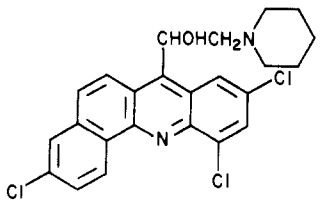
Syntheses of 9-Acridine- and 2-Phenanthridinemethanols as Potential Antimalarials

Chester W. Muth,* Howard L. Minigh,[1a] Suchart Chookruvong,[1b] Larry A. Hall,[1c] and Hung-Tai Chao[1d]

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506. *Received May 27, 1980*

α-(1-Piperidinylmethyl)-9-acridinemethanol (**3**), α-[(dibutylamino)ethyl]-9-acridanmethanol (**4a**), and α-[(dibutylamino)methyl]-2-phenanthridinemethanol (**5**) have been made and all are ineffective as antimalarials against *Plasmodium berghei* in mice. 9-Acridinyloxirane showed no significant mutagenicity for strains TA 98 or TA 100 of *Salmonella typhimurium*.

Since **1**[2] and **2**[3] have considerable antimalarial activity (infra), we chose compounds **3** and **4** as targets for synthesis and for antimalarial testing. Compound **3** is like **1** except that **3** lacks the benzo group and the chlorines of **1**. Compound **4** is a chain homologue of **2** and **3**. The dihydrochloride of **3** is ineffective against *P. berghei* in mice and *P. berghei* in vitro (infra). We have been unable to synthesize **4**. We did make the 9,10-dihydro derivative of **4** which has negligible activity against *P. berghei* in mice.



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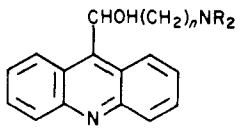
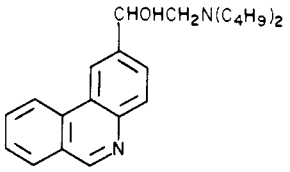


2, $n = 3$; R = C_4H_9
3, $n = 1$; R = $(CH_2)_5$
4, $n = 2$; R = C_4H_9



5

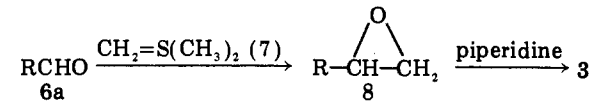
We have also made **5** which is analogous to phenanthrenemethanols, one of which have been found to be clinically useful.[4] Compound **5** has no appreciable activity against *P. berghei* in mice.

Chemistry. Compound **3** was best made from **6a** as shown in Scheme I. When **7**, prepared in the conventional manner,[5] was added to **6a**, the isolation of **8** was difficult and the yields were usually less than 20%, whereas when phase-transfer catalysis was used, the yield of **8** was 56%. Treatment of **8** with dibutylamine (4 days at 150 °C) or $NaNH_2$ (refluxing THF for 4 h) failed to open the oxirane. The peri hydrogens of acridine apparently provide steric hindrance to attack of the oxirane.[2] Three groups[6-8] have reported unsuccessful efforts to prepare compounds like **3**.

The synthesis of **4** was attempted (Scheme II), but **4a** was obtained. Addition of the stoichoimetric amount of BH_3 to reduce only the amide of **10a** gave **4a**. Unsuccessful attempts were made to convert **4a** to **4** by treating **4a** with (a) $FeCl_3$,[9] (b) chloranil,[10] (c) $C_6H_5NO_2$,[11] (d) $AgNO_3$,[12] and (e) Fehling's solution. Also, the synthesis of **4** from 9-acetylacridine and $CH_2{=}N^+(CH_3)_2Cl^-$ was unsuccessful.

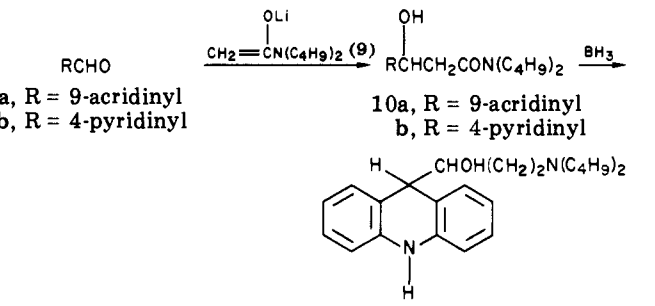
As a model reaction for preparing **4**, 4-pyridinecarboxaldehyde (**6b**) was used in place of **6a**. The expected 4-pyridinemethanol was obtained in 36% overall yield. The lower yield of **10a** in comparison to **10b** is probably due to steric hindrance of the peri hydrogens of **6a**. The 1,4 addition of hydrogen to **4** to yield **4a** is analogous to the

