aminopyrrolo[2,3-*d*]pyrimidine 2'-Phosphate (**4**).

To cold (0°, ice-salt bath) trimethylphosphate (TMP, 62 ml) was added phosphorus oxychloride (4.7 ml, 0.05 mole) and the solution was stirred for 30 minutes. 7-(2-Hydroxyethoxymethyl)-4-aminopyrrolo[2,3-*d*]pyrimidine (**2**) (6.1 g, 0.029 mole) was added and stirring was continued at 0-5° for an additional 1.5 hours. Cold water (60 ml) was added and the cold solution was neutralized with ammonium hydroxide to *p*H ~6.4. The mixture was then heated on the steam bath for 0.5 hours and cooled to room temperature. The crystals formed were collected by filtration and air dried to yield 5.5 g of white solid, mp 245-250° dec. This crude product was repeatedly washed wtih hot water (3 × 150 ml) to afford the title compound, 3.7 g, (41%) mp 260-262° dec.

Anal. Calcd. for $C_9H_{13}N_4O_5P$: C, 37.64; H, 4.55; N, 19.51; P, 10.78. Found: C, 37.52; H, 4.42; N, 19.20; P, 10.97.

7-(2,3-Dihydroxypropyl)-4-chloropyrrolo[2,3-*d*]pyrimidine (**5**).

A mixture of 4-chloropyrrolo[2,3-*d*]pyrimidine (2.30 g, 15 mmoles) glycidol (2.2 g, 30 mmoles) and potassium carbonate (anhydrous, 5 mg) in acetonitrile (15 ml), under a nitrogen atmosphere, was refluxed for 5 hours at wich time additional glycidol (2 g, 27 mmoles) was added. After refluxing overnight, the solution was evaporated *in vacuo* and the residue chromatographed over a column of silica gel (EM Labs) with methanol in ethyl acetate. The concentration of methanol was gradually increased to 10%. The faster moving (product) band was collected and the volatiles removed to yield a viscous oil (2 g) which slowly solidified. Recrystallization from ethyl acetate-hexanes (1:1) gave 1.25 g (37%) of analytically pure title compound, mp 98-101°.

Anal. Calcd. for $C_9H_{10}ClN_3O_2$: C, 47.48; H, 4.43; N, 18.46; Cl, 15.57. Found: C, 47.54; H, 4.50; N, 18.21; Cl, 15.81.

2′,3′-*O*-Isopropylidene-4-chloro-7-(2,3-dihydroxypropyl)pyrrolo[2,3-*d*]-pyrimidine (**6**).

A solution of 4-chloropyrrolo[2,3-*d*]pyrimidine (1.54 g, 10 mmoles) in *N,N*-dimethylformamide (anhydrous, 15 ml) under a nitrogen atmosphere was treated with sodium hydride (50%, 0.5 g, 10.5 mmoles). After hydrogen gas evolution ceased, the mixture was treated with 1-*O*-*p*-toluenesulfonyl-2,3-*O*-isopropylidene-sn-glycerol (5) (3.38 g, 12.5 mmoles) and heated at 100° for 2 hours. After cooling, the mixture was diluted with water (100 ml) and extracted with chloroform (3 × 100 ml). The chloroform layer was washed with water, dried (potassium carbonate) and evaporated *in vacuo* to a gum which was chromatographed over silica gel (EM Labs). Elution with methanol in chloroform (percentage gradually increased to 3%) brought down the title compound which preceeded colored impurities. Evaporation of product-containing fractions gave 1.9 g (71%) of the title compound as viscous oil which was used without further purification.

2′,3′-*O*-Isopropylidene-4-amino-7-(2,3-dihydroxypropyl)pyrrolo[2,3-*d*]pyrimidine (**7**).

A solution of the above compound (0.95 g, 3.5 mmoles) in ethanol (50 ml) was cooled to 0° and saturated with ammonia. This solution was placed in a steel bomb and heated at 125° for 5 hours. After cooling, the solution was evaporated *in vacuo* and the residue extracted with boiling acetonitrile (2 × 50 ml). The combined extracts were filtered and evaporated *in vacuo* to give nearly pure title compound (0.6 g,68%) as a viscous oil which was suitable for further transformation. An analytical sample was obtained from ethanol-ligroin (60-110°), mp 120-122°.

