Antimalarials. 11. 2-Vinylogs of Substituted 2-Aryl-4-quinoline Amino Alcohols

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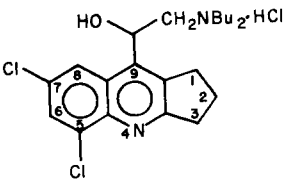
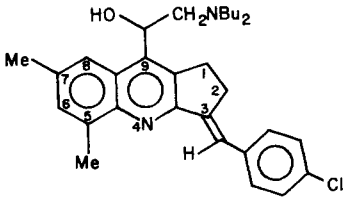
3-(*p*-Chlorobenzylidene)-5,7-dimethyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline-9-(di-*n*-butylaminomethyl)methanol and 2-[β-(*p*-chlorostyryl)]-6,8-dimethylquinoline-4-(di-*n*-butylaminomethyl)methanol were synthesized from 6,-8-dimethyl-4-hydroxycarbostyril by 3,3-dichlorination, dimethoxylation to the 3-ketal, basic hydrolysis to the glyoxal acetal, Pfitzinger condensation with cyclopentanone or acetone to the 2,3-trimethylene or 2-methylquinoline, condensation with *p*-ClPhCHO at the 2-methylene or 2-methyl group, hydrolysis to the 4-quinaldehyde, methylenation to the epoxide, and condensation with Bu_2NH. Both were curative against *P. berghei* in mice. The first was the more effective: active at 10 mg/kg, completely curative at 40 mg/kg, and only mildly phototoxic in animals.

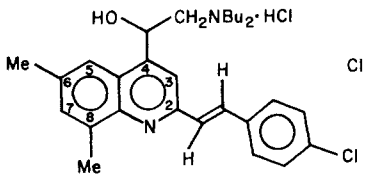
Since 6,8-dichloro-2,3-trimethylene-4-quinoline-(di-*n*-butylaminomethyl)methanol (1)[1] was moderately active against *Plasmodium berghei* in mice and nonphototoxic in animals,[5] the 2-(*p*-chlorobenzylidene)-6,8-dimethyl analog **2** and the 2-[β-(*p*-chlorostyryl)]-6,8-dimethyl-4-quinoline analog **3** were synthesized for comparisons with the highly curative 2-aryl-4-quinolylamino alcohols of type **4**.[2] Compound **2** has a rigid tricyclic nucleus in which the quinoline moiety is conjugated through the vinyl group with the *p*-ClPh in a presumably trans and relatively planar chalcone-like system where quinoline C=N replaces the chalcone C=O; and **3** has the simple trans chalcone-like system planarized by resonance.



