Synthesis of Potential Antimalarials

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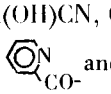
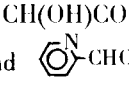
A series of quinoline derivatives containing a 2-thienyl ring in the 2-position and CO_2H, CH_2OH, CHO, CH(OH)CN, $CH(OH)CO_2H$, $CO_2C_2H_5$, $COCH[N(C_2H_5)_2]CO_2C_2H_5$, $COCH_2N(C_2H_5)_2$, $COCH_3$,  and  substituents in the 4-position was synthesized. Both intermediate and target compounds were tested for antimalarial activity. A second series with a 5-bromo-2-thienyl group in the 2-position and $CHOHCH_2N(C_2H_5)_2$, $CHOHCH_2N(CH_2)_6$, and $CHOHCH_2N(CH_2C_6H_5)_2$ substituents in the 4-position was also prepared. It was found that, although these quinoline methanols were moderately active antimalarials, they exhibited a high degree of phototoxicity. A third series of compounds with 2-alkyl substituents (methyl, *t*-butyl) was also synthesized, and these were found to combine a modest degree of antimalarial activity with low phototoxicity. Several novel synthetic routes to the above compounds were developed and are detailed.

Alkaloids in the cinchona family possess chemotherapeutic properties that are useful for the treatment of malaria; quinine, in particular, has been used extensively for this purpose. Early attempts to produce effective antagonists toward malaria adhered closely to the structural model presented by quinine, since it was anticipated that the structural features necessary for antimalarial activity are the methoxyquinoline nucleus and the ethanolamine side chain. This assumption was substantiated by subsequent synthetic efforts.

Biochemical studies on the metabolic fate of quinine in animals (1) led to the interesting observation that the alkaloid is oxidized to the corresponding carbostyryl 2′-hydroxyquinine (2), which is ineffective as an antimalarial. This result led to the suggestion that the potency of quinine might be enhanced by introducing substituents into the 2-position of the quinoline ring, thereby blocking the point of attack of quinine oxidase. The successful synthesis of 2′-phenyldihydrocinchonidine (3) and the demonstration that it was far more potent as an antimalarial than the parent alkaloid opened a new avenue of research.

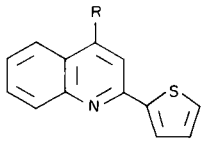
From the extensive synthetic programs that followed, the following structure-activity relationships emerged. The most effective substituent in the 2-position appears to be *p*-chlorophenyl, and in general, di-*n*-butylaminomethyl-4-quinolinemethanols are more active than other dialkylamino analogs. Activity is increased by a 6-methoxy group and particularly by a 7-chloro substituent. Substitution of chlorine at position 6 or 8 is less effective, but disubstitution at the 6- and 8-positions is highly effective.

A difficulty arises, however, with the introduction of an aromatic ring into the 2-position since the compound now serves as a photosensitizing agent. This side reaction is serious enough to preclude the use of this series of compounds for therapeutic purposes. In an attempt to circumvent these side effects, we have synthesized a number of 4-quinoline methanols that contain heterocyclic and aliphatic substituents and now report the results of our findings.

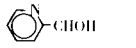
Synthetic Approaches.

The preparation of 2-substituted 4-quinolinecarboxylic acids from a methyl ketone and an isatin (4) derivative is relatively straight-forward. As a result, these carboxylic acids are attractive starting materials for building up the necessary ethanolamine side chain. In view of the fact that the published routes (4,5) for converting the carboxylic acid group to an ethanolamine side chain are rather lengthy, several new approaches were attempted.

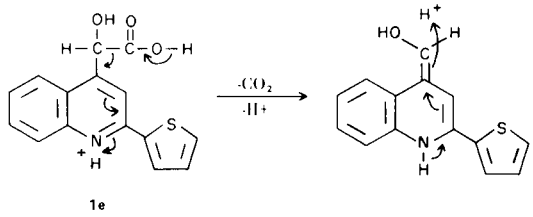
Isatin and 2-acetylthiophene reacted smoothly to give 2-(2-thienyl)cinchoninic acid (**1a**) (6) in 85% yield. Reduction of **1a** with lithium aluminum hydride gave the methanol (**1b**), which was oxidized easily to the aldehyde (**1c**) by selenium dioxide. Conversion of the aldehyde to the cyanohydrin (**1d**) gave a derivative that contained the necessary atoms for construction of the ethanolamine side chain, and attempts were then made to convert **1d** to the α-hydroxycarboxylic acid (**1e**) through hydrolysis of the nitrile group. Despite the wide variety of hydrolysis conditions that were attempted, the only product of reaction that could be isolated was the methanol, **1b**. This



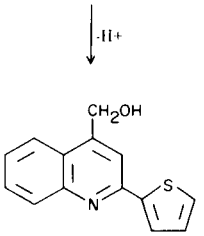
1

1a. $-CO_2H$
1b. $-CH_2OH$
1c. $-CHO$
1d. $-CH(OH)CN$
1e. $-CH(OH)CO_2H$
1f. $-CO_2C_2H_5$
1g. $-COCH[N(C_2H_5)_2]CO_2C_2H_5$
1h. $-COCH_2N(C_2H_5)_2$
1i. $-COCH_3$
1j. 
1k. 

observation suggests that the α-hydroxy acid, **1e**, must be very unstable and decarboxylates after it is formed. The following mechanism for decarboxylation appears to be reasonable. Hydrolysis of the nitrile in ethanol-sulfuric



1e

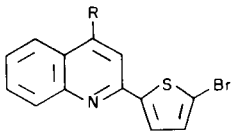


1b

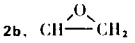
acid or the attempted reduction of the nitrile group did not give any useful products. Consequently, we were forced to abandon this approach.

