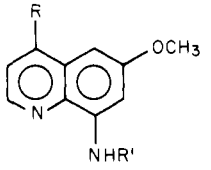
Primaquine Analogues: Derivatives of 4-Amino-2-methoxyacridine[1]

John P. Scovill, Daniel L. Klayman,* Thomas S. Woods, and Thomas R. Sweeney

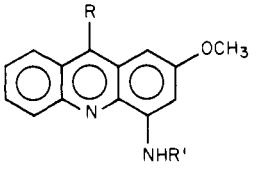
Walter Reed Army Institute of Research, Division of Experimental Therapeutics, Washington, D.C. 20012.
Received May 11, 1979

Based on the antimalarial activity of primaquine (**1a**) and its 4-methyl analogue **1b**, 4-aminoacridinyl analogues, 4-[(4-amino-1-methylbutyl)amino]-2-methoxyacridine (**2a**) and 4-[(4-amino-1-methylbutyl)amino]-2-methoxy-9-methylacridine (**2b**), were prepared and evaluated as potential tissue schizonticidal agents. These compounds were found to be substantially less active than primaquine against *Plasmodium cynomolgi* in the rhesus monkey. The antileishmanial activity in hamsters of 4-[[6-(diethylamino)hexyl]amino]-2-methoxy-9-methylacridine (**2d**) was found to be considerably less than that of 8-[[6-(diethylamino)hexyl]amino]-6-methoxy-4-methylquinoline (**1c**).

8-Aminoquinoline derivatives related to primaquine (**1a**)



1a, R = H; R′ = $CH(CH_3)CH_2CH_2CH_2NH_2$
b, R = CH_3; R′ = $CH(CH_3)CH_2CH_2CH_2NH_2$
c, R = CH_3; R′ = $CH(CH_2)_4CH_2N(C_2H_5)_2$

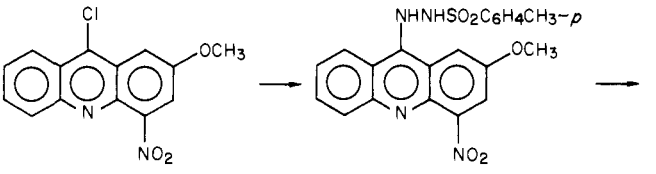


2a, R = H; R′ = $CH(CH_3)CH_2CH_2CH_2NH_2$
b, R = CH_3; R′ = $CH(CH_3)CH_2CH_2CH_2NH_2$
c, R = CH_3; R′ = $CH_2CH_2CH_2CH(CH_3)NH_2$
d, R = CH_3; R′ = $CH_2(CH_2)_4CH_2N(C_2H_5)_2$

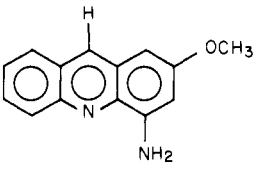
continue to be of interest as antimalarials inasmuch as they are the only agents known to be clinically effective against the exoerythrocytic forms of *Plasmodium vivax*. They are, thus, capable of preventing relapses of disease caused by this parasite.[2] After testing hundreds of 8-aminoquinoline analogues, it has become apparent that modification of the side-chain portion of the molecule exclusively has not resulted in any marked improvement in therapeutic index over that of primaquine.[3] With this in mind, our attention has been directed toward both adding substituents to the quinoline ring and replacing it with a related ring system. The possibility of using the 4-amino-2-methoxyacridyl framework as an alternative was an idea which appeared at an early stage in the development of antimalarial chemotherapy. Clemo and Hook[4] and Samant[5] initiated studies in this area; however, they reported no biological testing data.

In this paper, we describe the synthesis of 4-[(4-amino-1-methylbutyl)amino]-2-methoxyacridine (**2a**), 4-[(4-amino-1-methylbutyl)amino]-2-methoxy-9-methylacridine (**2b**), and 4-[[6-(diethylamino)hexyl]amino]-2-methoxy-9-methylacridine (**2c**) and their antimalarial properties. Because the placement of a methyl group at the 4 position of the quinoline ring is reported to not only enhance antimalarial activity[6] (as in **1b**) but also to lead to potent antileishmanial properties[7] (as in **1c**), **2c** was prepared and tested against *Leishmania donovani*.