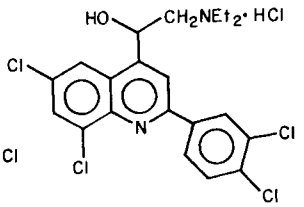
1,[1] REL 949, WR 135616



2, REL 982, WR 160991



3, REL 986



4,[2] REL 558, WR 30090

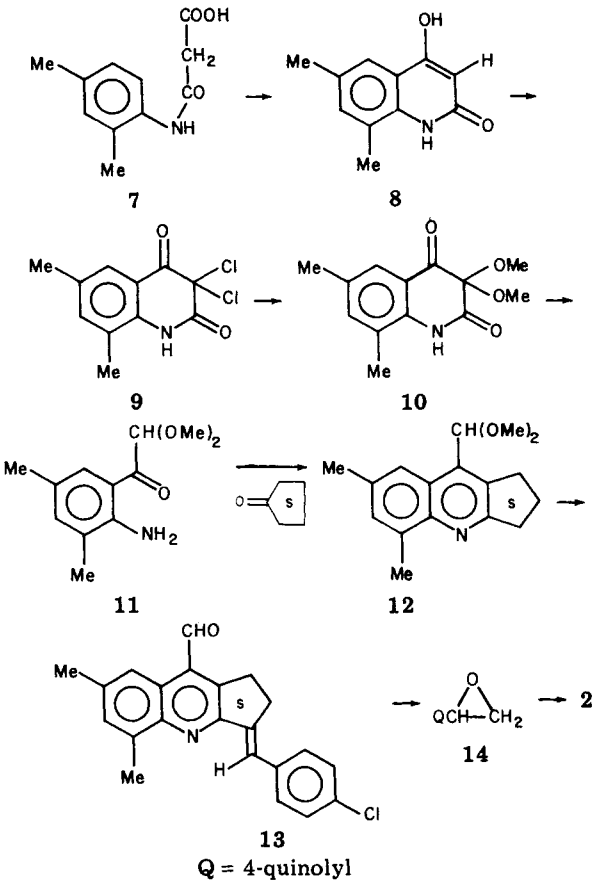
Chemistry. In an attempted synthesis of the 5,7-dichloro analog of **2**, *p*-ClPhCHO was condensed at the active CH_2 of the 2,3-trimethylenecarboxylic ester (**39** → **40**), but the acid chloride on diazomethylation and hydrobromination[2a] failed to give the bromo ketone and exhausted supplies of intermediates. The Ziegler synthesis[3] of 4-quinaldehydes was then utilized, starting from 2,4-Me_2PhNH_2 rather than the preferred 2,4-Cl_2PhNH_2 because of the reported much better yield of intermediate **9** (Scheme I). Condensation of ethyl malonate with 2,4-Me_2PhNH_2 and hydrolysis of **5** to malonamic acid **7**, cyclization to 6,8-dimethyl-4-hydroxycarbostyryl (**8**), 3,3-dichlorination to **9**, dimethoxylation to the 3-ketal **10**, and basic hydrolysis gave glyoxal acetal **11**. Pfitzinger condensation with cyclopentanone to the 2,3-trimethylenequinoline **12**, condensation at the 2-CH_2 with *p*-ClPhCHO, acid hydrolysis to quinaldehyde **13**, methylenation[4] to the epoxide **14**, and condensation with Bu_2NH gave amino alcohol **2**.

The route to the parent 2-vinylog of the 2-aryl-4-quinoline amino alcohols, 2-[β-(*p*-chlorostyryl)] analog **3**, branched from Scheme I by condensation of **11** with acetone (Scheme II).