Esterification of **1a** produced **1f**, which was treated with ethyl *N,N*-diethylaminoacetate in the presence of sodium hydride. The keto-ester, **1g**, was isolated in high yield. All attempts to hydrolyze the ester and decarboxylate the resulting acid to give **1h** were unsuccessful since acyl cleavage occurred preferentially; **1a** was isolated as the reaction product. Reduction of **1g** with sodium borohydride converted both the ketone and the ester group to alcoholic functions, and a series of these compounds were submitted for testing as antimalarial agents.

Condensation of **1f** with ethyl acetate followed by acid hydrolysis and decarboxylation yielded the methyl ketone, **1i**. The reaction of **1i** with two moles of bromine in glacial acetic acid produced a mixture of products in which the α-bromoketone (**2a**) was the major product. The reaction of **2a** with sodium borohydride gave the epoxide (**2b**) in yields of 40-45%. Reaction of **2b** with a series of secondary amines, $[(C_2H_5)_2NH$, $(CH_2)_6NH$, $(C_6H_5CH_2)CH_3NH]$ produced a number of 4-quinolinemethanols that were submitted for evaluation of their chemotherapeutic properties. These compounds were all extremely phototoxic.



2

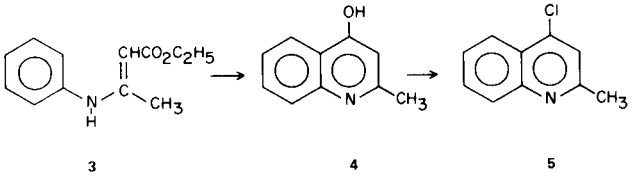
R
2a. $-COCH_2Br$
2b. 

A more direct route to a quinoline methanol derivative from **1a** was found through application of the procedure developed by Boykin and co-workers (7a,b). Reaction of **1a** with 2-pyridyllithium yielded **1j** in 70% yield. However, all attempts to hydrogenate the pyridine ring were unsuccessful because of the poisoning effect of the thiophene ring on the hydrogenation catalyst. Reduction of the carbonyl group with sodium borohydride produced the pyridyl alcohol (**1k**) in nearly quantitative yields.

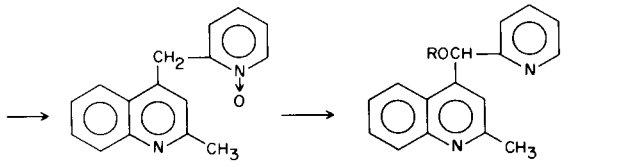
Since sufficient evidence had been accumulated by this time that the presence of any aromatic ring in the 2-position of the quinoline nucleus would result in phototoxic side effects, further synthetic efforts along these lines were abandoned and the introduction of alternative substituents was undertaken. Our initial efforts in this direction were concerned with the preparation of compounds containing aliphatic side chains.

Reaction of isatin with acetone yielded 2-methylcinchoninic acid (8). The attempted reaction of the acid with 2-pyridyllithium was not successful, however, due to the insolubility of this material in either ether or tetrahydrofuran. This proved to be a troublesome factor in a number of instances. As a result, we began to explore other methods for introducing the necessary side chain at the 4-position of the quinoline ring. The following approach was designed to take advantage of the facile nucleophilic displacements that are possible in the 2- and 4-positions of the quinoline ring.

Ethyl β-anilinocrotonate (**3**) (9) was prepared in excellent yield from aniline and ethyl acetoacetate and subsequently converted to 4-hydroxy-2-methylquinoline (**4**) in good yield by refluxing in Dowtherm (9). Reaction of **4** with phosphorus oxychloride gave 4-chloro-2-methylquinoline (**5**). Condensation of **5** with 2-picoline-*N*-oxide (10) was accomplished by using potassium *t*-butoxide as a base in refluxing benzene. The condensation proceeded smoothly, and **6** was isolated in 42% yield. When the *N*-oxide was refluxed with acetic anhydride for 24 hours,