Chemistry. The synthesis of the 4-[(4-aminoalkyl)-amino]-2-methoxyacridines followed the classical route employed by Elderfield et al.[8] for the preparation of primaquine. Because the original procedure for obtaining 4-amino-2-methoxyacridine (**5**) was not suitable to the production of sufficiently large amounts of starting material, the development of a new route to this compound was necessary. Thus, 9-chloro-2-methoxy-4-nitroacridine (**3**), prepared by Samant's procedure,[5] was converted to the *p*-toluenesulfonylhydrazino derivative **4**. Catalytic reduction of **4** in alkaline ethylene glycol afforded 4-amino-2-methoxyacridine **5**.

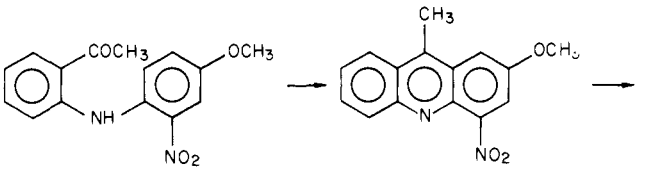


3 **4**

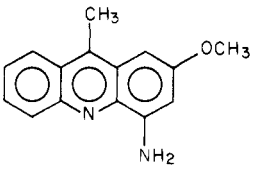


5

Reaction of *o*-aminoacetophenone with 4-chloro-3-nitroanisole produced 2′-acetyl-4-methoxy-2-nitrodiphenylamine (**6**). Ring closure of **6** with concentrated



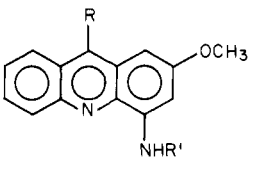
6 **7**



8

H_2SO_4 gave 2-methoxy-9-methyl-4-nitroacridine (**7**), which was reduced by stannous chloride in concentrated HCl to 4-amino-2-methoxy-9-methylacridine (**8**).

Alkylation of **5** and **8** by 2-bromo-5-phthalimidopentane gave the corresponding 2-methoxy-4-[(4-phthalimido-1-methylbutyl)amino]acridines **9** and **10**, respectively. The



9, R = H; R′ = $CH(CH_3)CH_2CH_2CH_2Phth$
10, R = CH_3; R′ = $CH(CH_3)CH_2CH_2CH_2Phth$
11, R = CH_3; R′ = $CH_2CH_2CH_2CH(CH_3)Phth$

0022-2623/79/1822-1164$01.00/0

Table I. Tissue Schizonticidal Activities of Compounds 2a and 2b in Rhesus Monkeys Infected with *P. cynomolgi*

compd	dose, mg/kg[a]	results
2a	1.0	relapsed posttreatment, day 17
2a	3.16	relapsed posttreatment, day 11
2a	3.16	relapsed posttreatment, day 17
2a	10	relapsed posttreatment, day 51
2a	10	cured
2b	1	relapsed posttreatment, day 5
2b	3.16	relapsed posttreatment, day 9

[a] Amount of drug administered per day for 7 days in combination with 5.0 (mg/kg)/day of chloroquine. The ED_{90} dose for primaquine in this system is 1.3 mg/kg.

phthalimido-protecting groups were removed by hydrazinolysis, and the resulting 4-[(4-amino-1-methylbutyl)-amino]acridines **2a** and **2b**, respectively, were converted to crystalline fumarate salts. Alkylation of **8** with 1-iodo-4-phthalimidopentane gave 2-methoxy-9-methyl-4-[(4-phthalimidopentyl)amino]acridine (**11**). Hydrazinolysis produced 4-[(4-aminopentyl)amino]-2-methoxy-9-methylacridine (**2c**), while 4-[[6-(diethylamino)hexyl]-amino]-2-methoxy-9-methylacridine (**2d**) was prepared by reaction of **8** with 1-bromo-6-(diethylamino)hexane hydrobromide.