Scheme I

$CH_2(COOEt)_2 + Me_2PhNH_2 \rightarrow$

$Me_2PhNHCOCH_2COOEt + CH_2(CONHPhMe_2)_2 \rightarrow$

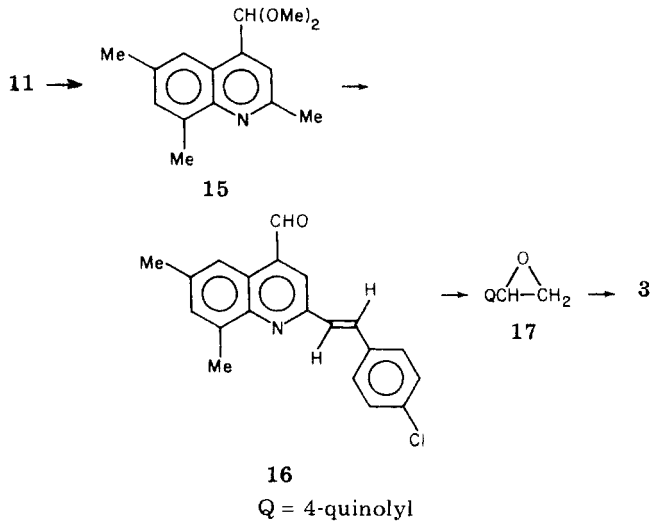


Q = 4-quinolyl

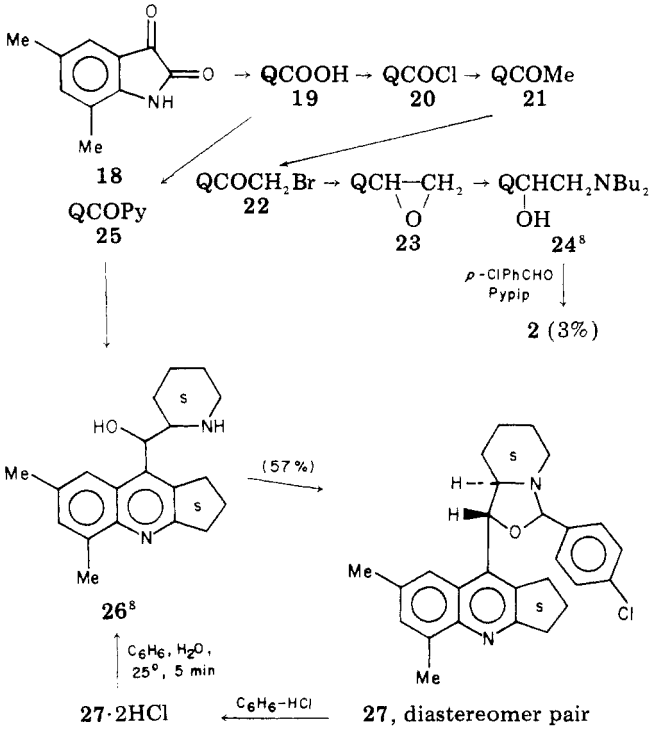
Antimalarial Activities.[5] The 2-(*p*-chlorobenzylidene)-2,3-trimethylene-4-quinoline amino alcohol **2** was active against *P. berghei* in mice at 10 mg/kg, cured two of five mice at 20 mg/kg, and was completely curative at 40 mg/kg. It was mildly phototoxic[5] in animals (MED, ip, mg/kg; 100).[2b,c] The quinoline-2-(*p*-chlorostyryl) analog **3** was less effective, active at 20 mg/kg and completely curative at 160 mg/kg. Considering the manifold increases in antimalarial activity in other series[6a,b] upon replacing 6,8-Me_2 by the pharmacophorically more effective 6,8-Cl_2, it would be of interest to make and test the 6,8-Cl_2 and 8-CF_3 analogs of **2**, **3**, and related compounds including representative cis isomers[2d] and saturated analogs.

Attempts to synthesize the 2,3-trimethylene compound **2** and its α-piperidyl analog by classical routes[2a,7] were carried out independently by Corson et al.[8] to obtain samples for clinical trial. These utilized last-step condensations of the amino alcohols **24** and **26** with *p*-ClPhCHO (Scheme III).

Scheme II



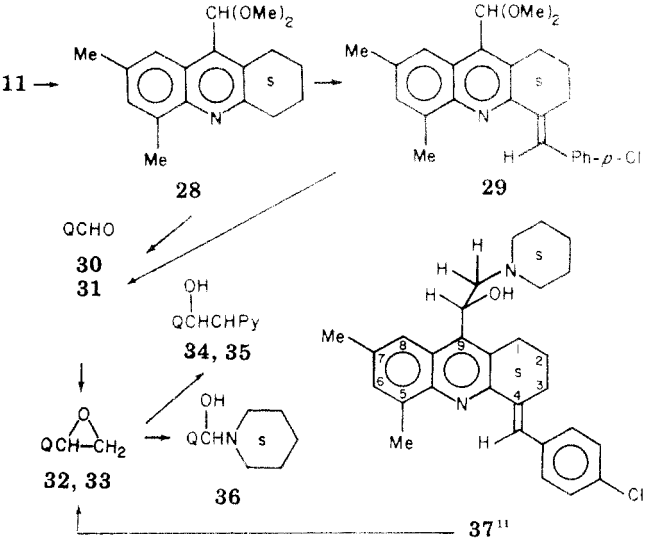
Scheme III



Attempted synthesis of the 2-piperidyl analog of **2**, via pyridylation of **19** to **25**,[7] hydrogenation to **26**, and condensation with *p*-ClPhCHO, gave, instead of the desired amino alcohol, an isomer which has now been shown (by REL) to be the oxazolidine **27**, the cyclic azaketal of the secondary amino alcohol **26**.[9] Possibly the azaketal might serve protectively here in forced condensations at the 2-methylene group, to be followed by acid-hydrolytic regeneration of the secondary amino alcohol.[8c]