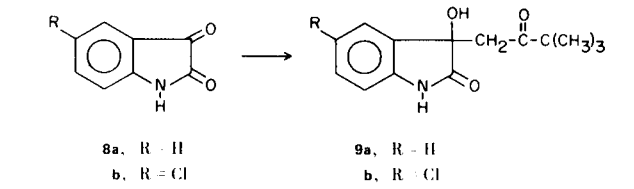
3 4 5



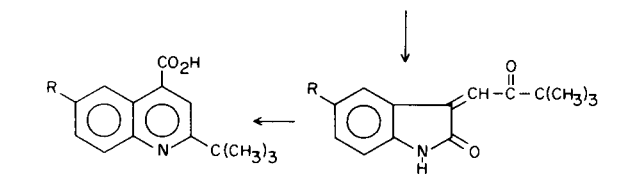
6 7a, R = CH_3CO- b, R = H

the acetate (**7a**) was obtained in good yield; saponification of **7a** afforded the alcohol (**7b**), which was purified as its hydrochloride salt. The above sequence of reactions is relatively straightforward, but there were some difficulties associated with purification of the final product. Despite this problem, the above route appears to offer considerable promise for the synthesis of 4-quinolinemethanols.

The preparation of compounds containing a *t*-butyl group in the 2-position offers some interesting deviations from the previously described routes. The condensation of isatin and 5-chloroisatin (**8a,b**) with pinacolone, utilizing potassium hydroxide and diethylamine, respectively, as the base, produced the β-hydroxy ketone (**9a,b**) in yields that varied between 30 and 60%. Compound **9a,b** was conveniently dehydrated in refluxing acetic acid containing a catalytic amount of *p*-toluenesulfonic acid to give **10a,b** in quantitative yields. Rearrangement of **10a,b** to the cinchoninic acid (**11**) proceeded smoothly in acidic solvents. Attempts to prepare **11a,b** by the normal Pfitzinger reaction failed to produce the desired acid, and the maximum yield of **11a,b** that could be obtained by the Doebner-Miller reaction was 11% (11).

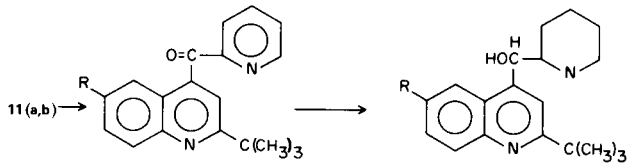


8a, R = H b, R = Cl 9a, R = H b, R = Cl



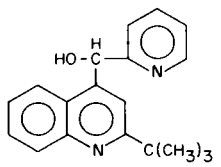
11a, R = H b, R = Cl 10a, R = H b, R = Cl

The reaction of **11a,b** with 2-pyridyllithium proceeded without difficulty, and the pyridyl ketone (**12a,b**) was



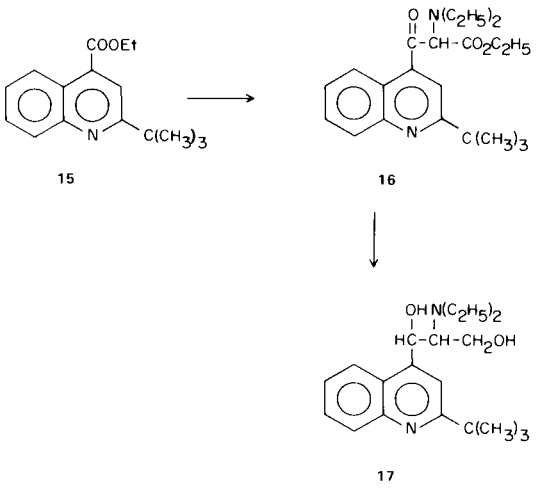
12a, R = H b, R = Cl 13a, R = H b, R = Cl

isolated in 65% yield. Hydrogenation of **12a,b** using platinum as the catalyst gave the piperidyl alcohol (**13a,b**). The purification of **13b** was unusually tedious, and numerous recrystallizations were necessary to obtain a product that was analytically pure. This is probably caused by some concomitant dehalogenation during the hydrogenation reaction. Sodium borohydride reduction of **12a** gave the pyridyl alcohol (**14**). Esterification of **11a**



14

produced **15**, which was treated with ethyl *N,N*-diethylaminoacetate in the presence of sodium hydride to give **16** in high yield. Reduction of **16** with sodium borohydride gave the diol (**17**). The results of tests for antimalarial activity of these compounds showed that they were only moderatley active.



EXPERIMENTAL

2-(2-Thienyl)cinchoninic Acid (**1a**).

This acid was prepared in 77.1% yield from isatin and 2-acetylthiophene by the method of Hartmann and Wybert (6). The procedure was modified slightly by using sodium hydroxide solution as the base and by extending the reflux period to 16 hours. The product had m.p. 209-211° [lit. (6) m.p. 211°].

2-(2-Thienyl)-4-quinolinemethanol (**1b**).

Acid **1a** was reduced to the corresponding carbinol by means of lithium aluminum hydride in diethyl ether. The product, obtained in 88% yield, was a brown oil, which eventually set to a glassy solid. Crystallization from chloroform afforded a white powder with m.p. 124-125°.

Anal. Calcd. for $C_{14}H_{11}NOS$: C, 69.67; H, 4.59; N, 5.81. Found: C, 69.42; H, 4.63; N, 5.62.