Results and Discussion

The insensitivity of blood schizonts to the 8-aminoquinolines[6,9] is reflected in the protocol of the tissue schizonticidal test. Here it is necessary to use chloroquine to clear the blood infection in order to detect any effect upon the exoerythrocytic parasites. Thus, no blood schizonticidal activity was anticipated from the 4-aminoacridines **2a** and **2c**, and this expectation was confirmed.

The results of the tissue schizonticidal test for the two primaquine analogues **2a** and **2b** indicate that these compounds possess a low level of tissue schizonticidal activity in comparison to primaquine, as shown in Table I. In contrast to the 4-quinolyl series, substitution of a methyl group into the analogous position of the acridine ring, that is, the 9 position, seems to produce a dystherapeutic effect.

The activity of 4-[[6-(diethylamino)hexyl]amino]-2-methoxy-9-methylacridine (**2d**) against *Leishmania donovani* was considerably less than that of the quinoline analogue **1c**. While significant suppression of parasites in liver was observed at 52 and 13 (mg/kg)/day, this compound had a glucantime index (G) of only 0.2 at the SD_{50} level (cf. Table II). Compound **1c** possessed a glucantime index of 472 at the SD_{90} level.

Experimental Section

IR spectra were determined on a Perkin-Elmer Model 283 grating spectrophotometer. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected.

2-Methoxy-4-nitro-9-[(*p*-toluenesulfonyl)hydrazino]-acridine Hydrochloride (4). A solution of 13.8 g (0.074 mol) of *p*-toluenesulfonylhydrazine in 500 mL of $CHCl_3$ was added to a solution of 21.4 g (0.074 mol) of 9-chloro-2-methoxy-4-nitroacridine[4] in 500 mL of $CHCl_3$. The mixture thus formed was agitated thoroughly and allowed to cool overnight. The crystals which separated were collected and washed with $CHCl_3$ to yield 32.4 g (100%) of 2-methoxy-4-nitro-9-[(*p*-toluenesulfonyl)-hydrazino]acridine hydrochloride as an orange powder, mp 175 °C dec. The material was used in the subsequent step without further purification.

Table II. Suppression of *Leishmania donovani* in the Golden Hamster by Compound **2d**

dose, mg/kg	toxicity	suppression, %
208	toxic, 6/6	
52	toxic, 1/6	53[a]
13		36

[a] $G = 0.20$ at SD_{50}.

4-Amino-2-methoxyacridine Hydrochloride (5). A suspension of 5.0 g (11.5 mM) of *finely ground* **4** and 0.5 g of 10% Pd on charcoal in 300 mL of a hydrogenation medium, prepared by dissolving 4.08 g (0.033 mol) of $Na_2CO_3 \cdot H_2O$ in 75 mL of H_2O and 225 mL of ethylene glycol, was shaken in a Parr apparatus under 31 psi of hydrogen for 22 h. The catalyst was removed by filtration, and the filtrate was extracted with six 150-mL portions of $CHCl_3$. After the combined $CHCl_3$ extracts were washed with H_2O, two times with 10% NaOH, and again with H_2O, they were dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was adjusted to pH 2 with 1 N HCl, and 24 mL of EtOH was added. The volume of the mixture was reduced to near dryness under reduced pressure, and 20 mL of H_2O was added. The precipitate which formed was collected and obtained as a dark purple powder in two crops, yielding 1.87 g (62%) of 4-amino-2-methoxyacridine hydrochloride (**5**·HCl), mp 208–212 °C. Recrystallization of the product from EtOH gave dark purple crystals, mp 212–214 °C (lit.[4] mp 254–256 °C dec). The free base was made by stirring a suspension of the hydrochloride in 10% NH_4OH until the salt was converted entirely to a yellow solid. The base could be crystallized from MeOH: mp 135–136 °C (lit.[4] mp 135–136 °C dec); IR (KBr) 3487, 3380, 1631, 1208, 1158, 1025, 913, 848, 839, 762, 743 cm^{-1}. Anal. ($C_{14}H_{12}N_2O \cdot HCl$) C, H, N, Cl.