Scheme I[a]



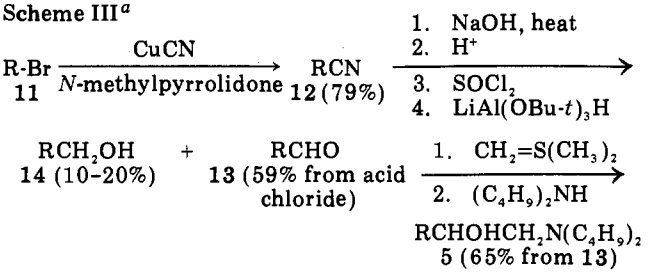
[a] R = 9-acridinyl.

Scheme II



4a

Scheme III[a]



[a] R = 2-phenanthridinyl.

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recently reported reaction of quinoline with borane to yield 1,2,3,4-tetrahydroquinoline.[13]

For the synthesis of **5** a normal ylide method[5] was used to convert aldehyde **13** to an oxirane (not isolated) which was treated with $(C_4H_9)_2NH$. The necessary aldehyde (**13**) was prepared in an 11-step synthesis starting from 2-aminobiphenyl. The final and new steps are shown in Scheme III.

Biological Activity and Discussion

In contrast to 3,9,11-trichloro-7-(α-piperidinylmethyl)-benz[*c*]acridinemethanol (**1**) which has been reported[2] to be curative against *P. berghei* in mice and nontoxic, **3a**·2HCl against *P. berghei* in mice at a dosage of 640 mg/kg of body weight increased the life span only 0.5 day.[14] Because of the instability of **3**·2HCl (**3** is less stable than its hydrochloride), freshly prepared **3**·2HCl was tested by VanDyke's method:[15] *P. berghei* showed 50% inhibition of hypoxanthine uptake and 31% inhibition of adenosine uptake, whereas quinacrine in the same tests showed 92 and 80% inhibition, respectively. The explanation for the difference in antimalarial activities of **1** and **3**·2HCl must be due to the presence of the benzo and/or chloro groups of **1**.

The lack of antimalarial activity of **3**·2HCl is in contrast to the activity of **2** (0.3 that of quinine against *P. gallinaceium*),[3] but it must be noted that different test systems were used.

The fact that **4a** decreased the life span of mice treated (dosage 640 mg/kg) with *P. berghei* by 0.2 day is in agreement with the lack of activity of α-[(diethylamino)-methyl]-9-acridanmethanol,[16] the lower homologue, against *P. lophurae* in White Pekin ducks. Again it must be noted that different test systems were used. α-[(Dibutylamino)methyl]-4-pyridinemethanol, which was made as a synthesis model for **4**, caused a decrease in life span of 0.4 day in mice (dosage 160 mg/kg) treated with *P. berghei*. This result is not surprising because of the lack of ring substitution.

The antimalarial activity of **5** against *P. berghei* in mice was negligible (a 0.1-day increase in survival at a dose of 320 mg/kg). This and the results for 6-phenanthridinemethanols[17] are in contrast to antimalarial activity reported for some 9-phenanthrenemethanols.[4]

Some hydrocarbon oxiranes, like 1-pyrenyloxirine and 9-anthracenyloxirane, show mutagenic responses[18] at 1000 nmol/plate or lower. 9-Acridinyloxirane (**8**) has been found to have no significant level of mutagenicity for either strain TA 98 or TA 100 of *Salmonella typhimurium*.[19]

Experimental Section

Melting points were determined with a Mel-Temp Apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer IR-137 or a Beckman IR-8 spectrometer. ^1H NMR spectra were recorded [$(CH_3)_4Si$ as internal standard] using a Varian EM-360 or T-60 NMR spectrometer. Tetrahydrofuran was dried by distillation from $LiAlH_4$, and dimethyl sulfoxide was dried by distillation under reduced pressure from CaH_2. Elemental analyses (by Galbraith Laboratories, Inc., Knoxville, TN) were within ±0.4% of the theoretical values. Silica gel for column chromatography was from EM Laboratories, 70–230 mesh, activity II–III (unless indicated otherwise). Eastman Chromatogram plates were used for TLC.