2-(2-Thienyl)-4-cinchoninaldehyde (**1c**).

Selenium dioxide (17 g., 0.15 mole) was added in portions over a period of 30 minutes to a stirred solution of 75 g. (0.31 mole) of carbinol **1b** in 300 ml. of dioxane. Simultaneously, the temperature of the solution was increased to 100°. After 2-3 hours at reflux, the solution was cooled, filtered, and concentrated to afford 66 g. (89%) of crude product. Crystallization from chloroform gave a yellow material with m.p. 111.1-112.0°.

Anal. Calcd. for $C_{14}H_9NOS$: C, 70.29; H, 3.79; N, 5.85. Found: C, 70.34; H, 3.92; N, 5.88.

The semicarbazone, m.p. 252-253° was prepared.

Anal. Calcd. for $C_{15}H_{12}N_4OS$: C, 60.77; H, 4.08; N, 18.91. Found: C, 60.37; H, 4.28; N, 18.60.

α-Hydroxy-2-(2-thienyl)-r-quinolineacetonitrile (**1d**).

The sodium bisulfite adduct of aldehyde **1c** was prepared in excellent yield by treating an ethanol solution of the aldehyde with saturated sodium bisulfite solution. The adduct (17 g., 0.050 mole) was combined with 100 ml. of diethyl ether. To this mixture was added with stirring 4 g. (0.1 mole) of potassium cyanide in 25 ml. of water. The ethereal layer was separated, dried with anhydrous magnesium sulfate, and concentrated to give 11.8 g. (86%) of crude product. Crystallization from chloroform gave white needles with m.p. 133-134°.

Anal. Calcd. for $C_{15}H_{10}N_2OS$: C, 67.65; H, 3.78; N, 10.52. Found: C, 68.32; H, 3.68; N, 10.35.

Ethyl 2-(2-Thienyl)cinchoninate (**1f**).

A mixture of 30 g. (0.12 mole) of acid **1a**, 55 ml. of triethyl orthoformate, and 0.3 g. of *p*-toluenesulfonic acid was refluxed until all the reactant acid had dissolved (*ca.* 6 hours). The low-boiling by-products, ethyl formate and ethanol, were removed by distillation as the reaction proceeded. Removal of the triethyl orthoformate under reduced pressure left a crude oily material, which readily solidified. Crystallization from 2-propanol afforded 25 g. (75%) of the desired product, m.p. 81.0-82.5° [lit. (6) m.p. 83°].

Ethyl *N,N*-Diethyl-2-(2-thienyl)cinchoninoylglycinate (**1g**).

A mixture of 26 g. (0.092 mole) of ester **1f**, 25 g. (0.16 mole) of ethyl *N,N*-diethylaminoacetate, 8.0 g. of sodium hydride (containing 58.6% mineral oil), and 60 ml. of dry toluene was stirred and heated at 90-100° for 36 hours. After decomposition of the excess sodium hydride with ethanol and acidification of the reaction mixture with a slurry of ice and aqueous acetic acid, 31 g. of product was collected by suction filtration. Concentration of the toluene layer afforded 3 g. more of product for a total of 34 g. (93%). After crystallization from 2-propanol, the product had m.p. 172-174°.

Anal. Calcd. for $C_{22}H_{24}N_2O_3S$: C, 66.64; H, 6.10; N, 7.06. Found: C, 66.82; H, 6.11; N, 7.33.

1,3-Dihydroxy-*N,N*-diethyl-1-[2-(2-thienyl)quinolin-4-yl]isopropylamine.

Keto-ester **1g** was dissolved in 100% ethanol, and the solution was treated with sodium borohydride. After crystallization from ethanol, the product had m.p. 134-136°.

Anal. Calcd. for $C_{20}H_{24}N_2O_2S$: C, 67.38; H, 6.78; N, 7.86. Found: C, 67.89; H, 6.61; N, 7.95.

Ethyl 2-(2-Thienyl)cinchoninoylacetate.

A mixture of 20 g. (0.071 mole) of ester **1f**, 14 g. (0.16 mole) of ethyl acetate, 11 g. (0.16 mole) of sodium ethoxide, and 21 ml. of dry benzene was stirred at reflux for 18 hours. The reaction mixture was then cooled and poured with stirring into 200 ml. of 5% sodium hydroxide solution. The salt, which soon precipitated, was collected by suction filtration. After acidification with cold, aqueous acetic acid, a gummy product settled upon standing overnight. Repeated crystallization from ethanol afforded a yellow material with m.p. 72-74°.

Anal. Calcd. for $C_{18}H_{15}NO_3S$: C, 66.41; H, 4.64; N, 4.31. Found: C, 66.14; H, 4.79; N, 4.53.

4-Aceto-2-(2-thienyl)quinoline (**1i**).

Crude ethyl 2-(2-thienyl)cinchoninoylacetate was heated at 100° for 15 hours with a 2:1 mixture of water and concentrated sulfuric acid. The reaction mixture was then cooled, poured into ice water, and neutralized with ammonium hydroxide. Collection by suction filtration and drying under vacuum afforded 16.5 g. (92%, based on starting amount of **1f** in the preparation of the acetate) of crude product. Crystallization from ethanol gave green needles with m.p. 105-107°.

