# Synthesis and Antischistosomal Activity of Certain Pyrazolo[1,5-*a*]pyrimidines

Keitaro Senga,[1] Thomas Novinson, Henry R. Wilson,

*ICN Pharmaceuticals, Inc., Covina, California 91722*

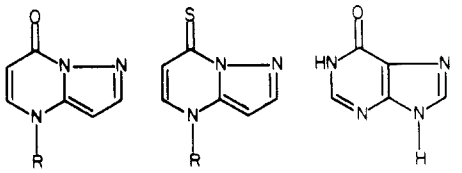
and Roland K. Robins*

*Department of Chemistry, Brigham Young University, Provo, Utah 84602.* *Received November 17, 1980*

Several 7-hydroxypyrazolo[1,5-*a*]pyrimidines (**1–21**), 7-mercaptopyrazolo[1,5-*a*]pyrimidines (**37–49**), and 4-alkylpyrazolo[1,5-*a*]pyrimidin-7-ones (**50–55**) and the corresponding 4-alkylpyrazolo[1,5-*a*]pyrimidine-7-thiones (**56–60**) were synthesized and tested for antischistosomal activity against *Schistosoma mansoni*. Of the compounds examined, the greatest degree of activity in vitro was found with the 7-mercaptopyrazolo[1,5-*a*]pyrimidines. In particular, compounds **37** and **47** proved lethal at 100 μg/mL after an exposure of only 1 h. The 7-hydroxypyrazolo[1,5-*a*]-pyrimidines were not as active. None of the compounds exhibiting in vitro activity were active against *S. mansoni* in vivo.

Schistosomiasis is considered to be one of the most difficult diseases to treat. Accordingly considerable attention has been directed toward the development of useful chemotherapeutic agents. Recent studies on chemotherapeutically useful nitrothiazoles, xanthones, thioxanthones, anilines, quinolines, and nitrofuran derivatives have been well documented.[2] Early studies by Jaffe and his colleagues[3] indicated that purine dependence of *Schistosoma mansoni* might be useful to develop a new type of antischistosomal agent, since tubercidin (7-deazaadenosine)[4] was found to be effective against *S. mansoni*. Further, extensive work on the purine metabolism in *S. mansoni* has subsequently been done by Senft and his group. The following observations are a result of their studies: (1) *S. mansoni* is not able to utilize the de novo pathway for the synthesis of purine nucleotides but resorts to the salvage pathway for purine nucleotide production; (2) adenine, adenosine, inosine, and hypoxanthine are suitable precursors for ATP production; (3) the principal pathway of adenosine utilization involves deamination to inosine, cleave to hypoxanthine, conversion to IMP, and subsequent synthesis of ATP by the parasite.

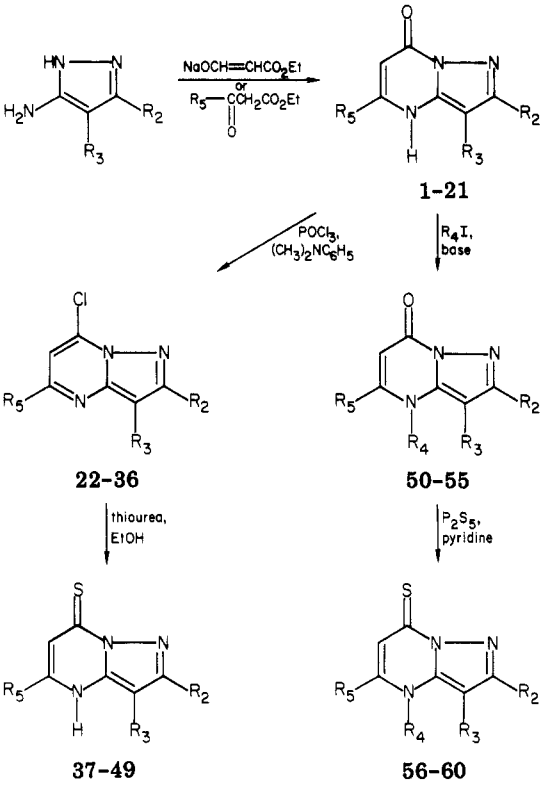
In conjunction with our current research with pyrazolo[1,5-*a*]pyrimidine,[5] we were prompted to explore the possibility of developing antischistosomal compounds represented by structures I, II, III, and IV. These com-



