Synthesis of Potential Antimalarial Agents. III. (1) The Preparation of 6-Substituted 9-[[4-(Diethylamino)-1-methylbutyl]amino]-9*H*-purines

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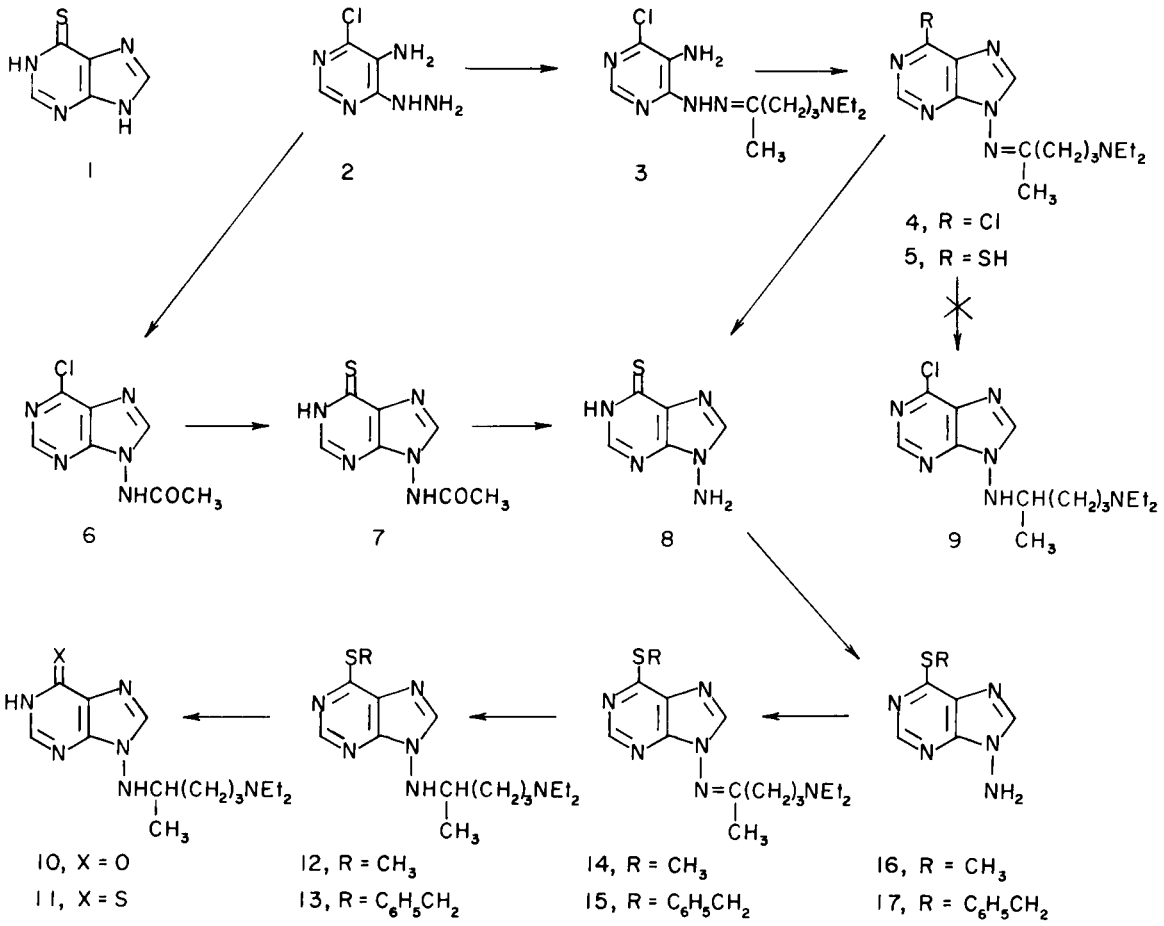
The antimalarial activity of chloroquine is attributed to the greater accumulation of the drug in parasitized (*P. berghei*) than in nonparasitized erythrocytes (2). Purine-6(1*H*)-thione (**1**) and its 9-alkyl derivatives are known to inhibit cell growth (3), but apparently have no specificity for parasitized erythrocytes (4). Compound **11**, in which the [4-(diethylamino)-1-methylbutyl]amino moiety common to a number of antimalarial drugs is attached to the 9-nitrogen of the purine ring, might selectively concentrate in parasitized erythrocytes. Two routes were considered for the preparation of **11**, which are outlined in Scheme I.