Anal. Calcd. for $C_{15}H_{11}NOS$: C, 71.12; H, 4.38; N, 5.53. Found: C, 70.78; H, 4.29; N, 5.61.

4-Bromoaceto-2-[2-(5-bromothienyl)]quinoline (**2a**).

To a stirred solution of 37.5 g. (0.148 mole) of ketone **1i** in 500 ml. of glacial acetic acid heated at 60° was added dropwise 49.0 g. (0.300 mole) of bromine in 150 ml. of glacial acetic acid. The temperature of the reaction mixture increased to reflux spontaneously during the addition of bromine, and reflux was

maintained until the evolution of hydrogen bromide ceased. The reaction mixture was then cooled and filtered. The solid salt was neutralized with aqueous sodium carbonate, and the free amine was extracted with ether. The ethereal extract was dried and concentrated to give 29.9 g. (44.2%) of product. After crystallization from ethanol, the product had m.p. 123.5-125°.

Anal. Calcd. for $C_{15}H_9Br_2NOS$: C, 43.82; H, 2.21; N, 3.41. Found: C, 44.13; H, 2.54; N, 3.38.

2-[2-(5-Bromothienyl)]quinolin-4-ylethylene Oxide (**2b**).

To a stirred and ice-cooled suspension of 28.0 g. (0.0681 mole) of ketone **2a** in 165 ml. of methanol was added 6.3 g. (0.17 mole) of sodium borohydride in portions. After the initial reaction had subsided, the mixture was refluxed for 1 hour and then cooled to 0°. The solid product, after collection by suction filtration and drying, weighed 10.0 g. (44.3%). Crystallization from ethanol gave a product with m.p. 125-126°.

Anal. Calcd. for $C_{15}H_{10}BrNOS$: C, 54.11; H, 3.03; N, 4.21. Found: C, 53.73; H, 3.24; N, 4.14.

Reactions of 2-[2-(5-Bromothienyl)]quinolin-4-ylethylene Oxide with Amines.

The oxide (**2b**) was heated under varying conditions with each of four secondary amines. After removal of the excess amine by vacuum distillation, the residue was dissolved in ether. The hydrochloride salt was prepared, unless otherwise noted, by passing hydrogen chloride gas through the ether solution.

1. α-(*N*,*N*-Diethylaminomethyl)-2-[2-(5-bromothienyl)]-4-quinolinemethanol Dihydrochloride Dihydrate.

A mixture of 10.0 g. (0.0301 mole) of the oxide (**2b**), 15.0 g. of diethylamine, and 50 ml. of benzene was refluxed for 18 hours to yield 9.5 g. (62%) of the salt after the described work-up. Crystallization from ethanol afforded a yellow powder with m.p. 167-169°.

Anal. Calcd. for $C_{19}H_{23}BrCl_2N_2OS{\cdot}2H_2O$: C, 44.37; H, 5.29; N, 5.45. Found: C, 44.95; H, 5.22; N, 5.35.

2. α-(*N*,*N*-Di-*n*-butylaminomethyl)-2-[2-(5-bromothienyl)]-4-quinolinemethanol Dihydrochloride.

A mixture of 10.0 g. (0.0301 mole) of the oxide (**2b**), 30 ml. of di-*n*-butylamine, and 10 ml. of toluene was heated at 100-110° for 24 hours to yield 14.0 g. (87%) of the dihydrochloride salt after work-up. After crystallization from absolute ethanol, the product had m.p. 205-208° dec.

Anal. Calcd. for $C_{23}H_{31}BrCl_2N_2OS$: C, 51.69; H, 5.85; N, 5.24. Found: C, 51.32; H, 6.11; N, 5.15.

3. α-(1-Azacycloheptylmethyl)-2-[2-(5-bromothienyl]-4-quinolinemethanol Dihydrobromide.

A suspension of 5.7 g. (0.017 mole) of the oxide (**2b**) in 35 ml. of freshly distilled azacycloheptane was stirred at 100° for 18 hours. The reaction mixture was cooled, poured into ether, and filtered. The filtrate was concentrated to give 6.9 g. (94%) of an oil. The dihydrobromide salt (8.9 g., 89%) was prepared. Crystallization from ethanol gave a sample with m.p. 212.5-214° dec.

Anal. Calcd. for $C_{21}H_{25}Br_3N_2OS$: C, 42.51; H, 4.25; N, 4.72. Found: C, 42.11; H, 4.96; N, 4.22.

4. α-(*N*-Benzyl-*N*-methylaminomethyl)-2-[2-(5-bromothienyl)]-4-quinolinemethanol Dihydrochloride.

A solution of 3.0 g. (0.0090 mole) of the oxide (**2b**) in 30 ml. of *N*-methylbenzylamine was heated at 110-115° for 16 hours to give 4.4 g. (92%) of the dihydrochloride salt, after the described work-up. The salt had m.p. 194.5-195.5° after crystallization from ethanol.