I, R = H; II, R = alkyl; III, R = H; IV, R = alkyl; V

pounds are of interest due to their structural resemblance to hypoxanthine (V), which plays a central role in the ATP production of *S. mansoni*.[6] Analogues of hypoxanthine

Scheme I



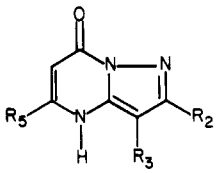
are of special interest as potential antiparasitic agents, since allopurinol has been shown to inhibit the trypanosomid flagellate *crithidia fasciculata*[7] and *Trypanosoma cruzi*.[8] Allopurinol is also effective in vitro against *Leishmania mexicana, Leishmania donovani*, and *Leishmania braziliensis*.[9]

**Chemistry.** The 7-hydroxypyrazolo[1,5-*a*]pyrimidines (**1–21**) prepared are listed in Table I. Condensation of the requisite 3-aminopyrazole with the sodium salt of ethyl formylacetate[10] provided the desired 7-hydroxypyrazolo-

(1) Pharmaceutical Institute, School of Medicine, Keio University, Tokyo, Japan.
(2) S. Archer and A. Yarinsky, *Prog. Drug Res.*, **16**, 11 (1972).
(3) J. J. Jaffe, E. Meymarian, and H. M. Doremus, *Nature (London)*, **230**, 408 (1971).
(4) S. Suzuki and S. Marumo, *J. Antibiot., Ser. A*, **14**, 34 (1961).
(5) (a) T. Novinson, R. Hanson, M. K. Dimmitt, L. N. Simon, R. K. Robins, and D. E. O'Brien, *J. Med. Chem.*, **17**, 645 (1974); (b) K. Senga, T. Novinson, R. H. Springer, R. P. Rao, D. E. O'Brien, R. K. Robins, and H. R. Wilson, *ibid.*, **18**, 312 (1975).
(6) (a) A. W. Seft, R. P. Miech, P. R. Brown, and D. G. Senft, *Int. J. Parasitol.*, **2**, 249 (1972); (b) A. W. Senft, D. G. Senft, and R. P. Miech, *Biochem. Pharmacol.*, **22**, 437 (1973); (c) A. W. Senft, G. W. Crabtree, K. C. Agarwal, E. M. Scholar, R. P. Agawal, and R. E. Parks, *ibid.*, **22**, 449 (1973); (d) R. J. Stegman, A. W. Senft, P. R. Brown, and R. E. Parks, *ibid.*, **22**, 459 (1973); (e) G. W. Crabtree and A. W. Senft, *ibid.*, **23**, 649 (1974); (f) A. W. Senft and G. W. Crabtree, *ibid.*, **26**, 1847 (1977).
(7) V. C. Dewey and G. W. Kidder, *J. Protozool.*, **20**, 678 (1973).
(8) J. J. Marr, R. L. Berens, and D. J. Nelson, *Science*, **201**, 1018 (1978).
(9) J. J. Marr and R. L. Berens, *J. Infect. Dis.*, **136**, 724 (1977).