Preliminary studies were directed toward the preparation of **11** *via* the 6-chloropurine **9**. Treatment of **2** (5) with ethanolic 5-diethylamino-2-pentanone at room temperature for 72 hours gave crude **3**, which was dissolved in ethyl orthoformate containing concentrated hydrochloric acid and stirred at room temperature for 48 hours to give the crude hydrochloride of **4** (6). The preparation of **9** was attempted by reduction of the azomethine bond of **4** with sodium borohydride in ethanol, but this reaction resulted in a complex mixture (TLC) containing the



hypoxanthine **10** (see below). Replacement of the chloro group of **4** prior to reduction was also unsuccessful when reaction of **4** with thiourea to give **5** resulted in cleavage of the side chain to give 9-aminopurine-6(1*H*)-thione **8**. The use of **8** in the preparation of **11** was then considered.

Previously we reported that treatment of **2** with the ethyl orthoformate-acetic anhydride reagent gave **6**, which was reacted with thiourea to give **7** (5). Hydrolysis of the acetamido group of **7** was carried out in hot ethanolic hydrogen chloride to give **8**. The opening of the imidazole ring of **7** and recyclization of the resulting pyrimidine intermediate to a dihydropyrimido[5,4-*e*]-*as*-triazine was not observed although this type of rearrangement has been reported for 9-formamido-6-methyl-9*H*-purine (7,8). The condensation of **8** with 5-diethylamino-2-pentanone in ethanol was unsuccessful, which was attributed in part to the insolubility of **8** in this solvent. The more soluble 6-(methylthio)- and 6-(benzylthio)purines **16** and **17**, respectively, were prepared by the alkylation of **8** with methyl iodide and benzyl chloride in aqueous sodium hydroxide.

The reaction of **16** with 5-diethylamino-2-pentanone to give **14** was effected in a 10:1 toluene-DMF mixture by the azeotropical removal of the water of condensation. The azomethine bond of the crude condensation product was reduced with sodium borohydride in ethanol to give a low yield of purified **12**. A by-product of this reaction was identified (TLC) as the hypoxanthine compound **10**, which was also prepared by treatment of **12** with aqueous sodium hydroxide.

Similarly **17** was converted *via* **15** to the 6-(benzylthio)-purine **13**, which was used without purification for the preparation of **11**. The removal of the benzyl group of **13** was attempted by the classical method using sodium-liquid ammonia (9). This procedure removed the benzyl group, but also cleaved the hydrazine linkage to give **1**. Treatment of **13** with 30% hydrogen bromide in acetic acid, however, cleaved the benzylthio linkage to give a low yield (23%) of purified **11**. The most successful method for the preparation of **11** involved the reaction of **13** with aluminum bromide in benzene (10). Although a considerable amount of **13** (35%) was recovered presumably because of the formation of an insoluble complex between this purine and aluminum bromide, the purified yield of **11** was 55%.

EXPERIMENTAL (11)

Purine-6(1*H*)-thione (**1**).

A suspension of **13**·hydrochloride (4.3 g., 10 mmoles) in liquid ammonia (150 ml.) was treated with metallic sodium until the blue color persisted for 15 minutes. The resulting solution was allowed to evaporate to dryness, and the residue was extracted with water (3 x 100 ml.). The solid that was obtained from the combined extracts was identified as the title compound by TLC on silica gel H (3:1 chloroform-methanol); yield, 0.62 g. (41%).

Anal. Calcd. for $C_5H_4N_4S$: C, 39.47; H, 2.65. Found: C, 39.14; H, 2.88.