Anal. Calcd. for $C_{23}H_{23}BrCl_2N_2OS$: C, 52.48; H, 4.37; N, 5.32. Found: C, 52.91; H, 4.62; N, 5.82.

2-(2-Thienyl)cinchoninoylpyridine (**1j**).

A solution of 38 ml. (0.061 mole) of *n*-butyllithium (in hexane) and 100 ml. of anhydrous ether was cooled at -60° and stirred under a nitrogen atmosphere while 10 g. (0.063 mole) of 2-bromopyridine was added rapidly. After 45 minutes of stirring under the described conditions, 5.0 g. (0.019 mole) of acid **1a** in dry tetrahydrofuran was added over a 10-minute period. Stirring was continued at -60° and under nitrogen for 4 hours. After hydrolysis with 100 ml. of moist ether followed by 100 ml. of water, the mixture was extracted with ether. The water-washed, dried, and concentrated extract afforded 4.3 g. (70%) of crude product. Crystallization from benzene gave yellow crystals with m.p. 178-180°.

Anal. Calcd. for $C_{19}H_{11}N_2OS$: C, 72.36; H, 3.52; N, 8.88. Found: C, 72.61; H, 3.83; N, 9.05.

α-(2-Pyridyl)-2-(2-thienyl)-4-quinolinemethanol (**1k**) Dihydrobromide Monohydrate.

Ketone **1j** in 100% ethanol was treated with sodium borohydride to give the desired alcohol in 95% yield. The dihydrobromide monohydrate salt was prepared by dissolving the free amine in hot 95% ethanol and adding 48% hydrobromic acid. The salt, m.p. 247-249° dec., was collected by suction filtration.

Anal. Calcd. for $C_{19}H_{16}Br_2N_2OS{\cdot}H_2O$: C, 45.81; H, 3.64; N, 5.62. Found: C, 46.49; H, 3.98; N, 5.33.

2-Methylcinchoninic Acid.

This acid was prepared according to the method of Pfitzinger (8). To a stirred solution of 100 ml. of ethanol, 750 ml. of water, 200 g. of sodium hydroxide, and 200 g. (1.35 mole) of isatin was added 200 g. of acetone. This mixture was heated at reflux for 24 hours, cooled, and poured into water. After acidification with acetic acid, the white solid product was collected by suction filtration, washed with water, and dried. The yield was 170 g. (65%). After crystallization from glacial acetic acid, the product had m.p. 240-241° [lit. (12) m.p. 240-241°].

Ethyl β-Anilinocrotonate (**3**).

This ester was prepared in 88% yield according to the method of Hauser and Reynolds (9). The product had b.p. 130° (2 mm.) [lit. (9) b.p. 155° (10 mm.)].

4-Hydroxy-2-methylquinoline (**4**).

Crotonate **4** was cyclized in refluxing Dowtherm according to the method of Hauser and Reynolds (9). A helpful modification was found to be the collection and removal of ethanol by means of a Dean-Stark trap as the cyclization proceeded. By this modification, the yield was increased to 82%. The product had m.p. 231-233° [lit. (9) m.p. 229-230°].

4-Chloro-2-methylquinoline (**5**).

A mixture of 15.9 g. (0.100 mole) of alcohol **4** and 50 ml. of phosphorus oxychloride was refluxed and stirred for 30 minutes. The mixture was cooled, poured onto crushed ice, and refrigerated overnight. Neutralization with 25% sodium hydroxide solution was then carried out at 10°. The solid product was collected by suction filtration, washed with ice water, and dissolved in benzene. Water and benzene were removed by distillation at atmospheric pressure, and the residue was distilled at

reduced pressure [b.p. 83° (0.7 mm.); lit. (13) b.p. 269-270°, m.p. 42-43° (monohydrate)] and gave 14.4 g. (81.2%) of a clear, colorless product that solidified when cooled.

2-Picoline *N*-Oxide.

This compound was prepared by the method described by Boekelheide and Linn (10). The *N*-oxide, obtained in 66% yield, had b.p. 103-104° (3 mm.) [lit. (10) b.p. 123-124° (15 mm.)].

α-[(2-Methylquinolin-4-yl)]-2-picoline *N*-Oxide (**6**).

Potassium *t*-butoxide (0.031 mole) was prepared in 200 ml. of refluxing dry benzene under nitrogen in a Morton flask fitted with a high-speed stirrer. 2-Picoline *N*-oxide (3.4 g., 0.031 mole) was added, and reflux and stirring were continued for 10 minutes. 4-Chloro-2-methylquinoline (**5**) (5.0 g., 0.028 mole) in 20 ml. of dry benzene was added. After 24 hours of reflux and stirring under nitrogen, the reaction mixture was cooled and then treated with 4 g. of glacial acetic acid followed by 50 ml. of water. The extract was washed with water, dried and concentrated to give 2.5 g. (43%) of **6**. The product had m.p. 174-175° after crystallization from benzene.