Anal. Calcd. for $C_{12}H_{16}N_4O_2$: C, 58.05; H, 6.50; N, 22.57. Found: C, 57.85; H, 6.48; N, 22.33.

4-Amino-7-(2,3-dihydroxypropyl)pyrrolo[2,3-*d*]pyrimidine (**8**).

The preceding crude compound was refluxed in 80% aqueous acetic acid (18 ml) for 1 hour. The volatiles were removed *in vacuo* and the residue co-evaporated with water (4 × 5 ml) and finally ethanol (3 × 5 ml). The residue was recrystallized from ethanol-petroleum ether (60-110°) with charcoaling to give the title compound, 0.3 g, mp 188-190°, (40%).

Anal. Calcd. for $C_9H_{12}N_4O_2$: C, 51.91; H, 5.81; N, 26.91. Found: C, 51.64; H, 6.09; N, 26.93.

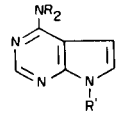
2′,3′-*O*-Isopropylidene-4-dimethylamino-7-(2,3-dihydroxypropyl)pyrrolo-[2,3-*d*]pyrimidine.

A solution of 2′,3′-*O*-isopropylidene-4-chloro-7-(2,3-dihydroxypropyl)-pyrrolo[2,3-*d*]pyrimidine (**6**) (18 g, 67 mmoles) in ethanol (50 ml) was treated with a cold solution of dimethylamine (30 g, 0.67 mole) in ethanol (100 ml) and the resulting solution heated at *ca.* 130° in a steel bomb for 12 hours. The volatiles were removed *in vacuo* and the residue was chromatographed over a column of silica gel (Merck, 250 g) with chloroform-

Table I

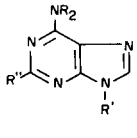
Physical Constants

A. 7-Substituted Pyrrolo[2,3-*d*]pyrimidines



No.	R	R′	Mp, °C (Solvent)	Yield (%)	Formula	Anal. (a)
2	H	$CH_2OCH_2CH_2OH$	127-129 (CH_3CN)	47	$C_9H_{12}N_4O_2$	
3	CH_3	$CH_2OCH_2CH_2OH$	117-119 (C_6H_6)	68	$C_{11}H_{16}N_4O_2$	
4	H	$CH_2OCH_2CH_2OPO_3H_2$	260-262 (H_2O)	41	$C_9H_{13}N_4O_5P$	P
8	H	$CH_2CH(OH)CH_2OH$	188-190 (EtOH-Petroleum ether)	40	$C_9H_{12}N_4O_2$	
9	CH_3	$CH_2CH(OH)CH_2OH$	132-135 (CH_3CN)	57	$C_{11}H_{16}N_4O_2$	
10	H	$CH_2CH(OH)CH_2OPO_3H_2$	>127	74	$C_9H_{18}N_5O_6P$	P

B. 9-Substituted Purines



No.	R	R′	R″	Mp, °C (Solvent)	Yield (%)	Formula	Anal. (a)
11	H	$CH_2CH(OH)CH_2OH$	F	250-252 (Water)	42	$C_8H_{10}FN_5O_2$	F
20	CH_3	$CH_2CH(OH)CH_2NH_2$	H	256-258 (Methanol)	67	$C_{10}H_{18}Cl_2N_6O$	Cl

(a) In addition to C, H, N, all values are ± 0.4% of theory.

methanol (gradually increasing to 2.5% methanol). The product containing fractions were combined and the solvent was removed *in vacuo* to give 10.5 g (56%) of an oil which was used without further purification.

4-Dimethylamino-7-(2,3-dihydroxypropyl)pyrrolo[2,3-*d*]pyrimidine (**9**).

The preceding compound (10.5 g) was refluxed with 20% aqueous acetic acid (13 ml/g) for 2 hours. The volatiles were removed *in vacuo* and the residue was co-evaporated *in vacuo* with water (4 × 30 ml) followed by ethanol (3 × 40 ml). The residue was chromatographed over a column of silica gel (Merck, 250 g) with chloroform-methanol. Elution with 2.5% methanol removed a fast moving impurity. Elution with 7.5% methanol eluted the product. The product containing fractions were combined and evaporated *in vacuo* to give crude title compound. Recrystallizing from acetonitrile afforded 6 g (57%) of pure title compound, mp 132-135°.