2′-Acetyl-4-methoxy-2-nitrodiphenylamine (6). A mixture of 25 g (0.185 mol) of *o*-aminoacetophenone, 32 g (0.17 mol) of 4-chloro-3-nitroanisole, 20 g (0.189 mol) of sodium carbonate, and 1.5 g of Cu powder (electrolytic dust, Fisher) was heated for 3 h at ~200 °C. After 3 h, the reaction mixture was steam distilled until the distillate was clear (ca. 2 L of distillate was collected), and the residue, a thick resinous material, was poured from the flask and allowed to cool. The brittle solid was pulverized, giving about 55 g of a cokelike material. This was exhaustively extracted in a Soxhlet extractor with diethyl ether. After about 1 h, orange crystals began to separate from the extract. Extraction was continued for another 5–6 h to give 13.3 g (18%) of 2′-acetyl-4-methoxy-2-nitrodiphenylamine (**6**), mp 128–130 °C. The material was sufficiently pure for the succeeding steps; however, it could be recrystallized either from EtOH or MeCN: mp 131–133 °C; IR (KBr) 1696, 1577, 1515, 1445, 1303, 1293, 1245, 1147, 1034, 962, 767, 759 cm^{-1}; NMR ($CDCl_3$) δ 2.63 (s, 3 H, $COCH_3$), 3.83 (s, 3 H, O-CH_3), 6.65–7.90 (m, 7 H), 11.47 (br s, 1 H, NH). Anal. ($C_{15}H_{14}N_2O_4$) C, H, N.

2-Methoxy-9-methyl-4-nitroacridine (7). Finely ground 2′-acetyl-4-methoxy-2-nitrodiphenylamine (**6**; 8.5 g, 29.7 mM) was dissolved in a solution composed of 15 mL of glacial HOAc and 3 mL of concentrated H_2SO_4. The resulting solution was heated to 100 °C and maintained at that temperature. After 1 h, the reaction mixture was cooled to room temperature and the crystals, which began to separate from the hot solution after 0.5 h, were collected. They were washed with glacial HOAc and then with MeOH, giving 6.5 g (60%) of 2-methoxy-9-methyl-4-nitroacridine (**7**) hemisulfate. The crude salt was sufficiently pure for the next step. It could be recrystallized from glacial HOAc, mp >250 °C dec. Anal. ($C_{15}H_{12}N_2O_3 \cdot H_2SO_4$) C, H, N, S.

The free base was prepared by suspending 3.0 g of the hemisulfate in a solution of 10 mL of concentrated NH_4OH and 20 mL of H_2O to give 2.1 g (88%) of 2-methoxy-9-methyl-4-nitroacridine (**7**) as a brownish-yellow solid. The latter could be recrystallized in small quantities from MeCN: mp 184–185 °C dec; IR (KBr) 1696, 1540, 1477, 1439, 1285, 1237, 1138, 1041, 843, 788, 756, 600 cm^{-1}. Anal. ($C_{15}H_{12}N_2O_3$) C, H, N.

4-Amino-2-methoxy-9-methylacridine (8). To a suspension of 6.5 g (17.75 mM) of crude 2-methoxy-9-methyl-4-nitroacridine hemisulfate in 10 mL of concentrated HCl at 10 °C was cautiously added dropwise a solution of 12.6 g (53.7 mM) of $SnCl_2 \cdot 2H_2O$ in 10 mL of concentrated HCl, causing a strong exothermic reaction.

The yellow suspension was warmed gently on a steam bath for 0.5 h and then treated with ~50 mL of H_2O, and the resulting red solid was collected. The material was washed thoroughly with H_2O, transferred to a beaker, and treated with dilute NH_4OH (10 mL of concentrated NH_4OH + 30 mL of H_2O), and the sticky yellow material which formed was broken up by rubbing with a stiff spatula. The yellow solid was extracted into 100 mL of $CHCl_3$ (**caution: excessive shaking causes emulsion formation**), the $CHCl_3$ extract was filtered, and the solvent was removed under reduced pressure. The residue was further extracted into Et_2O using a Soxhlet extractor. The Et_2O was evaporated, giving 2.9 g (68%) of 4-amino-2-methoxy-9-methylacridine (8) as a brownish-yellow solid. An analytical sample was prepared by sublimation under reduced pressure: mp 141–143 °C; NMR ($CDCl_3$) δ 2.93 (s, 3 H, C-CH_3), 3.93 (s, 3 H, OCH_3), 6.56 (d, 1 H, J = 2 Hz), 6.65 (d, 1 H, J = 2 Hz). Anal. ($C_{15}H_{14}N_2O$) C, H, N.