9-Acridinyloxirane (8). Phase-Transfer Method.[20] Compound **6** (from 9-methylacridine by an adapted procedure[21]) (7.0 g, 33.8 mmol) in 140 mL of dichloromethane, 140 mL of 50% (w/w) NaOH, 8.41 g (41.2 mmol) of trimethylsulfonium iodide, and 0.94 g (2.54 mmol) of tetrabutylammonium iodide were stirred and heated together under reflux for 25 h. The mixture was poured into 70 mL of ice–water and CH_2Cl_2 was added to dissolve solid material. The organic layer was washed four times with H_2O and with saturated NaCl solution, dried ($MgSO_4$), and concentrated in vacuo to yield a brown solid. Dry column chromatography (1.5 × 15.0 cm of silica gel, $CHCl_3$) of this residue, followed by recrystallization from EtOH, yielded 4.19 g (56%) of yellow crystals of **8**, mp 88–91 °C. Anal. ($C_{15}H_{11}NO$) C, H, N.

α-(1-Piperidinylmethyl)-9-acridinemethanol Dihydrochloride (3·2HCl) and 3. Compound **8** (3.0 g, 13.5 mmol) and 30 mL of piperidine under an atmosphere of nitrogen were heated (105–110 °C) for 11 h. The mixture was concentrated in vacuo and the residue was dissolved in Et_2O. The ethereal solution was dried (Na_2SO_4) and evaporated to give a yellow solid, which was treated successively with ethanolic HCl and anhydrous Et_2O to yield 3.26 g (64%) of yellow crystals (**3**·2HCl), mp 160–162 °C. The analytical sample had mp 164–166 °C (EtOH). Anal. ($C_{20}H_{24}N_2OCl_2$) N, Cl.

Treatment of **3**·2HCl with dilute NaOH yielded a solid which was recrystallized from benzene–petroleum ether (62–75 °C) to give **3**: yellow crystals; mp 98–102 °C; IR (KBr) 3500–3450 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 8.8–7.2 (m, 8, aromatic), 6.4–6./ (2 d, 1, C*H*OH), 4.7–4.3 (s, 1, OH), 3.4–2.2 [m, 6, $N(CH_2)_3$], 2.0–1.2 [m, 6, $CH_2(CH_2)_3CH_2$]; TLC (silica gel–Et_2O) R_f 0.20; mass spectrum (70 eV), *m/e* 306 (M^+). Anal. ($C_{20}H_{22}N_2O$) C, H, N, O.

3-Hydroxy-3-(9-acridinyl)-*N,N*-dibutylpropanamide (10a). To 19 mmol of lithium diisopropylamide[22] in 40 mL of THF at 0 °C was added 2.0 mL (10 mmol) of *N,N*-dibutylacetamide. After the mixture was stirred for 15 min, 4.00 g (19 mmol) of **6** in 40 mL of THF was added, and the mixture was allowed to attain room temperature. After 4 h, 20 mL of 1 M acetic acid in ether was injected. Lithium acetate was removed by filtration. The filtrate was concentrated, the residue was dissolved in ether, and the resulting solution was washed with water and with saturated NaCl solution and dried ($MgSO_4$). The solution was concentrated to yield a yellow solid, which was chromatographed (2 × 15 cm of silica gel, $CHCl_3$) to produce a yellow solid which was recrystallized three times from EtOH–DMF (10:1) to give 0.03 g of **10a** as yellow crystals: mp 107–108 °C; IR (KBr) 1625 cm^{-1} (C=O). Anal. ($C_{24}H_{30}N_2O_2$) C, H, N.

α-[(Dibutylamino)ethyl]-9-acridanmethanol (4a). Under nitrogen and with stirring, 1.09 g (2.87 mmol) of **10a** (yellow gum) in 10 mL of THF was added to 20 mmol of borane[23] in THF (Aldrich) at 0 °C. The mixture was heated under reflux for 15 h. Water (20 mL) and 10 mL of concentrated HCl were added, and the mixture was heated under reflux for 2 h. The mixture was made basic with NaOH and extracted with Et_2O. The ethereal layer was washed with H_2O, dried, and concentrated to yield 0.92 g of solid, which was recrystallized from EtOH to yield 0.142 g (19%) of **4a**: white crystals; mp 143–145 °C; IR (KBr) 3310 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 6.8–7.92 (m, 8), 6.50 (s, 1), 3.85–4.45 (m, 2), 1.8–3.0 (m, 6), 0.5–1.8 (m, 16). Anal. ($C_{24}H_{34}N_{20}$) C, H, N.