Anal. Calcd. for $C_{11}H_{16}N_4O_2$: C, 55.92; H, 6.83; N, 23.71. Found: C, 55.64; H, 6.67; N, 23.42.

4-Amino-7-(2,3-dihydroxypropyl)pyrrolo[2,3-*d*]pyrimidine-3′-phosphate Ammonium Salt Monohydrate (**10**).

To an ice-cold mixture of phosphorous oxychloride (0.77 ml, 1.22 g, 8 mmoles) in trimethylphosphate (14 ml) under a nitrogen atmosphere was added 4-amino-7-(2,3-dihydroxypropyl)pyrrolo[2,3-*d*]pyrimidine (**8**) (1.04 g, 5 mmoles) in one portion. The mixture was stirred with continual cooling and the reaction became homogeneous after *ca.* 20 minutes. After stirring one additional hour (tlc analysis indicated disappearance of starting material) the reaction was diluted slowly at 0° with water (100 ml). This solution was passed onto a column of Dowex 50W-X2 (50 ml). Elution with water removed impurities and the target compound was then eluted with 1.0 *N* ammonium hydroxide. Product containing fractions were pooled and evaporated *in vacuo* to a white solid. This material was dissolved in water (10 ml), filtered and evaporated *in vacuo* (2 ×). The resulting solid was dissolved in water (20 ml) and freeze dried to give 1.2 g (74%) of pure title compound which dehydrates above 127°.

Anal. Calcd. for $C_9H_{16}N_5O_6P$: C, 33.44; H, 5.61; N, 21.67; P, 9.58. Found: C, 33.18; H, 5.64; N, 21.40; P, 9.43.

9-(2,3-Dihydroxypropyl)-2-fluoroadenine (**11**).

A suspension of 2-fluoroadenine (6) (2.30 g, 15 mmoles) in *N,N*-dimethylformamide (anhydrous, 75 ml) under a nitrogen atmosphere was treated with potassium carbonate (anhydrous, 5 mg) and glycidol (3.3 g, 45 mmoles) and heated at 60°. After 18 hours, additional glycidol (2.2 g, 30 mmoles) was added and heating continued for 36 hours. The solids (starting adenine mixed with a small amount of product) were removed by filtration and discarded. The *N,N*-dimethylformamide was removed *in vacuo* and the residue recrystallized from water to give 1.43 g (42%) of nearly pure compound, mp 240-247° dec. Further recrystallizations from water and then from ethanol gave analytically pure title compound, mp 250-252°.

Anal. Calcd. for $C_8H_{10}N_5FO_2$: C, 42.29; H, 4.44; N, 30.83; F, 8.36. Found: C, 42.46; H,4.61; N, 30.64; F, 8.53.

6-Chloropurine (**12**).

Following the procedure of Bendich, *et al.* (8), a mixture of hypoxanthine (10 g, 74 mmoles), dimethylaniline (25 ml) and phosphorous oxychloride (80 ml, 890 mmoles) was refluxed for ½ hour, cooled overnight and the volatiles removed *in vacuo*. The residue was poured onto ice (450 g) and the *p*H adjusted to 12-14 with concentrated aqueous sodium hydroxide. The dark solution was washed with ether until the ether extract was colorless and then the aqueous layer was acidified with concentrated hydrochloric acid. This solution was continuously extracted with ether (1 *l*) for 48 hours. The ether was evaporated and the residue recrystallized from water to give 5.3 g (47%) of pure title compound mp >300°.

Anal. Calcd. for $C_5H_3ClN_4$: C, 38.85; H, 1.96; N, 36.25; Cl, 22.94. Found: C, 38.71; H, 2.21; N, 36.06; Cl, 22.86.

6-Dimethylaminopurine (**13**).

To a suspension of the above compound (5.25 g, 34 mmoles) in cold ethanol (75 ml) was added dimethylamine (16 g, 360 mmoles). The resulting solution was heated in a steel bomb at *ca.* 150° for 12 hours. The ethanol was decanted from solids. The solids were dissolved in water, combined with the ethanol and evaporated *in vacuo*. The residue was recrystallized from ethanol to give 4.5 g (81%) of pure title compound, mp 258-260°.

Anal. Calcd. for $C_7H_9N_5$: C, 51.52; H, 5.56; N, 42.94. Found: C, 51.22; H, 5.34; N, 42.67.