0022-2623/81/1824-0610$01.25/0 

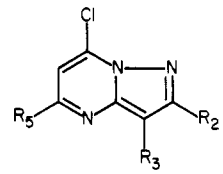
**Table I.** 7-Hydroxypyrazolo[1,5-*a*]pyrimidines



| no. | $R_2$ | $R_3$ | $R_5$ | yield, % | mp, °C | recrystn solvent | formula[a] | antischistosomal act.: MAC,[b] μg/mL |
|---|---|---|---|---|---|---|---|---|
| 1 | H | H | H | 31 | 335-337 dec[c] | EtOH-$H_2O$ | $C_6H_5N_3O$ | |
| 2 | H | H | $CH_3$ | 85 | 297-299[d] | DMF-EtOH | $C_7H_7N_3O$ | |
| 3 | H | H | $C_6H_5$ | 40 | 248-250 | DMF-$H_2O$ | $C_{12}H_9N_3O$ | >100 |
| 4 | $C_6H_5$ | H | H | 44 | 345-348 dec[e] | DMF-$Me_2SO$ | $C_{12}H_9N_3O$ | >100 |
| 5 | $C_6H_5$ | H | $CH_3$ | 90 | 332-334 dec[f] | DMF-$H_2O$ | $C_{13}H_{11}N_3O$ | 100 |
| 6 | $C_6H_5$ | H | $C_6H_5$ | 56 | 338-340[g] | EtOH | $C_{18}H_{13}N_3O$ | >100 |
| 7 | 3-$ClC_6H_4$ | H | $CH_3$ | 69 | 350-352 dec | DMF-$H_2O$ | $C_{13}H_{10}N_3ClO$ | >100 |
| 8 | 3-$ClC_6H_4$ | H | $C_6H_5$ | 73 | 235-237 | DMF-EtOH | $C_{18}H_{12}N_3ClO \cdot H_2O$ | >100 |
| 9 | 3,4,5-$(CH_3O)_3C_6H_2$ | H | $CH_3$ | 84 | 289-291 dec | DMF-$H_2O$ | $C_{16}H_{17}N_3O_4 \cdot H_2O$ | >100 |
| 10 | 3,4,5-$(CH_3O)_3C_6H_2$ | H | $C_6H_5$ | 62 | 294-297 | DMF-EtOH | $C_{21}H_{19}N_3O_4$ | >100 |
| 11 | H | $C_6H_5$ | H | 79 | 322-324 dec | DMF-$H_2O$ | $C_{12}H_9N_3O$ | 100 |
| 12 | H | $C_6H_5$ | $CH_3$ | 83 | 291-293 dec | EtOH | $C_{13}H_{11}N_3O$ | 100 |
| 13 | H | $C_6H_5$ | $C_6H_5$ | 37 | 250-252 | EtOH | $C_{18}H_{13}N_3O$ | 10 |
| 14 | H | 4-$ClC_6H_4$ | $CH_3$ | 92 | 307-310 dec | DMF-EtOH | $C_{13}H_{10}N_3ClO$ | |
| 15 | H | 4-$ClC_6H_4$ | $C_6H_5$ | 56 | 251-253 | DMF-EtOH | $C_{18}H_{12}N_3ClO$ | 100 |
| 16 | H | 4-$FC_6H_4$ | H | 51 | 325-327 dec | DMF-$H_2O$ | $C_{12}H_8N_3FO$ | |
| 17 | H | 3-$CH_3C_6H_4$ | H | 74 | 308-310 dec[h] | DMF-$H_2O$ | $C_{13}H_{11}N_3O$ | 100 |
| 18 | H | 3-$CH_3C_6H_4$ | $CH_3$ | 90 | 272-274 | DMF-EtOH | $C_{14}H_{13}N_3O$ | 100 |
| 19 | H | 3-$CH_3C_6H_4$ | $C_6H_5$ | 57 | 220-221 | DMF-EtOAc | $C_{19}H_{15}N_3O$ | 1.0 |
| 20 | H | COOEt | $CH_3$ | 41 | 215-218[i] | EtOH | $C_{10}H_{11}N_3O_3$ | |
| 21 | H | COOEt | $C_6H_5$ | 63 | 199-200 | EtOH | $C_{15}H_{13}N_3O_3$ | >100 |