2-Methoxy-4-[(4-phthalimido-1-methylbutyl)amino]acridine (9). A solution of 6.5 g (25 mM) of 4-amino-2-methoxyacridine, 22.4 g (75 mM) of 4-bromopentylphthalimide[8] and 6.8 g (0.05 mM) sodium acetate in 24 mL of EtOH was heated at reflux under N_2 for 80 h. The solution was filtered and the EtOH removed under reduced pressure. The oily residue was extracted five times with 100-mL portions of boiling hexane to remove excess alkylating agent. The residue was triturated three times with 50-mL portions of boiling MeOH and recrystallized from MeCN, affording 4.8 g (44%) of orange crystals of 2-methoxy-4-[(4-phthalimido-1-methylbutyl)amino]acridine (9): mp 135–136 °C; IR (KBr) 3383, 2980, 2950, 1780, 1720, 1637, 1533, 1418, 1403, 1213, 1170, 1065, 768, 748, 731, 726 cm^{-1}. Anal. ($C_{27}H_{25}N_3O_3$) C, H, N.

2-Methoxy-9-methyl-4-[(4-phthalimido-1-methylbutyl)amino]acridine (10). A solution of 11.9 g (50 mM) of 4-amino-2-methoxy-9-methylacridine and 7.4 g (25 mM) of 4-bromopentylphthalimide in 100 mL of MeCN was heated under N_2 at reflux for 40 h. The dark red precipitate of the aminoacridine hydrobromide was filtered off, and the filtrate was chilled overnight. The crystals which formed were collected and washed with MeOH, affording 5.4 g (48%) of orange crystals of 2-methoxy-9-methyl-4-[(4-phthalimido-1-methylbutyl)amino]acridine (10), mp 151–156 °C. This product was sufficiently pure for the succeeding step. An analytical sample was prepared by three crystallizations from MeCN: mp 155–156 °C; IR (KBr) 3400, 1778, 1716, 1630, 1535, 1216, 1167, 1061, 825, 752, 722 cm^{-1}. Anal. ($C_{28}H_{27}N_3O_3$) C, H, N.

2-Methoxy-4-[(4-phthalimidopentyl)amino]-9-methylacridine (11). A solution of 4.76 g (20 mM) of 4-amino-2-methoxy-9-methylacridine and 3.43 g (10 mM) of 1-iodo-4-phthalimidopentane[10] in 20 mL of MeCN was heated at reflux under N_2 for 8 h. The red precipitate of aminoacridine hydriodide was filtered off, and the filtrate was chilled. The crystals which formed were collected and washed with MeOH, affording 3.7 g (41%) of yellow crystals of 2-methoxy-4-[(4-phthalimidopentyl)amino]-9-methylacridine (11). The product was sufficiently pure for the succeeding step. An analytical sample was prepared by crystallization from MeCN: mp 135–136 °C; IR (KBr) 3400, 1780, 1710, 1635, 1535, 1398, 1375, 1215, 1177, 1060, 768, 755, 723 cm^{-1}. Anal. ($C_{27}H_{27}N_3O_3$) C, H, N.