1-Benzyloxy-2,3-dihydroxypropane.

Following the procedure of Holy (5,7) a solution of 2,2-dimethyl-1,3-dioxolane-4-methanol (110.4 g, 0.836 mole) in methanol (50 ml) under a nitrogen atmosphere was added over 1 hour to a solution of sodium (20.1 g, 0.875 mole) in methanol (400 ml). Methanol was distilled and replaced with dry toluene until the temperature of the distillate reached 105°. The cooled solids were broken up and suspended in dry toluene (450 ml total volume) and treated with a solution of benzyl chloride (100.8 g, 0.875 mole) in dry toluene (50 ml). The resulting mixture was refluxed with mechanical stirring for 1½ hours, cooled and the salts filtered off. The toluene was distilled and the residue refluxed with 20% aqueous acetic acid for 8 hours. The volatiles were removed *in vacuo* and the residue distilled to give 124.5 g (82%) of the title compound, bp 145°/0.2 mm Hg, which was used without further purification.

4-Benzyloxymethyl-2-oxo-1,3-dioxolane.

The preceding compound (124 g, 0.68 mole) was treated with ethylene carbonate (100 ml) and sodium methoxide (~ 10 mg). The mixture was heated at 135° for 2 hours, neutralized with phosphoric acid (0.1 ml) and fractionated through the 6″ vigreaux column to give 85 g (62%) of pure title compound, bp 185-192°/2.25 mm Hg, which was used without further purification.

6-Dimethylamino-9-(3-benzyloxy-2-hydroxypropyl)purine (**14**).

A mixture of 6-dimethylaminopurine (2 g, 12 mmoles), potassium carbonate (anhydrous, 0.5 g, 4 mmoles) and the preceding compound (3 g, 14 mmoles) in *N,N*-dimethylformamide (12 ml) was refluxed under a nitrogen atmosphere for 2½ hours. After cooling, the mixture was filtered and the volatiles removed *in vacuo*. The residue was chromatographed over a column of silica gel (Merck, 100 g) with cloroform-methanol (gradually increased to 3% methanol). The product containing fractions were combined and evaporated to 3.8 g of purified title compound. Recrystallization from ether-petroleum ether (1:1) gave 1.9 g (49%) of analytically pure material, mp 74-78°.

Anal. Calcd. for $C_{18}H_{22}N_4O_2$: C, 62.37; H, 6.47; N, 21.39. Found: C, 62.15; H, 6.23; N, 21.59.

9-(2-Benzoyloxypropyl-3-benzyloxy)-6-dimethylaminopurine (**15**).

A mixture of 9-(3-benzyloxy-2-hydroxy)-6-dimethylaminopurine (**14**) (20 g, 0.061 mole), benzoyl cyanide (11 g, 0.084 mole), triethylamine (6.7 g, 0.066 mole) and acetonitrile (220 ml) was stirred at room temperature for 1 hour. The volatiles were removed *in vacuo* and the residue chromatographed over silica gel (300 g), and eluted with chloroform:methanol (800:2). The product-containing fractions were combined and evaporated *in vacuo* to give 26 g (99%) of chromatographically pure title compound which was used in the next step without further purification.

9-(2-Benzoyloxypropyl-3-hydroxy)-6-dimethylaminopurine (**16**).

A solution of 9-(2-benzoyloxypropyl)-3-benzyloxy-6-dimethylaminopurine (**15**) (53 g, 0.12 mole) in methanol (800 ml) was mixed with concentrated hydrochloric acid (24 ml), acetic acid (24 ml), 5% palladium on carbon (20 g) and 20% palladium chloride (8 ml) and hydrogenated at 45 psig in a Parr shaker for 3.5 hours. The mixture was filtered and the catalyst washed well with methanol. The combined filtrate was neutralized with ammonium hydroxide and concentrated *in vacuo*. The residue was partitioned between chloroform (300 ml) and water (300 ml). The water layer was extracted with chloroform (2 × 300 ml). The combined chloroform layer was washed with water (2 × 300 ml), dried (sodium sulfate) and concentrated *in vacuo* to dryness. Crystallization of the residue from ethyl acetate (~ 350 ml) afforded the title compound, 27 g (64%), mp

154-156°.