[a] All compounds were analyzed for C, H, and N within 0.4% of theoretical values. [b] MAC, minimum active concentration: minimum concentration of compound to cause severe damage or death of worms at 96 h. [c] Literature[5b] mp 331 °C dec. [d] Literature[11] mp 298-299 °C. [e] H. Reimlinger, M. A. Peiren, and R. Merenyi, *Chem. Ber.*, 103, 3252 (1970), reports mp 303-306 °C. [f] S. Checchi, P. Papini, and M. Ridi, *Gazz. Chim. Ital.*, 85, 1160 (1955), reports mp 320 °C. [g] V. Sprio and S. Plescia, *J. Heterocycl. Chem.*, 9, 951 (1972), reports mp 339-340 °C. [h] Literature[5b] mp 308-310 °C dec. [i] Literature[11] mp 218-220 °C.

**Table II.** 7-Chloropyrazolo[1,5-*a*]pyrimidines



| no. | $R_2$ | $R_3$ | $R_5$ | yield, % | mp, °C | recrystn solvent | formula[a] |
|---|---|---|---|---|---|---|---|
| 22 | H | H | H | 60 | 96-98 | *n*-heptane | $C_6H_4N_3Cl$ |
| 23 | H | H | $CH_3$ | 25 | 37-39[b] | *n*-heptane | $C_7H_6N_3Cl$[b] |
| 24 | H | H | $C_6H_5$ | 81 | 103-104 | *n*-heptane | $C_{12}H_8N_3Cl$ |
| 25 | $C_6H_5$ | H | H | 72 | 109-110 | *n*-hexane-acetone | $C_{12}H_8N_3Cl$ |
| 26 | $C_6H_5$ | H | $CH_3$ | 85 | 184-186 | *n*-hexane-acetone | $C_{13}H_{10}N_3Cl$ |
| 27 | $C_6H_5$ | H | $C_6H_5$ | 79 | 138-140 | $CH_3CN$ | $C_{18}H_{12}N_3Cl$ |
| 28 | 3-$ClC_6H_4$ | H | $CH_3$ | 84 | 152-154 | EtOAc | $C_{13}H_9N_3Cl_2$ |
| 29 | 3-$ClC_6H_4$ | H | $C_6H_5$ | 50 | 140-141 | *n*-heptane-acetone | $C_{18}H_{11}N_3Cl$ |
| 30 | 3,4,5-$(CH_3O)_3C_6H_2$ | H | $CH_3$ | 78 | 162-164 | *n*-heptane-acetone | $C_{16}H_{16}N_3ClO_3$ |
| 31 | H | $C_6H_5$ | H | 85 | 138-139 | *n*-heptane-acetone | $C_{12}H_8N_3Cl$ |
| 32 | H | $C_6H_5$ | $CH_3$ | 65 | 151-152 | *n*-hexane-$CHCl_3$ | $C_{13}H_{10}N_3Cl$ |
| 33 | H | 4-$ClC_6H_4$ | $CH_3$ | 75 | 137-138 | *n*-hexane | $C_{13}H_9N_3Cl_2$ |
| 34 | H | 3-$CH_3C_6H_4$ | H | 82 | 131-132 | *n*-heptane | $C_{13}H_{10}N_3Cl$ |
| 35 | H | 3-$CH_3C_6H_4$ | H | 90 | 165-167 | *n*-hexane-acetone | $C_{14}H_{12}N_3Cl$ |
| 36 | H | COOEt | $CH_3$ | 74 | 120-121 | *n*-hexane | $C_{10}H_{10}N_3ClO_2$ |

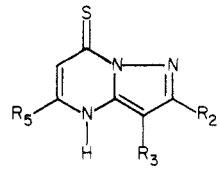
[a] All compounds were analyzed for C, H, and N within 0.4% of theoretical values. [b] Y. Makisumi, *Chem. Pharm. Bull.*, 10, 620 (1962), reports mp 38.5-39.5 °C.