9-Amino-9*H*-purine-6(1*H*)-thione (**8**)

A mixture of **7** (10.5 g., 50.2 mmoles) in ethanolic hydrogen chloride (250 ml.) was heated at reflux for 3 hours. The mixture was cooled, and the solid was collected by filtration, washed with ethanol (3 x 10 ml.), and recrystallized from boiling water; yield, 5.63 g. (67%); m.p. dec. without melting above 270°.

Anal. Calcd. for $C_5H_5N_5S$: C, 35.92; H, 3.01; N, 41.89; S, 19.18. Found: C, 36.12; H, 3.06; N, 41.75; S, 19.08.

9-[[4-(Diethylamino)-1-methylbutyl]amino]hypoxanthine Dihydrochloride Dihydrate (**10**).

Crude **12**·hydrochloride (10 g., 31 mmoles) was dissolved in water (25 ml.), treated with 1 *N* sodium hydroxide (62 ml.), and allowed to stand at room temperature for about 1 week. The resulting suspension was extracted with chloroform (4 x 100 ml.) and the aqueous layer was neutralized with 1 *N* hydrochloric acid (62 ml.), evaporated to dryness, and dried azeotropically with ethanol. The residue was extracted with acetonitrile (5 x 100 ml.) and the extracts were evaporated to dryness; yield, 4.2 g. (41%). This oily residue was dissolved in boiling ethanol, treated with charcoal, filtered through Celite, and evaporated to dryness. The yellow foam residue was dissolved in 1 *N* hydrochloric acid (30 ml.), again treated with charcoal, filtered through Celite, and re-evaporated to dryness. The residue was dried azeotropically with ethanol and the residual yellow foam was collected and dried at room temperature *in vacuo* over phosphorus pentoxide; yield, 3.14 g. (26%); m.p. indefinite, softens from 60°.

Anal. Calcd. for $C_{14}H_{24}N_6O \cdot 2HCl \cdot 2H_2O$: C, 41.90; H, 7.53; Cl, 17.67; N, 20.94. Found: C, 41.97; H, 7.68; Cl, 17.51; N, 20.82.

9-[[4-(Diethylamino)-1-methylbutyl]amino]-9*H*-purine-6(1*H*)-thione Monohydrobromide (**11**).

A.

The free amine of **13** was prepared by treatment of the hydrochloride (4.3 g., 10 mmoles) with a solution of sodium methoxide (0.54 g., 10 mmoles) in methanol (50 ml.). The resulting mixture was evaporated to dryness *in vacuo*, and the residue was extracted with benzene (30 ml.). This extract was added dropwise to a cooled solution of aluminum bromide (4.0 g., 15 mmoles) in benzene (30 ml.), and the resulting mixture was stirred at room temperature for 48 hours. Then, another solution of aluminum bromide (4.0 g.) in benzene (10 ml.) was added, and the whole was stirred for an additional 44 hours. The solvent was removed by decantation, the residue was dissolved in water (50 ml.), and the solution was extracted with chloroform (3 x 50 ml.) to give unreacted **13** (1.4 g., 35% recovery). The aqueous solution was carefully neutralized with sodium hydroxide, and the gelatinous precipitate was removed by filtration through Celite.

After the filtrate was acidified to *p*H 6, the crude hydrobromide slowly precipitated; yield, 2.5 g. (64%). This solid was washed with chloroform (45 ml.) and recrystallized from hot ethanol (900 ml.); yield, 1.4 g. (55% based on recovered **8**); m.p. 242-244° dec.

Anal. Calcd. for $C_{14}H_{24}N_6S \cdot HBr$: C, 43.19; H, 6.47; Br, 20.52; N, 21.58; S, 8.23. Found: C, 43.24; H, 6.50; Br, 20.24; N, 21.45; S, 8.45.

B.

A suspension of **13**·hydrochloride (1.7 g., 4.0 mmoles) in 30% hydrogen bromide in acetic acid (20 ml.) containing phenol (50 mg.) was stirred at room temperature for 20 hours. The resulting solution was evaporated to dryness *in vacuo*, the residue was dissolved in water (25 ml.), and the solution was extracted with ether (3 x 50 ml.). The aqueous layer was treated with charcoal, evaporated to dryness *in vacuo*, and the resulting residue was triturated with acetonitrile (3 x 50 ml.); yield, 0.36 g. (23%); m.p. 242-243° dec.