Proof of structure **27** rests on (a) total inactivity against *P. berghei* in mice in contrast to total curativity of **2** at 40 mg/kg,[5] (b) facility at 25° of hydrolytic cleavage[8,9] of **27**·2HCl to **26** and *p*-ClPhCHO,[8] (c) absence of N–H and O–H ir absorptivity at 3400–3500 cm^{-1} (KBr or $CHCl_3$) (shown by **2**), (d) lack of chalcone-type uv absorptivity above 350 nm (shown by **2**), (e) NMR spectral compatability with **27** as a pair of diastereomers[8] (unseen by TLC), δ $CDCl_3$ (or C_6D_6) 5.70, 6.16 [J = 8 Hz, 26 (30)], IH-dd with all-equal peak intensities rather than the 1:2

Scheme IV



peak intensity ratios calculated for each of the doublets were they coupled (LACOON III, least-squares fit simulation); D_2O caused no D exchange required by O–H and D–H, and (f) chemical ionization mass spectrum (D. F. Hunt[10]), substituting D_2O for H_2O as reagent gas failed to increase the molecular weight of the abundant M + 1 ion (M + H m/e 433, M + D m/e 434), thus excluding O–H and N–H (spectrum compatible).

Synthesis of 4-(*p*-chlorobenzylidene)-5,7-dimethyl-1,2,3,4-tetrahydroacridine-9-(*N*-piperidinomethyl)methanol (**37**, a 2,3-tetramethylenequinoline analog of **2**) was carried out independently by Bass and Hirjibehdin[11] via Scheme IV. Steric interference impeded reactions of groups at position 9.

Experimental Section

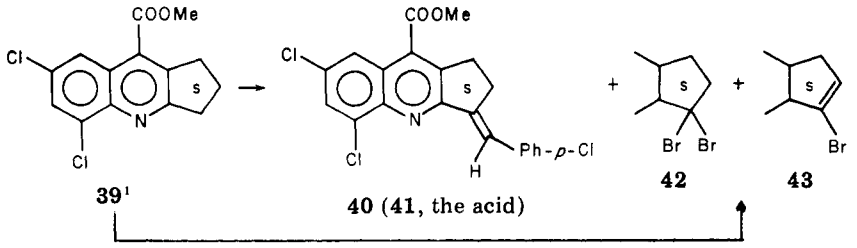
Instruments: Thomas-Hoover apparatus for melting point; ir, Perkin-Elmer 337; NMR, Hitachi Perkin-Elmer R-20; mass spectra were compatible, Hitachi Perkin-Elmer RMU 6E. Microanalyses were performed by Gailbraith Lab., Inc. (correct to ±0.4%).

Intermediates for synthesis of 2 utilized reaction of 2,4-dimethylaniline with diethyl malonate (1:6 mixture, 190° until evolution of EtOH ceased). Mixtures of **5** and **6** were obtained by pouring into MeOH (chilling), concentrating in vacuo, and Et_2O extraction. Recrystallization (Et_2O–hexane) gave **ethyl *N*-(2,4-dimethylphenyl)malonamate (5)**: mp 102–104°; characterized by ir 3340, 3320, 1730, 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (t, 3, J = 7.5 Hz), 2.30 (s, 6), 3.49 (s, 2), 4.28 (q, 2, J = 7.5 Hz), 7.08 (m, 2), 7.81 (s, 1), 9.15 (s, broad, 1). Two successive treatments of the **5**–**6** mixture with boiling 10% $NaHCO_3$ (6 h, cooling, filtration) gave **malonic acid bis(2,4-dimethylanilide) (6)**: mp 126–164° (containing no **5**, TLC, silica gel G, EtOH); characterized by mass spectrum, m/e 310 (M^+), 163, 149, 148, 122, 121 (base peak), 120, 106, 77 (this should be convertible to **10** by $AlCl_3$).[3] Acidification of $NaHCO_3$ filtrates from **6** (HCl) precipitated **N-(2,4-dimethylphenyl)malonamic acid(7)** which was recrystallized (EtOH) (75%): mp 158–159°. Anal. ($C_{11}H_{13}NO_3$) H, N; C: calcd, 63.76; found, 65.0.