3-Hydroxy-3-(4-pyridinyl)-*N,N*-dibutylpropanamide (10b) was prepared by the procedure used for **10a**: yield of **10b**, 80%; mp 66–68 °C. Recrystallized **10b** (cyclohexane) melted at 68–69 °C. Anal. ($C_{16}H_{26}O_2N_2$) C, H, N.

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α-[(Dibutylamino)ethyl]-4-pyridinemethanol (4b) was prepared by the procedure used for **4a**: yield of **4b** as dipicrate, 46%; mp 108–111 °C (EtOH). Anal. ($C_{28}H_{34}O_{15}N_8$) C, H, N.

2-Cyanophenanthridine (12) was prepared by adapting the method of Newman and Boden.[24] The yield of **12** was 79%: yellow crystals; mp 221–222 °C; IR (KBr) 2220 cm^{-1} (CN). Anal. ($C_{14}H_8N_2$) C, H, N.

2-Phenanthridinecarboxaldehyde (13). Compound **12** (32.3 g, 0.147 mol) and 17.1 g of NaOH in 300 mL of water were heated under reflux for 20 h. The mixture was filtered to recover 3.7 g of **12**. The pH of the filtrate was adjusted to 2 by adding 6 M HCl to produce a finely divided tan precipitate, which was collected using a sintered glass funnel. The tan solid was dissolved in approximately 1 L of boiling dimethylformamide, treated with charcoal, and filtered. Water was added to the cooled filtrate to precipitate finely divided white crystals, mp 316–318 °C, which weighed 23.8 g.

Freshly distilled $SOCl_2$ (30 mL) and 5.05 g of the foregoing solid were heated under reflux for 6.5 h. Most of the thionyl chloride was removed by reduced pressure distillation and the remainder by codistillation with dry benzene at reduced pressure to yield 5.26 g of a pale yellow powder of 2-phenanthridinecarboxoyl chloride hydrochloride: mp 237–247 °C dec; IR (KBr) 1725 cm^{-1} (C=O); derivative, 2-(ethoxycarbonyl)phenanthridine (80%), mp 96–97.5 °C (C_2H_5OH). Anal. ($C_{16}H_{13}NO_2$) C, H, N.

To 2-phenanthridinecarboxoyl chloride hydrochloride (11.1 g, 0.04 mol) in 40 mL of dry, ice-cooled THF under a N_2 atmosphere was added dropwise, with stirring during 2 h, 18.3 g (0.072 mol) of $LiAl(OBu\text{-}t)_3H$ in 225 mL of dry THF. The mixture was kept at 0–5 °C for 30 min, the ice bath was removed, and stirring was continued for 1 h. Chloroform (200 mL) was added and the resulting mixture was poured into 500 mL of ice–water. The precipitate which resulted was removed by filtration and discarded. The filtrate was extracted repeatedly with $CHCl_3$, and the $CHCl_3$ extract was washed with Na_2CO_3 solution, dried ($MgSO_4$), and concentrated to yield 7.7 g of light yellow solid: mp 171–180 °C; TLC (alumina–CH_2Cl_2) R_f 0.69 (**13**, major) and 0.21 [2-phenanthridinylmethanol (**14**), minor].

The crude product was purified by chromatography using Florisil (Fisher 60–100 mesh, 3.5 × 35 cm) and Et_2O. Aldehyde **13** was the first component to be eluted from the column. Evaporation of Et_2O left a white powder, mp 185–188 °C, which was sublimed at 120 °C (0.15 mm) to yield **13** (59%): mp 185–199 °C; IR (KBr) 1685 cm^{-1} (C=O); ^1H NMR δ 10.2 (s, CHO, 1), 9.4 (s, 1, aromatic), 9.0 (s, 1, aromatic), 8.8–7.6 (m, 6, aromatic).