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.80; H, 5.60; N, 11.20. Found: C, 76.82; H, 5.74; N, 11.50.

α-(2-Pyridyl)-2-methyl-4-quinolinemethanol (**7b**) Dihydrochloride.

A mixture of 1 g. (0.004 mole) of *N*-oxide **6** and 50 ml. of acetic anhydride was refluxed for 24 hours. After concentration under reduced pressure, the residue was dissolved in ether. The ethereal solution was passed through 25 g. of alumina (grade I). After hydrolysis of the ester, the product (**7b**) was dissolved in ether. Dry hydrogen chloride gas was passed through the ethereal solution to precipitate the dihydrochloride salt, which was recovered by suction filtration. The yield was 33%. Repeated crystallizations from ethanol were necessary to obtain a product with m.p. 238-240° dec.

Anal. Calcd. for $C_{16}H_{16}Cl_2N_2O$: C, 59.43; H, 4.95; N, 8.67. Found: C, 59.58; H, 5.25; N, 8.60.

3-(3,3-Dimethyl-2-ketobut-1-yl)-3-hydroxyoxindole (**9a**).

Isatin (25 g., 0.17 mole) was stirred for 15 minutes at room temperature in 700 ml. of 60% ethanol that had been made 0.15% in potassium hydroxide. Pinacolone (30 g., 0.30 mole) was added, and stirring was continued for 24 hours. The reaction mixture was neutralized with acetic acid, and concentrated. The residue yielded 38 g. (90%) of crude product, which had m.p. 169-170° after crystallization from ethanol.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.01; H, 6.89; N, 5.66. Found: C, 68.19; H, 7.24; N, 5.75.

5-Chloro-3-(3,3-dimethyl-2-ketobut-1-yl)-3-hydroxyoxindole (**9b**).

A mixture of 40 g. (0.22 mole) of 5-chloroisatin, 250 ml. of diethylamine, and 600 ml. of 95% ethanol was stirred at room temperature during the addition of 30 g. (0.30 mole) of pinacolone. Stirring was continued overnight. The product, which was recovered by suction filtration, weighed 20.6 g. (33%). Crystallization from ethanol gave a white solid with m.p. 250-252.5°.

Anal. Calcd. for $C_{14}H_{16}ClNO_3$: C, 59.68; H, 5.73; N, 4.97. Found: C, 59.43; H, 5.60; N, 5.38.

5-Chloro-3-(3,3-dimethyl-2-ketobutyliden-1-yl)oxindole (**10b**).

A mixture of 41.0 g. (0.146 mole) of oxindole **9b**, 0.4 g. of *p*-toluenesulfonic acid, and 500 ml. of glacial acetic acid was refluxed for 30 minutes. The mixture was concentrated, and the concentrate was cooled and diluted with water. The product, which weighed 37.6 g. (97.9%), was collected by suction filtration. Crystallization from ethanol-water afforded orange needles, with m.p. 170-171°.

Anal. Calcd. for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.87; H, 5.72; N, 5.53.

3-(3,3-Dimethyl-2-ketobutyliden-2-yl)oxindole (**10a**).

This compound was prepared in 95% yield from oxindole **9a** in the manner described for the preparation of **10b**. The crystallized product had m.p. 160-161°.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.31; H, 6.30; N, 6.22.

2-*t*-Butylcinchoninic Acid (**11a**).

A mixture of 28 g. (0.12 mole) of oxindole **10a**, 200 ml. of concentrated hydrochloric acid, and 100 ml. of ethanol was refluxed for 8 hours. The reaction mixture was then cooled and neutralized with sodium hydroxide. After acidification with acetic acid, the yellow solid product formed and was collected by suction filtration. The yield was 18 g. (66%). After crystallization from ethanol, the product had m.p. 146-147°, [lit. (11) m.p. 147-149°].

2-*t*-Butyl-6-chlorocinchoninic Acid (**11b**).

Method A.

A mixture of 8.0 g. (0.030 mole) of oxindole **10b**, 60 ml. of concentrated hydrochloric acid, and 60 ml. of 95% ethanol was refluxed for 16 hours. The mixture was then cooled. The hydrochloride salt of the product was collected by suction filtration and neutralized with 5% sodium hydroxide. After acidification with a slurry of ice and acetic acid, the product (5.8 g., 73%) was collected by suction filtration. Crystallization from ethanol gave material with m.p. 209.5-210.5°.

Anal. Calcd. for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.50; H, 5.74; N, 5.65.

Method B.

To a warm solution of 52 g. (0.60 mole) of pivalaldehyde in 250 ml. of absolute ethanol was added 76 g. (0.60 mole) of *p*-chloroaniline. After 10 minutes at reflux, 53 g. (0.60 mole) of pyruvic acid in 55 ml. of absolute ethanol was added. Reflux was continued for 15 hours. The reaction mixture was then cooled and filtered. The filtrate was poured into water, and this solution was extracted with ether. The hydrochloride salt was prepared by passing hydrogen chloride gas through the ethereal extract. The salt was collected by suction filtration and then dissolved in 50% sodium hydroxide solution. Acidification with acetic acid and collection by suction filtration afforded 17.4 g. (11%) of a pale yellow solid. Crystallization from ethanol gave white crystals with m.p. 208-210°. M.m.p. with acid prepared by Method A showed no depression.