[1,5-*a*]pyrimidines (**1**, **4**, **11**, **16**, and **17**) (Scheme I). The 7-hydroxy-5-methylpyrazolo[1,5-*a*]pyrimidines (**2**, **5**, **7**, **9**, **12**, **14**, **18**, and **20**) were obtained by the reaction of the requisite 3-aminopyrazole with ethyl acetoacetate by using acetic acid in according to the general procedure of Makisumi.[11] Similarly, the reaction of 3-aminopyrazoles with ethyl benzoylacetate in acetic acid afforded 7-hydroxy-5-

(10) H. L. Wheeler and H. F. Merriam, *Am. Chem. J.*, **29**, 478 (1903).

(11) Y. Makisumi, *Chem. Pharm. Bull.*, **10**, 612 (1962).

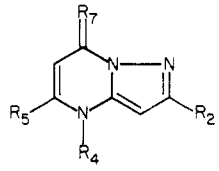
Table III. 7-Mercaptopyrazolo[1,5-*a*]pyrimidines



| no. | $R_2$ | $R_3$ | $R_5$ | yield, % | mp, °C | recrystn solvent | formula[a] | antischistosomal act.: MAC,[b] μg/mL |
|---|---|---|---|---|---|---|---|---|
| **37** | H | H | H | 56 | >330 | DMF | $C_6H_5N_3S$ | 1.0 |
| **38** | H | H | $CH_3$ | 60 | 284 dec | EtOH-$H_2O$ | $C_7H_7N_3S$ | 3.2 |
| **39** | H | H | $C_6H_5$ | 65 | 282 | DMF-EtOH | $C_{12}H_9N_3S$ | 1.0 |
| **40** | $C_6H_5$ | H | H | 74 | 321-325 dec | DMF-EtOH | $C_{12}H_9N_3S$ | 1.0 |
| **41** | $C_6H_5$ | H | $CH_3$ | 58 | 289 dec | DMF-EtOH | $C_{13}H_{11}N_3S \cdot 0.5H_2O$ | 1.0 |
| **42** | $C_6H_5$ | H | $C_6H_5$ | 70 | 251-253 | DMF-EtOH | $C_{18}H_{13}N_3S \cdot H_2O$ | 1.0 |
| **43** | 3,4,5-$(CH_3O)_3C_6H_2$ | H | $CH_3$ | 64 | 307-310 dec | DMF | $C_{16}H_{17}N_3O_3S \cdot H_2O$ | 1.0 |
| **44** | H | $C_6H_5$ | H | 69 | 303-305 dec | DMF | $C_{12}H_9N_3S$ | 1.0 |
| **45** | H | $C_6H_5$ | $CH_3$ | 72 | 256-257.5 | DMF-EtOH | $C_{13}H_{11}N_3S$ | 1.0 |
| **46** | H | 4-$ClC_6H_4$ | $CH_3$ | 58 | 296-298 dec | DMF | $C_{13}H_{10}N_3ClS$ | 100 |
| **47** | H | 3-$CH_3C_6H_4$ | H | 72 | 303-305 dec | DMF | $C_{13}H_{11}N_3S$ | 0.32 |
| **48** | H | 3-$CH_3C_6H_4$ | $CH_3$ | 63 | 298-300 dec | $Me_2SO$ | $C_{14}H_{13}N_3S$ | 100 |
| **49** | H | COOEt | $CH_3$ | 63 | 210-212 | EtOH-$H_2O$ | $C_{10}H_{11}N_3O_2S \cdot H_2O$ | 10 |

[a] All compounds were analyzed for C, H, and N within 0.4% of theoretical values. [b] See footnote *b* in Table I.