4-[(4-Amino-1-methylbutyl)amino]-2-methoxyacridine Hydrogen Fumarate (2a). A solution of 2.2 g of 9 (5 mM) and 1 mL of hydrazine hydrate (85%) in 50 mL of EtOH was heated at reflux for 6 h. The white precipitate of phthalhydrazide was filtered off and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in a solution of 20 mL of H_2O containing 5 mL of concentrated HCl and filtered. The filtrate was neutralized with 10% NaOH solution, and the precipitated oil was extracted into 100 mL of Et_2O. The Et_2O was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was treated with a solution of 0.6 g (5 mM) fumaric acid in 10 mL of EtOH. The solution was cooled and the orange crystals which separated were crystallized from THF, affording 1.5 g (69%) of 4-[(4-amino-1-methylbutyl)amino]-2-methoxyacridine hydrogen fumarate (2a): mp 136–138 °C; IR (KBr) 1635, 1533, 1502, 1418, 1215, 1170, 1047, 988, 750, 652 cm^{-1}. Anal. ($C_{19}H_{23}N_3O \cdot C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

4-[(4-Amino-1-methylbutyl)amino]-2-methoxy-9-methylacridine Hydrogen Fumarate (2b). Hydrazinolysis of 10 and treatment of the free base with fumaric acid, as described above for 2a, gave a 40% yield of yellow crystals of 4-[(4-amino-1-methylbutyl)amino]-2-methoxy-9-methylacridine hydrogen fumarate (2b). An analytical sample was prepared by recrystallization from THF: mp 136–137 °C; IR (KBr) 1633, 1535, 1380, 1215, 1175, 1075, 1050, 985, 750, 650 cm^{-1}. Anal. ($C_{20}H_{25}N_3O \cdot C_4H_4O_4$) C, H, N.

4-[(4-Aminopentyl)amino]-2-methoxy-9-methylacridine (2c). A solution of 8.0 g (17.6 mM) of 2-methoxy-9-methyl-4-[(4-phthalimidopentyl)amino]acridine (11) and 4 mL of 85% hydrazine hydrate in 100 mL of EtOH was heated at reflux for 4 h. The phthalhydrazide was filtered off and the solvent was removed under reduced pressure. The free base was extracted into Et_2O, and the Et_2O was evaporated under reduced pressure to give an orange solid. Recrystallization from petroleum ether afforded 2.21 g (39%) of orange crystals of 4-[(4-aminopentyl)amino]-2-methoxy-9-methylacridine, mp 87–89 °C. An analytical sample was prepared by two recrystallizations from petroleum ether: mp 90–91 °C; IR (KBr) 1635, 1535, 1423, 1217, 1177, 1048, 813, 760, 752 cm^{-1}. Anal. ($C_{20}H_{25}N_3O$) C, H, N.

4-[[6-(Diethylamino)hexyl]amino]-2-methoxy-9-methylacridine Hydrobromide (2d). A solution of 2.38 g (10 mM) of 4-amino-2-methoxy-9-methylacridine and 3.17 g (10 mM) of 6-(diethylamino)hexyl bromide hydrobromide[11] in 50 mL of MeCN was heated at reflux for 8 h. The purple aminoacridine hydrobromide was removed by filtration, and the solution was evaporated to a thick oil under reduced pressure. Rubbing the oil with 10 mL of cold MeCN caused it to solidify. Recrystallization of the product from MeCN afforded 1.6 g (68%) of orange crystals of 4-[[6-(diethylamino)hexyl]amino]-2-methoxy-9-methylacridine hydrobromide: mp 170–171 °C; IR (KBr) 3418, 2940, 2660, 1635, 1535, 1485, 1471, 1425, 1395, 1215, 1179, 818, 765, 755 cm^{-1}. Anal. ($C_{25}H_{35}N_3O \cdot HBr$) C, H, N, Br.

Antimalarial Test Methods. The blood schizonticidal activity of the potential antimalarials was determined against a drug-sensitive strain of *Plasmodium berghei* (strain KBG 173) in mice. Young ICR/HA Swiss mice, ranging in weight from 18 to 22 g, are administered intraperitoneally a standard inoculum of plasmodia. The latter consists of 0.5 mL of a 1:100 dilution of heparinized heart's blood containing 4×10^7 cells, a minimum of 90% of which are parasitized. The cells are drawn from donor mice which had been infected 1 week earlier with *Plasmodium berghei*. All the untreated infected animals, which serve as controls, die after 6–8 days and with a mean survival time of 6.2 days. Every compound is tested at several dose levels. At each level, the candidate drug is given subcutaneously in a single dose as a peanut oil suspension to 5 mice 72 h after they are infected. The compounds are judged to be "toxic" if the infected mice die before the 6th day, i.e., before the time when the untreated mice begin to die; "active", if the mean survival time of the mice is at least doubled; and "curative", if the mice survive 60 days postinfection. Details of the test procedure were given by Osdene, Russell, and Rane.[12]