2-(6-Chloro-2-*t*-butylcinchoninoyl)pyridine (**12b**).

n-Butyllithium was prepared in ether solution under a nitrogen atmosphere from 0.53 g. (0.076 mole) of lithium wire and 8.6 g. (0.063 mole) of *n*-butyl bromide. This solution was cooled to -60°, and 6.1 g. (0.039 mole) of 2-bromopyridine was added with stirring. Stirring was continued at -60° for 45 minutes. Acid **11b** (3.0 g., 0.011 mole) was added, and the addition of 100 ml. of dry ether followed. Stirring was continued at -60° under nitrogen for 3 hours. Hydrolysis was carried out at -5° by the addition of 100 ml. of moist ether followed by 50 ml. of water. After extraction with ether, the extract was dried and concentrated. The yield of product, after crystallization from ethanol, was 2.4 g.

(65%). Repeated crystallization from ethanol gave white plates with m.p. 123-124.5°.

Anal. Calcd. for $C_{19}H_{17}ClN_2O$: C, 70.25; H, 5.28; N, 8.63. Found: C, 70.29; H, 5.21; N, 8.45.

2-(2-*t*-Butylcinchoninoyl)pyridine (**12a**).

This compound was prepared from acid **11a** in 71% yield in the manner described above for the preparation of **12b**. After crystallization from ethanol, the product had m.p. 128-129°.

Anal. Calcd. for $C_{19}H_{18}N_2O$: C, 78.51; H, 6.21; N, 9.66. Found: C, 78.20; H, 6.26; N, 9.46.

α-(2-Piperidyl)-2-*t*-butyl-4-quinolinemethanol (**13a**).

Ketone **12a** (5.0 g., 0.017 mole) was dissolved in 300 ml. of absolute ethanol to which 5 ml. of concentrated hydrochloric acid had been added. Hydrogenation was carried out in a Parr apparatus at 45 p.s.i. of hydrogen and in the presence of Adams catalyst. After filtration and concentration, the residue was poured into sodium carbonate solution. Extraction with ether was performed, and the dried extract was concentrated to give virtually quantitative recovery of the crude product. After crystallization from acetonitrile, the product had m.p. 157-158°.

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.50; H, 8.73; N, 9.40. Found: C, 76.62; H, 8.80; N, 9.24.

α-(2-Piperidyl)-2-*t*-butyl-6-chloro-4-quinolinemethanol (**13b**).

Hydrogenation of ketone **12b** was carried out in the manner described for the preparation of methanol **13a**. However, the yield was only 47%. Purification of the final product was difficult; repeated crystallization from acetonitrile gave material with m.p. 163-167°,

Anal. Calcd. for $C_{19}H_{25}ClN_2O$: C, 68.55; H, 7.57. Found: C, 68.38; H, 7.24.

α-(2-Pyridyl-2-*t*-butyl-4-quinolinemethanol (**14**).

Ketone **12a** in dry methanol was treated with sodium borohydride to give the crude alcohol in almost qunatitative yield. After crystallization from ethanol, the product had m.p. 165°.

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.08; H, 6.85; N, 9.59. Found: C, 78.57; H, 7.06; N, 9.88.

Ethyl 2-*t*-Butylcinchoninate (**15**).

Acid **11a** was esterified in the manner described for the preparation of ester **1f**. After removal of excess triethyl orthoformate, the residue was extracted with ether. The extract was washed with carbonate solution, washed with water, dried and concentrated to give the product in excellent yield. Crystallization from ethanol gave material with m.p. 47° [lit. (11) m.p. 47-48°].

Ethyl 2-*t*-Butylcinchoninoyl-*N*,*N*-diethylglycinate (**16**).

A mixture of 22.5 g. (0.0876 mole) of ester **15**, 24 g. (0.15 mole) of ethyl *N*,*N*-diethylaminoacetate, 7.5 g. (0.15 mole) of sodium hydride (51.6% mineral oil), and 60 ml. of dry benzene was refluxed for 70 hours. The solution was cooled, and 9.6 ml. of 95% ethanol was added slowly and with stirring. After acidification with a slurry of ice and acetic acid, the mixture was extracted with ether. The extract was washed with water, dried, and concentrated to give 31.4 g. (96.9%) of crude product. The product had m.p. 159-160° after crystallization from cyclohexane.

Anal. Calcd. for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.00; H, 8.00; N, 7.38.

1-(2-*t*-Butylquinolin-4-yl)-*N*,*N*-diethyl-1,3-dihydroxyisopropylamine (**17**).

Glycinate **16** in 100% ethanol was reduced with sodium borohydride to give the desired product in 69% yield. Crystallization from cyclohexane gave small, white plates with m.p. 134-136°.

Anal. Calcd. for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.83; H, 8.94; N, 8.15.

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