Crude **14** was obtained by further elution. An analytical sample of **14** was obtained by further column chromatography: basic alumina, Woelm activity I, 2.5 × 15 cm for 3 g of mixture, and $CHCl_3$ as developer. Evaporation of $CHCl_3$ left a nearly white solid: mp 135–137 °C; IR (KBr) 3200 cm^{-1} (OH). Anal. ($C_{14}H_{11}NO$) C, H, N.

α-[(Dibutylamino)methyl]-2-phenanthridinemethanol (5). To dimethylsulfonium methylide[5] (10 mmol) at 0 °C in 15 mL of Me_2SO was added, with stirring, 1.3 g (6.3 mmol) of **13** in 60 mL of THF. Stirring at 0 °C was continued for 30 min and then for 1 h as the solution warmed to room temperature. Ice–water (150 mL) was added and the mixture was extracted with Et_2O. To eight-ninths of the ethereal solution was added 3.0 g of dibutylamine. Ether was removed by distillation, and the residue was heated to 150 °C for 30 min under nitrogen. After reduced pressure distillation of the volatiles, a bright orange viscous liquid (1.4 g) remained as the residue. This was chromatographed (Florisil, Fisher, 60–100 mesh, 2.5 × 20 cm, Et_2O). The lead band was **5**: yield 1.1 g (65%); yellow oil; IR (neat) 3380 cm^{-1} (OH); ^1H NMR (CS_2) δ 7.5–9.7 (m, 8), 4.7–5.0 (2 d, 1), 4.0 (s, 1), 2.4–2.7 (m, 6), 0.8–1.7 (m, 14). Anal. ($C_{23}H_{30}N_2O$) C, H, N.

Acknowledgment. We thank the U.S. Army Research and Development Command for help in initiating this program under Contract DA-17-68-C3099. We thank the U.S. Army Walter Reed Institute of Research, Washington, DC, for in vivo antimalarial test results, and Dr. Knox VanDyke and Joseph Undeniya, West Virginia University Medical Center, for in vitro antimalarial test results. Also, we thank Dr. Elizabeth C. Miller, University of Wisconsin Medical Center, Madison, WI, for mutagenicity tests and Lawrence E. Wilkinson for performing oxidation experiments.

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Book Reviews

Goodman and Gilman's The Pharmaceutical Basis of Therapeutics. Sixth Edition. By Alfred Goodman Gilman, Louis Goodman, and Alfred Gilman. Macmillan, New York. 1980. xvi + 1843 pp. 18.5 × 26 cm. $45.00.

The sixth edition of this classic textbook of pharmacology continues the philosophy and objectives of the earlier editions. Several major changes deserve emphasis. The section on general principles has been expanded and divided into three chapters, including a new introductory treatise on "Principles of Therapeutics". Pharmacokinetic data have become available at an accelerating rate, and there is thus continued attention to this topic. Fundamental discussion is presented in Chapter 1, and a practical approach to the optimal utilization of this information is presented in a major new unit which includes both explanatory text and readily utilized tables for a large number of drugs. The basic mechanisms of clinically relevant interactions are analyzed for individual drugs, and an index of drug interactions has been prepared for ready reference. Other major changes include a new chapter on "Neurohumoral Transmission and the Central Nervous System". An entire new section of the textbook is concerned with toxicology.

This sixth edition of "Goodman and Gilman" will prove invaluable to every researcher, practitioner, and student involved with the use, development, or dispensing of drugs.

Staff

The Chemistry of Heterocyclic Compounds. Volume 39. Triazoles: 1, 2, 3. By K. Thomas Finley. Series editors, Arnold Weissberger and Edward C. Taylor. Volume editor, John A. Montgomery. Wiley, New York. 1980. ix + 349 pp. 16.5 × 24 cm. $100.00.

For the medicinal chemist the investigation of novel compounds with interesting pharmacological activity is often synonymous with the investigation of novel heterocyclic systems. The search for compounds with a particular type of biological activity, however, may extend across the classical lines of heterocyclic research and involve the synthesis of structures based on many different heterocyclic systems. In this complex area of organic chemistry where each heterocyclic system is associated with its own unique physical properties, synthetic methods, and chemical behavior, such studies would be formidable if the investigator did not have a ready access to the appropriate heterocyclic literature. Such access has been provided by "The Chemistry of Heterocyclic Compounds". "Triazoles: 1, 2, 3", the 39th volume in this series, is a comprehensive review of the monocyclic 1,2,3-triazole literature