6,8-Dimethyl-4-hydroxycarbostyryl (8)[3b] was made by cyclization of **7** (PPA, 145°, 4 h) which was recrystallized (DMF): mp 355° dec (lit.[3b] 360°).

3,3-Dichloro-6,8-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (9). A refluxing solution of **8** in 12:2:3 dioxane–H_2O–concentrated HCl was treated dropwise with 30% H_2O_2 at a rate to maintain exothermic reaction at 90–95°; **9** precipitated. After 30 min (80–35°), cooling and diluting (ice–H_2O), **9** was filtered, washed (H_2O), and dried (100°, 20 h): yellow; mp 217–218° dec (lit.[3b] 215°); 61% from **7**; recrystallized (THF–hexane) mp 222–223° dec. Anal. ($C_{11}H_9Cl_2NO_2$) C, H, N.

Scheme V



3,3-Dimethoxy-6,8-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (10). Addition of a solution of 40 g of Na in MeOH (600 ml) to **9** (202 g in MeOH, 500 ml, exothermic reaction), refluxing (30 min), quenching (ice–5% HCl), filtration, and washing (H_2O) gave **10** which was recrystallized (MeOH, yellow): mp 206–208°; NMR compatible. Anal. ($C_{13}H_{15}NO_4$) C, H, N.

The diethoxy analog of 10 was prepared from **9** by NaOEt: mp 191–192° dec. Anal. ($C_{15}H_{19}NO_4$) C, H, N.

2-Amino-3,5-dimethylphenylglyoxal Dimethyl Acetal (11). A suspension of **10** in 1.15 l. of 6% aqueous NaOH was refluxed (1.25 h), cooled (10°), saturated with NaCl, and extracted portionwise with 1.6 l. of Et_2O, giving **11** (50% from dimethylaniline): bp 127–128° (0.23 mm); NMR ($CDCl_3$) δ 2.10 (s, 3), 2.22 (s, 3), 3.47 (s, 6), 5.32 (s, 1), 6.27 (s, broad, 2), 7.08 (s, 1), 7.32 (s, 1). Anal. ($C_{12}H_{17}NO_3$) C, H, N.

5,7-Dimethyl-9-(dimethoxymethyl)-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (12).[3e] A solution of Na (2.5 g, EtOH), **11** (29.3 g), and cyclopentanone (15 g) was refluxed (17 h) and quenched (saturated NaCl). Et_2O extraction, evaporation, and crystallizations (hexane) gave **12** (25.1 g, 70%, yellow), mp 78–80°. Anal. ($C_{17}H_{21}NO_2$) C, H, N.

3-(*p*-Chlorophenyl)-2-cyclopentenone (38) was prepared (21%) like the phenyl analog:[13] sublimed [75° (0.3 mm)]; mp 96–98°; NMR ($CDCl_3$) δ 2.60 (m, 2), 3.25 (m, 2), 6.59 (m, 1), 7.55 (m, 4). Anal. ($C_{11}H_9ClO$) C, H. Attempted condensation with **11** was unsuccessful.