Table IV. 4-Alkylpyrazolo[1,5-*a*]pyrimidin-7-ones and 4-Alkylpyrazolo[1,5-*a*]pyrimidine-7-thiones



| no. | $R_2$ | $R_4$ | $R_5$ | $R_7$ | yield, % | mp, °C | recrystn solvent | formula[a] | antischistosomal act.: MAC,[b] μg/mL |
|---|---|---|---|---|---|---|---|---|---|
| **50** | H | $CH_3$ | H | O | 50 | 195 dec | EtOH | $C_7H_7N_3O \cdot 0.5H_2O$ | >100 |
| **51** | H | $C_2H_5$ | H | O | 46 | 86-88 | EtOH-acetone | $C_8H_9N_3O \cdot H_2O$ | >100 |
| **52** | H | $CH_3$ | $CH_3$ | O | 43 | 252-254 dec[c] | EtOH-acetone | $C_8H_9N_3O$ | 100 |
| **53** | $C_6H_5$ | $CH_3$ | H | O | 78 | 211-213 | EtOH | $C_{13}H_{11}N_3O \cdot 0.5H_2O$ | >100 |
| **54** | $C_6H_5$ | *n*-$C_3H_7$ | H | O | 69 | 126-128 | acetone-*n*-hexane | $C_{15}H_{15}N_3O \cdot 0.5H_2O$ | 100 |
| **55** | $C_6H_5$ | $CH_3$ | $C_6H_5$ | O | 57 | 219-221 | benzene | $C_{19}H_{15}N_3O$ | 100 |
| **56** | H | $CH_3$ | H | S | 46 | 202-203 | EtOH | $C_7H_7N_3S \cdot 0.5H_2O$ | >100 |
| **57** | H | $C_2H_5$ | H | S | 33 | 133-134 | EtOH | $C_8H_9N_3S$ | 100 |
| **58** | H | $CH_3$ | $CH_3$ | S | 45 | 297-300 dec | DMF-EtOH | $C_8H_9N_3S$ | >100 |
| **59** | $C_6H_5$ | $CH_3$ | H | S | 33 | 250-252 | DMF-EtOH | $C_{13}H_{11}N_3S \cdot 0.5H_2O$ | 10 |
| **60** | $C_6H_5$ | *n*-$C_3H_7$ | H | S | 48 | 179-181 | EtOH | $C_{15}H_{15}N_3S$ | 10 |

[a] All compounds were analyzed for C, H, and N within 0.4% of theoretical values. [b] See footnote *b* in Table I. [c] Literature[13] mp 253-254 °C.

phenylpyrazolo[1,5-*a*]pyrimidines (**3**, **6**, **8**, **10**, **13**, **15**, **19**, and **21**) as described by Checchi et al.[12]

Chlorination of the 7-hydroxypyrazolo[1,5-*a*]pyrimidines with phosphorus oxychloride in the presence of *N,N*-dimethylaniline gave the corresponding 7-chloropyrazolo-[1,5-*a*]pyrimidines (**22**–**36**) (Table II), which upon treatment with thiourea in ethanol resulted in the formation of the corresponding 7-mercaptopyrazolo[1,5-*a*]pyrimidines (**37**–**49**) (Table III).

Alkylation of the 7-hydroxypyrazolo[1,5-*a*]pyrimidines with the appropriate alkyl iodide gave the corresponding 4-alkylpyrazolo[1,5-*a*]pyrimidin-7-ones (**50**–**55**). The structures of these alkylated products were suggested by the fact that methylation of **2** afforded known **52**.[13] Treatment of the 4-alkylpyrazolo[1,5-*a*]pyrimidin-7-ones with phosphorus pentasulfide in pyridine yielded the corresponding 4-alkylpyrazolo[1,5-*a*]pyrimidine-7-thiones (**56**–**60**) (Table IV).

Of the three chemical series examined, the greatest degree of antischistosomal activity was found with the 7-mercaptopyrazolo[1,5-*a*]pyrimidines (Table III). Compounds **37** and **47** proved lethal at 100 μg/mL after exposures of only 1 h. Worms transferred to fresh medium at this time did not recover motility and underwent progressive degenerative change. The 7-hydroxypyrazolo-[1,5-*a*]pyrimidines were, in general, not as active (Table I), with the exception of compounds **13** and **19**. However, no compounds tested exerted any appreciable effect in vivo, even at dose levels causing weight loss in treated mice. At 400 and 200 (mg/kg)/day of **37** and **44**, respectively, an interruption in oviposition occurred, but no significant difference in the number of worms was found between treated and control mice. Although no significant in vivo antischistosomal activity was found, it may be that thiohypoxanthine analogues could prove to be more potent schistosomicides than the corresponding oxygen analogues.