Anal. Calcd. for $C_{17}H_{19}N_5O_3$: C, 59.81; H, 5.61; N, 20.52. Found: C, 59.66; H, 5.51; N, 20.53.

9-(2-Benzyloxypropyl-3-*p*-toluenesulfonyloxy)-6-dimethylaminopurine (**17**).

p-Toluenesulfonyl chloride (30.6 g, 0.16 mole) was added to a precooled (~ 5°) solution of the above compound (27 g, 0.08 mole) in pyridine (300 ml) and the mixture was stirred at room temperature for 16 hours. The white precipitate was collected by filtration and the filtrate concentrated *in vacuo* to a pink solid. The white and pink solids were combined, washed well with cold water and air dried. Crystallization of the crude product from dichloromethane-ethyl acetate afforded 32 g (82%) of the title compound, mp 256-258°.

Anal. Calcd. for $C_{24}H_{25}N_5SO_5$: C, 58.17; H, 5.09; N, 14.13; S, 6.47. Found: C, 58.13; H, 5.10; N, 14.23; S, 6.66.

9-(3-Azido-2-benzoyloxypropyl)-6-dimethylaminopurine (**18**).

A solution of the preceding compound (32 g, 0.065 mole) and sodium azide (18 g, 0.28 mole) in dimethylsulfoxide (300 ml) was heated on the steam bath for 16 hours. Most of the dimethylsulfoxide was removed by distillation under reduced pressure. The residue was treated with cold water (300 ml) and the resulting white precipitate was collected by filtration and air dried. Recrystallization of the crude product from ethyl acetate-hexane afforded 19.5 g (82%) of the title compound, mp 103-105°.

Anal. Calcd. for $C_{17}H_{18}N_8O_2$: C, 55.73; H, 4.95; N, 30.58. Found: C, 55.53; H, 4.92; N, 30.64.

9-(3-Azido-2-hydroxypropyl)-6-dimethylaminopurine (**19**).

A suspension of the preceding compound (24 g, 0.065 mole) in 0.04 *M* methanolic sodium methoxide (480 ml) was stirred at room temperature for 4.5 hours. The mixture was concentrated to dryness *in vacuo* and the residue partitioned between chloroform (200 ml) and a solution of water (200 ml) and concentrated ammonium hydroxide (5 ml). The water layer was extracted with chloroform (2 × 250 ml). The combined chloroform layer was washed with water (2 × 200 ml), dried (sodium sulfate) and concentrated *in vacuo* to dryness. The residual solid was washed with ether (500 ml) and air dried to afford 15 g (87%) of the title compound, mp 111-113°.

Anal. Calcd. for $C_{10}H_{14}N_8O$: C, 45.80; H, 5.38; N, 42.72. Found: C, 46.07; H, 5.53; N, 42.47.

9-(3-Amino-2-hydroxypropyl)-6-dimethylaminopurine Dihydrochloride (**20**).

A solution of the preceding compound (6 g, 0.023 mole) in methanol (240 ml) was mixed with platinum oxide (1.2 g) and concentrated hydrochloric acid (6 ml). The mixture was hydrogenated at 45 psig on a Parr shaker for 1.5 hours. The resulting grey mixture was diluted with methanol (350 ml). The catalyst was filtered and washed with methanol. The combined filtrate was concentrated *in vacuo* to *ca.* 200 ml at which time precipitation began. The mixture was cooled in an ice bath, and the solid was collected by filtration. The above procedure was repeated and the two runs were combined. The crude product (14.0 g, mp248-253°) was recrystallized from methanol (150 ml, Norit A), to afford 12.5 g of fairly pure product (mp 250-256°) which was recrystallized from methanol (150 ml, Norit A) to afford 9.5 g (67%) of analytically pure product, mp 256-258°.

Anal. Calcd. for $C_{10}H_{18}Cl_2N_6O$: C, 38.85; H, 5.87; N, 27.18; Cl, 22.93. Found: C, 38.66; H, 6.01; N, 27.24; Cl, 22.75.

Acknowledgement.

This work was supported by the U. S. Army Medical Research and Development Command. This is contribution No. 1613 to the Army Research Program on Antiparasitic Drugs. The advice and timely suggestions of Dr. E. A. Steck and Mr. H. A. Musallam of the Walter Reed Army Institute of Reasearch are gratefully acknowledged.

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