9[[4-(Diethylamino)-1-methylbutyl]amino]-6-(methylthio)-9*H*-purine Monohydrochloride (**12**).

A solution of **16** (9.1 g., 50 mmoles) and 5-diethylamino-2-pentanone (8.6 g., 55 mmoles) in 10:1 toluene-DMF (220 ml.) containing a catalytic amount of toluenesulfonic acid was refluxed over a Dean-Stark trap for 96 hours. Additional 5-diethylamino-2-pentanone (3.9 g., 25 mmoles) was added after 48 hours. The reaction mixture was evaporated to a small volume at reduced pressure, and the resulting residual oil was dried at 80° *in vacuo* to give a chromatographically homogeneous product; yield, 18 g. (110%). Without further purification a portion of the crude condensation product (9.6 g.) was dissolved in hot ethanol (180 ml.) and treated dropwise with a suspension of sodium borohydride (4.5 g., 120 mmoles) in ethanol (90 ml.) over a period of 15 minutes. The solution was heated at reflux for an additional hour, cooled, and acidified to *p*H 1 with 6 *N* hydrochloric acid. The resulting mixture was evaporated to dryness *in vacuo* and dried azeotropically with ethanol. The crude product was extracted from the inorganic salts with acetonitrile (5 x 100 ml.), and the residue from these extracts was triturated in ethyl acetate to give an off-white solid; yield, 10.61 g. (98%). A 5.0-g. portion of the crude product was recrystallized from boiling dioxane (250 ml.); yield, 2.05 g. This product was dissolved in ethanol (100 ml.), treated with Norit, filtered through Celite, and evaporated to dryness. The residue was triturated in ethanol (5 ml.), collected by filtration, and dried at 78° for 4 hour *in vacuo* over phosphorus pentoxide; yield, 1.41 g. (28% recovery); m.p. 148-149°.

Anal. Calcd. for $C_{15}H_{26}N_6S\cdot HCl$: C, 50.20; H, 7.58; Cl, 9.88; N, 23.41; S, 8.93. Found: C, 50.35; H, 7.79; Cl, 9.90; N, 23.24; S, 8.99.

6-(Benzylthio)-9-[[4-(diethylamino)-1-methylbutyl]amino]-9*H*-purine Monohydrochloride (**13**).

This compound was prepared by a similar procedure from **17** (7.7 g., 30 mmoles) and 5-diethylamino-2-pentanone (9.8 g., 60 mmoles) in toluene (100 ml.) under a Dean-Stark trap. Reduction of the intermediate condensation product (12.7 g., 107%) in ethanol with sodium borohydride (4.5 g.) at room temperature (2 hours) gave the chromatographically homogeneous hydrochloride (11.5 g., 88%, m.p. 141-143° dec.), which was used without further purification.

9-Amino-6-(methylthio)-9*H*-purine (**16**).

A solution of **8** (2.0 g., 12 mmoles) in hot water (75 ml.) containing 1 *N* sodium hydroxide (12 ml.) was cooled and methyl iodide (1.7 g., 12 mmoles) was added to the resulting mixture. After stirring this mixture at room temperature for 20 hours, the solid was collected by filtration and dried *in vacuo* over phosphorus pentoxide; yield, 1.91 g. (88%). A 500-mg. sample of the crude product was recrystallized from boiling ethanol (75 ml.); yield, 400 mg. (80% recovery) of orange needles; m.p. 224-226° dec.

Anal. Calcd. for $C_6H_7N_5S$: C, 39.76; H, 3.89; N, 38.65; S, 17.69. Found: C, 39.85; H, 3.95; N, 38.51; S, 17.6.

9-Amino-6-(benzylthio)-9*H*-purine (**17**).

This compound was prepared by a similar procedure from 20 g. of **8**; yield, 29 g. (94%); m.p. 167-168°.

Anal. Calcd. for $C_{12}H_{11}N_5S$: C, 56.01; H, 4.31; N, 27.25. Found: C, 55.99; H, 4.51; N, 27.19.

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