The tissue schizonticidal potential of the candidate antimalarials was evaluated in rhesus monkeys by the procedure of Schmidt et al.[9] Monkeys are infected by iv inoculation of 10^6 freshly isolated *Plasmodium cynomolgi* sporozoites on day 0. After a 7–9-day prepatent period, a rapidly rising parasitemia develops, which typically exceeds 5000 parasites mm^{-3} by days 10–12. Administration of the test drug is initiated at this time. The test drug is given orally for 7 consecutive days concurrently with 5 (mg/kg)/day of chloroquine diphosphate to eliminate blood schizonts. Thus, any tissue schizonticidal activity of the test drug will be apparent even if it lacks blood schizonticidal activity. The effect of the test drug is determined by examining Giemsa stained blood films for the reappearance of blood parasites. Parasite counts are made daily through day 20 and every 2 days thereafter. Initially, a clearance of blood parasites results from the blood schizonticidal action of chloroquine. However, should exoerythrocytic parasites (tissue schizonts) survive the action of the test drug, there will be a relapse of blood parasites. If there is no relapse within 20 days of the initial clearance of blood parasites, the monkey is splenectomized and its parasitemia followed for an additional 30 days. Should no relapse occur during this period, the monkey is considered cured. Primaquine diphosphate cures 90% of monkeys in this test system when administered at a dose

of 1.3 mg/kg for 7 days in combination with 5 (mg/kg)/day of chloroquine.

Antileishmanial Test Method. The antileishmanial activity of **2d** was determined in golden hamsters by the method of Hanson et al.[13] Male golden hamsters were inoculated intracardially with 10^7 amastigotes of the Khartoum strain of *Leishmania donovani*. Administration of the drug was begun 3 days after inoculation and was continued twice daily for 4 days. On day 6 the hamsters were sacrificed and the ratio of the number of amastigotes per host liver cell nucleus was determined. Comparison was made of the suppressive effects of the test compound to that of the reference compound, glucantime (*N*-methylglucamine antimonate), and a glucantime index, *G*, was calculated using the formula: G = dose (SD_x) of glucantime/dose (SD_x) of test drug.

Acknowledgment. The authors gratefully acknowledge the interest and assistance of Col. David E. Davidson, Division of Experimental Therapeutics, Walter Reed Army Institute of Research. Data on efficacy in the rhesus monkey tissue schizonticidal model was provided by Dr. John Brown and Dr. Frank Chapple of the Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand. Antileishmanial testing was performed by Dr. William Hanson, University of Georgia School of Veterinary Medicine, Athens, Ga.

References and Notes

(1) This is contribution no. 1540 to the Army Research Program on Malaria.
(2) I. Rollo in "The Pharmacological Basis of Therapeutics", L. S. Goodman and A. Gilman, Eds., McMillan, New York, 1975, p 1060.
(3) R. M. Pinder in "Medicinal Chemistry", A. Burger, Ed., Wiley, New York, 1970, p 507.
(4) G. R. Clemo and W. Hook, *J. Chem. Soc.*, 608 (1936).
(5) B. Samant, *Ber. Dtsch. Chem. Ges.*, **75**, 1008 (1942).
(6) L. H. Schmidt, R. Fradkin, D. Vaughan, and J. Rasco, *Am. J. Trop. Med. Hyg.*, **26** 1116 (1977).
(7) K. E. Kinnamon, E. A. Steck, P. S. Loizeaux, W. L. Hanson, W. L. Chapman, Jr., and V. B. Waits, *Am. J. Trop. Med. Hyg.*, **27**, 751 (1978).
(8) R. C. Elderfield, H. E. Mertel, R. T. Mitch, M. Wempen, and E. Werbel, *J. Am. Chem. Soc.*, **77**, 4816 (1955).
(9) L. H. Schmidt, R. N. Rossan, R. Fradkin, and J. Woods, *Bull. W.H.O.*, **34**, 783 (1966).
(10) E. E. Mikhlina, A. D. Yanina, V. Y. Vorob'eva, Y. S. Tsizin, N. A. Komarova, I. A. Kuznetsova, E. N. Alekseeva, and L. N. Yakhontov, *Khim.-Farm. Zh.*, **7**, 3 (1973).
(11) K. N. Campbell, A. H. Sommers, J. F. Kervin, and B. K. Campbell, *J. Am. Chem. Soc.*, **68**, 1556 (1946).
(12) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).
(13) W. C. Hanson, W. L. Chapman, Jr., and K. E. Kinnamon, *Int. J. Parasitol.*, **2**, 443 (1977).