3-(*p*-Chlorobenzylidene)-5,7-dimethyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline-9-aldehyde (13).[3e] A mixture of **12** (7.89 g), *p*-ClPhCHO (4.26 g), dry NaOAc (2.51 g), Na_2CO_3 (10.6 g), and Ac_2O (300 ml) was refluxed (17 h), cooled, and hydrolyzed (15% NaOH). The precipitate, **13** acetal, was washed (H_2O, Et_2O; 9.76 g). A mixture of an aliquot (5.67 g), $CHCl_3$ (250 ml), and 5% HCl (50 ml) was stirred (1 h) (1:4 H_2O–THF dissolves **12** and may be preferable). Evaporation of $CHCl_3$ and Et_2O extracts gave **13** (5.45 g, 54% from **12**) which was recrystallized (THF): mp 237–239° dec. Anal. ($C_{22}H_{18}ClNO$) C, H, N.

3-(*p*-Chlorobenzylidene)-5,7-dimethyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline 9-Ethylene Oxide (14).[4] To a mixture of THF (100 ml) and NaH (5.24 g of 54% mineral oil dispersion in Me_2SO, 100 ml) (heated, 70°) was added THF (cooling to –5°), $Me_3{}^+SI^-$ (25 g in Me_2SO, 175 ml, over 3–5 min, ±5°), then THF (50 ml), and **13** [9 g suspended in THF[14] (150 ml) over 2–3 min (–5°)]. Stirring (15 min at –5° and 1.25 h at room temperature), quenching (saturated H_2O–NaCl), extraction (Et_2O and 2:1 Et_2O–THF), and crystallization (Et_2O) gave **14** (4.57 g, 49%) which was recrystallized (Et_2O): yellow; mp 205–207° dec. Anal. ($C_{23}H_{20}ClNO$) C, H, N.

3-(*p*-Chlorobenzylidene)-5,7-dimethyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline-9-(di-*n*-butylaminomethyl)methanol (2). A suspension of **14** (3.32 g) in Bu_2NH (7.5 g) was heated (under N_2, 145–150°, 9 h) with disappearance of **14** monitored by TLC (silica gel G, Et_2O–hexane). Removal of excess Bu_2NH [55° (3 mm)] and crystallization (Et_2O–THF) gave 3.63 g which was recrystallized: yellow; mp 153–155° dec; uv (EtOH) nm (ε × 10^{-3}) 235 sh (1.79), 294 (28.3), 299 (29.8), 350 sh (17.5), 364 (25.2), 381 (25.2). Anal. ($C_{31}H_{39}ClN_2O$) C, H, N.

2,6,8-Trimethylquinoline-4-aldehyde Dimethyl Acetal (15[3]). A solution of **11**[3] (10.7 g) and Me_2CO (3 g) in absolute EtOH (30 ml) was added rapidly to a 30-ml EtOH solution of Na (0.85 g). Refluxing (18 h), quenching (aqueous NaCl), Et_2O extraction, evaporation, and chromatography (Florisil, hexane and 9:1, 3:1, and 2:1 hexane–Et_2O) gave **15** [11.29 g (96%), TLC, single spot (silica gel G, 4:1 hexane–Et_2O)]: bp 125–125.5° (0.33 mm); colorless; NMR ($CDCl_3$) δ 2.5 (3 H, s), 2.8 (3 H, s), 3.38 (6 H, s), 5.9 (1 H, s), 7.44 (1 H, broad s), 7.57 (1 H, s), 7.86 (1 H, broad s). Anal. ($C_{15}H_{19}NO_2$) C, H, N.

2-[β-(*p*-Chlorostyryl)]-6,8-dimethylquinoline-4-aldehyde (16).[3] A mixture of **15** (12.7 g), *p*-ClPhCHO (7.9 g), dry NaOAc (9.8 g), dry Na_2CO_3 (14 g), and Ac_2O (300 ml) was refluxed (18 h) and quenched (ice–H_2O–KOH–NaCl). **16** acetal was isolated by repeated extraction (THF) and hydrolyzed (THF–H_2O–concentrated HCl, 300:150:25 ml, brief reflux). **16** was extracted (THF, Et_2O) and recrystallized (Et_2O–hexane): 7.51 g (50%); yellow; mp 167–169°; ir (KBr) 1700 cm^{-1}; NMR ($CDCl_3$) δ 2.50 (3 H, s), 2.78 (3 H, s), 7.12–7.65 (7 H, m), 7.81 (1 H, s), 8.47 (1 H, broad s), 10.14 (1 H, s). Anal. ($C_{20}H_{16}ClNO$) C, H, N.