(12) S. Checchi, M. Ridi, and P. Papini, *Gazz. Chim. Ital.*, **85**, 1558 (1955).
(13) H. Dorn and A. Zubek, *J. Prakt. Chem.*, **313**, 969 (1971).

It is noteworthy that the antiparasitic activity of the 7-thiopyrazolo[1,5-a]pyrimidines (Table III) was essentially abolished by alkyl substitution at nitrogen-4 (Table IV). This suggests that $N^4$ may be an important binding site for the purine-requiring enzymes of *S. mansoni*.

## Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by the Heterocyclic Chemical Co., Harrisonville, MO, and analyzed for C, H, and N within ±0.4% of theoretical values. IR and NMR spectra of all new compounds were consistent with the proposed structures.

**Antischistosomal Testing Procedures.** All compounds were initially evaluated in vitro to determine their effect against *S. mansoni*. The compound was dissolved in reagent dimethyl sulfoxide and subsequently diluted in Serumless Medium (GIBCO no. 163) containing 50 μg/mL reagent gentamycin sulfate. The final concentration of $Me_2SO$ was ≤1%, which does not affect the metabolism of *S. mansoni*.[14] Adult pairs of a 46-day infection of a Puerto Rican (M) strain, obtained from mice, were incubated at 37 °C in 2.0 mL of medium/pair of the diluted compound in tissue culture plates (Linbro FB-16-24-TC). Observations were made with an inverted microscope at intervals to 96 h, when the final reading was made.

Certain compounds (those which showed the best in vitro activity, **17, 19, 37, 38, 41, 43–45,** and **47**) were examined in vivo in mice with a 46-day infection of *S. mansoni*. Compounds were micronized and administered orally or intraperitoneally 2–4 times daily for 5 days at a maximum dose of 400 (mg/kg)/day.[15] Necropsies were performed 2 days after the first dose was given, and pairs of worms in the mescentric veins and orgrauis[16] were determined. Control pairs of worms usually were found to have good motility and sucker motion at 96 h in vitro.

**7-Hydroxypyrazolo[1,5-a]pyrimidines (1, 4, 11, 16, and 17).** A very fine suspension of Na (5.75 g, $2.5 \times 10^{-2}$ g-atom) in toluene (100 mL) was stirred while ethyl acetate (22 g, 0.25 mol) was added in one portion followed by the dropwise addition of ethyl formate (18.5 g, 0.25 mol). The temperature of the reaction mixture was maintained at 27 ± 3 °C during the addition of ethyl formate. After the addition of ethyl formate was complete, the mixture was stirred for 16 h at 25–30° C. To the resulting Na salt of ethyl formylacetate[10] was added an appropriate 3-aminopyrazole (0.125 mol) in EtOH (100 mL). The mixture was heated at reflux for 5 h with stirring and then evaporated to dryness in vacuo. The residue was dissolved in hot $H_2O$ (500 mL), treated with Norit, and then filtered through a layer of Celite 503. The pH of the filtrate was adjusted to 1 by the addition of 6 N HCl. The precipitated solid was collected by filtration, washed with $H_2O$, and dried. Recrystallization of the solid from an appropriate solvent gave pure 7-hydroxypyrazolo[1,5-a]pyrimidines.

**7-Hydroxy-5-methylpyrazolo[1,5-a]pyrimidines (2, 5, 7, 9, 12, 14, 18, and 20).** A mixture of an appropriate 3-aminopyrazole (0.5 mol) and ethyl acetoacetate (0.55 mol) in AcOH (50 mL) was heated at reflux for 15–20 h. After the reaction mixture cooled, the precipitated solid was filtered, washed with EtOH, and recrystallized from the solvent listed in Table I to give pure 7-hydroxy-5-methylpyrazolo[1,5-a]pyrimidine.