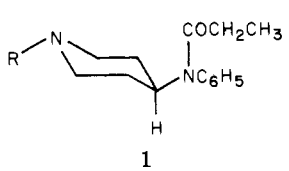
4-Anilidopiperidine Analgesics. 2. A Study of the Conformational Aspects of the Analgesic Activity of the 4-Anilidopiperidines Utilizing Isomeric N-Substituted 3-(Propananilido)nortropane Analogues

Thomas N. Riley* and Jerome R. Bagley

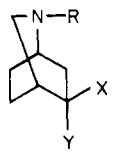
Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, University, Mississippi 38677.
Received March 30, 1979

Relatively little information is available concerning the influence of conformational factors on the potent analgesic actions of the 4-anilidopiperidines. A series of N-substituted 3α- and 3β-(propananilido)nortropanes have been designed, synthesized, and stereochemically characterized as semirigid analogues of the 4-anilidopiperidine analgesics in an attempt to study the influence of certain stereochemical factors on analgesia in this class of compounds. Conformational analysis of 3α-propananilides (**4**) reveals a boat conformation for the preferred conformation of the piperidine ring of these tropane analogues. Evaluation of the analgesic potencies of the isomeric N-substituted 3-(propananilido)nortropanes of this study indicates greater potency for the 3β-(propananilido) isomers (**5**) with *N*-benzyl and *N*-phenethyl substitution as compared to the corresponding N-substituted 3α-propananilides. Analysis of relative solubility differences among these isomers suggests that both structural and stereochemical influences predominate in affecting analgesic potency.

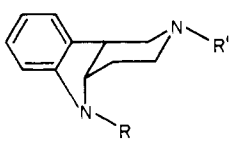
The 4-anilidopiperidine class of synthetic narcotic analgesics (**1**) is characterized by high analgesic potency,



1



2, X = H; Y = $N(C_6H_5)COCH_2CH_3$
X = $N(C_6H_5)COCH_2CH_3$; Y = H
R = CH_3 and $C_6H_5CH_2CH_2$



3, R′ = $-CH_2CH_2C_6H_5$; R = H or $COCH_2CH_3$

rapid onset of action, and relatively high therapeutic indices.[1,2] Extensive SAR studies of the 4-anilidopiperidines have adequately defined optimal structural features for these synthetic analgesics relative to pharmacological activity.[3-5] On the other hand, relatively few studies have been performed to characterize the stereochemical requirements for 4-anilidopiperidine analgesic activity. First-order approximations of NMR spectral data obtained for a series of N-substituted 4-anilidopiperidine derivatives[3] and for certain 3-methyl-4-(propananilido)-piperidines[6] suggest a preferred piperidine ring chair conformation with an equatorially oriented 4-anilido moiety (**1**). Studies with chiral 3-methyl-4-(propananilido)piperidines indicate a significant dependence of analgesic activity on both optical and geometric isomerism in these 4-anilidopiperidine derivatives. Investigations of conformationally restricted analogues of the 4-anilidopiperidine analgesics have included the use of isomeric N-substituted 5-(propananilido)-2-azabicyclo[2.2.2]octanes (**2**), which were found to be devoid of measurable analgesic activity at ip doses of 100 mg/kg in mice.[7,8] Berger and co-workers[9] have studied isomeric pyrido[4,3-*b*]indoles (**3**)

0022-2623/79/1822-1167$01.00/0