2-[β-(*p*-Chlorostyryl)]-6,8-dimethylquinoline 4-Ethylene Oxide (17).[4] **17** was prepared like **14** and recrystallized (Et_2O): yellow; mp 141–142°. Anal. ($C_{21}H_{18}ClNO$) C, H, N. Reaction with $NHBu_2$ (140–145°, 9 h, under N_2) was shown to be incomplete by H. R. Munson (TLC); mass spectrum *m/e* 464 (**3**), 142 (CH_2NHBu_2).

2-[β-(*p*-Chlorostyryl)]-6,8-dimethylquinoline-4-(di-*n*-butylaminomethyl)methanol Hydrochloride (3). To NaH (1.8 g, Et_2O-washed) in Me_2SO (10 ml, 70°, 1 h) was added THF (50 ml, cooling to and maintaining below 0°). Me_3SI (8 g in Me_2SO, 50 ml) was added slowly and then **16** (2.3 g in THF, stirring, 25°, 3 h). Pouring into H_2O, extraction (Et_2O), drying (Na_2SO_4), evaporation, addition of $NHBu_2$ (10 ml), heating (160°, under N_2, 18 h), vacuum evaporation of excess $NHBu_2$, chromatographing (silic gel, EtOAc–C_6H_6), and precipitation by Et_2O–HCl gave **3** (1.5 g, 40%): mp 125–130° dec (required vacuum drying). NMR and CI mass spectrum compatible. Anal. ($C_{29}H_{38}Cl_2N_2O$) C, H, N.

Derivatives of 5,7-Dichloro-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline-9-carboxylic Acid Methyl Ester (39–42) as potential intermediates for synthesis of antimalarials are shown in Scheme V.

3-(*p*-Chlorobenzylidine)-5,7-dichloro-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline-9-carboxylic Acid Methyl Ester (40). A mixture of **39**[1] (29.6 g), *p*-ClPhCHO (1.47 g), dry NaOAc (9 g), and Ac_2O (200 ml) was refluxed (18 h) and quenched (ice–H_2O). Stirring (1.5 h), basification (50% KOH), washing the precipitate (H_2O and Et_2O), and crystallizations ($CHCl_3$) gave **40** (25 g, 68%): yellow; mp 280–283° dec; mass spectrum compatible. Anal. ($C_{21}H_{14}Cl_3NO_2$) C, H, N. A similar reaction with the acid of **39** was unsuccessful.

Hydrolysis of ester 40 [2 g, suspended in H_2O–KOH (600 ml, 7.5 g), refluxed (20 h), and acidified (concentrated HCl)] gave acid **41** (20.9 g, 98%) which was recrystallized (H_2O–THF): yellow; mp 297–300° dec. Anal. ($C_{20}H_{12}Cl_3NO_2$) C, H, N.

Bromination of 39 [12 g suspended in AcOH–NaOAc (100 ml, 13.5 g, 50–70°)] by dropwise addition of Br_2 (13 g in 100 ml of AcOH) and quenching (ice–H_2O) gave 10.5 g of a **42–43** mixture (separated by chromatography, Florisil, hexane and 9:1 hexane–C_6H_6).

3,3-Dibromo-5,7-dichloro-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline-9-carboxylic Acid Methyl Ester (42). **42** was recrystallized (charcoal, Et_2O): mp 166–168°. Anal. ($C_{14}H_9Br_2Cl_2NO_2$) C, H, N.