**7-Hydroxy-5-phenylpyrazolo[1,5-a]pyrimidines (3, 6, 8, 10, 13, 15, 19, and 21).** A mixture of an appropriate 3-aminopyrazole (0.5 mol) and ethyl benzoylacetate (0.55 mol) in AcOH (50 mL) was heated at reflux for 15–20 h. The reaction mixture was treated as described above to give pure 7-hydroxy-5-phenylpyrazolo-[1,5-a]pyrimidine. When the product did not precipitate from the reaction mixture, the solution was evaporated to dryness in vacuo and treated with $Et_2O$ to solidify the product.

**7-Chloropyrazolo[1,5-a]pyrimidines (22–36).** A mixture of the proper 7-hydroxypyrazolo[1,5-a]pyrimidine (0.2 mol) and *N,N*-dimethylaniline (5 mL) in $POCl_3$ (50 mL) was heated at reflux for 1–3 h. The reaction mixture was evaporation in vacuo and the residue was poured onto ice. The solution was extracted with $CHCl_3$ (50 mL × 3) and the $CHCl_3$ layer was dried over $Na_2SO_4$. The $CHCl_3$ solution was evaporated to dryness in vacuo and recrystallized from the solvent listed in Table II to give pure 7-chloropyrazolo[1,5-a]pyrimidines.

**7-Mercaptopyrazolo[1,5-a]pyrimidines (37–49).** A mixture of an appropriate 7-chloropyrazolo[1,5-a]pyrimidine (0.1 mol) and thiourea (0.2 mol) in EtOH (50 mL) was heated at reflux for 5 h. After the reaction mixture cooled, the precipitated solid was collected by filtration. The solid was suspended in 5% KOH and acidified (pH 4) with AcOH. The precipitate was filtered, washed with $H_2O$, and recrystallized from the solvent listed in table III to afford pure 7-Mercaptopyrazolo[1,5-a]pyrimidines.

**4-Alkylpyrazolo[1,5-a]pyrimidin-7-ones (50–55).** A mixture of an appropriate 7-hydroxypyrazolo[1,5-a]pyrimidine (0.01 mol), alkyl iodide (0.02 mol), and anhydrous $K_2CO_3$ (0.01 mol) in DMF (50 mL) was stirred at room temperature for 20 h. The reaction mixture was evaporated to dryness in vacuo, and the residue was suspended in $H_2O$. The insoluble solid was collected by filtration and recrystallized from the solvent listed in Table IV to provide pure 4-alkylpyrazolo[1,5-a]pyrimidin-7-ones.

**4-Alkylpyrazolo[1,5-a]pyrimidine-7-thiones (56–60).** A mixture of the proper 4-alkylpyrazolo[1,5-a]pyrimidin-7-one (0.01 mol), $P_2S_5$ (6.66 g, 0.03 mol), and pyridine (50 mL) was heated at reflux for 5 h. The reaction mixture was evaporated to dryness in vacuo. The excess $P_2S_5$ was decomposed by the addition of $H_2O$ (100 mL). The solid was collected by filtration, washed with $H_2O$, and recrystallized from the solvent listed in Table IV to give pure 4-alkylpyrazolo[1,5-a]pyrimidine-7-thiones. When the precipitate did not appear from the $H_2O$ solution, the solution was extracted with $CHCl_3$ and the product was isolated by the evaporation of $CHCl_3$ in vacuo.

(14) A. F. Ross and J. J. Jaffee, *Biochem. Pharmacol.*, **21**, 3059 (1972).
(15) H. R. Wilson, G. R. Revankar, and R. L. Tolman, *J. Med. Chem.*, **17**, 760 (1974).
(16) J. Pellegrino, C. A. Oliveira, J. Faria, and A. S. Cunha, *Am. J. Trop. Med. Hyg.*, **11**, 201 (1962).