3-Bromo-5,7-dichloro-1*H*-cyclopenta[*b*]quinoline-9-carboxylic Acid Methyl Ester (43). **43** was recrystallized (C_6H_6, charcoaled): 0.29 g; mp 165–170°. Anal. ($C_{14}H_8BrCl_2NO_2$) C, H, N.

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of the Army Research Program on Malaria, was supported in large part by U.S. Army Medical Research and Development Command, Office of the Surgeon General, Contract No. DA-48-193-MD-2955, R. E. Lutz, Responsible Investigator, and in smaller parts by grants to the University of Virginia (R.E.L.) from the National Science Foundation (No. 8631) and A. H. Robins Co., Richmond, Va. Antimalarial and phototoxicity test data were supplied by Walter Reed Army Institute for Research. The test sample of 2-(*p*-chlorostyryl)amino alcohol **3** was prepared by D. A. Shamblee at Robins Co., Richmond, Va., working under S. J. Gillespie, Virginia Institute for Scientific Research, Richmond, Va. (Dec 1974). Work done independently and unpublished is here reported: (a) synthesis of **27** and a second synthesis of **2** by B. B. Corson, J. Pociask, H. C. Koppel, and J. Riedmaier, Aldrich Chemical Co., Milwaukee, Wis. (under support from WRAIR); and (b) synthesis of **36** and **37** by R. G. Bass and R. R. Hirjibehdin, Virginia Commonwealth University, Richmond, Va.

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Conformational Influence of a 19-Methyl Substituent in 19-Oxygenated Steroid Structures

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The crystal and molecular structure of (19*R*)-19-methyl-5-androstene-3β,17β,19-triol ($C_{20}H_{32}O_3$) has been determined. The crystals are orthorhombic and the space group is $P2_12_12_1$. The unit cell parameters are a = 11.179 Å, b = 21.485 Å, and c = 7.328 Å. The structure was solved using the direct methods program MULTAN and refined anisotropically to an R of 7.2% for all data. The methyl substituent on C(19) is located over the B ring and the hydroxyl between the A and C rings. The flexible B ring has a distorted half-chair conformation. The 19*R* configuration suggests that the reaction mechanism for the formation of this compound proposed by Wicha and Caspi is incorrect. Furthermore, these results indicate that the stereochemical assignment of C(19) by Skinner and Akhtar resulting from a tritiated sodium borohydride reduction is also suspect.

Chemical evidence combined with analysis of structural models or crystal structure data has led to two proposed mechanisms for the conversion of androgens to estrogens by the reaction of human placental microsomal aromatase.[1] These two mechanisms are very similar in many respects with the enzyme selectively attacking the hydrogen in the syn–anti–syn position, relative to C(1), C(5), and C(9), respectively, replacing it with a hydroxyl group (see Scheme I, step 1). The second step involves a rotation about the C(10)–C(19) bond followed by the enzymatic attack on one of the two remaining hydrogens (steps 2 and 3). Here, the two mechanisms differ. Skinner and Akhtar using tentatively assigned (19*R*)- and (19*S*)-^{3}H-19-hydroxyl substrate have postulated a 19-pro-*S* hydrogen (H_S) replacement, compound **2S**. Osawa using x-ray crystal structure data has assigned the opposite stereochemistry (**2R**) to the labeled substrate and proposed a 19-pro-*R* hydrogen (H_R) replacement. The latter requires the 19-hydroxyl to occupy the syn–syn–anti position over the A ring which is less sterically hindered than the anti–syn–syn position. The remaining steps in the mechanism are essentially the same.

The stereochemical assignments made by Skinner and Akhtar are based directly on previous work done by Caspi and Wicha.[2] The reaction sequence used by Caspi and Wicha (Scheme II) resulted in the formation of a methylated C(19) derivative **7**, but the stereoselective nature of the reaction should be the same as the reaction scheme used later by Skinner and Akhtar. The assignment of an *R* configuration to compound **7** was based on three ob-