Difference in Antimalarial Activity between Certain Amino Alcohol Diastereomers†

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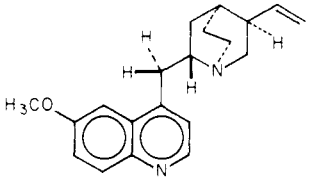
A striking difference in antimalarial activity between the diastereomers of 6-bromo-α-[2-(1-methylpiperidyl)]-9-phenanthrenemethanol, α-(3-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol, and α-(3-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol was observed. A possible explanation involving the N–O distance and active site binding requirements is suggested.

Antimalarial activity of the enantiomers as well as the diastereomers of different types of amino alcohols, including quinine (I) and other cinchona alkaloids, has been an interesting topic of study. Cohen and King[1] reported that antiplasmodial activity of cinchona alkaloids is not particularly sensitive to stereochemical modification. Brossi et al.[2] noted that the natural, the unnatural, and the racemic forms of dihydroquinine show identical toxicities and activities against *Plasmodium berghei*; on the other hand, unnatural dihydroquinidines and its natural enantiomer exhibited different toxicities. The antimalarial activity of the erythro and the threo isomers of α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol[3,4] (II), α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol[4] (III), and several α-(2-piperidyl)-4-pyridinemethanols[5] (IV) has also been studied. It was found that, although a difference exists in the dose levels of these isomers required to attain a given level of activity, and the threo form of a given amino alcohol is usually two to four times more active than its erythro isomer, both diastereomers are active antimalarials. It thus has been assumed that there is no strict stereospecificity among these amino alcohols in the plasmodia screening and that the absolute configuration of the parent structure is of little concern in antimalarial activity.



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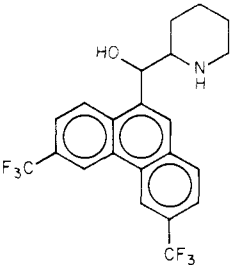

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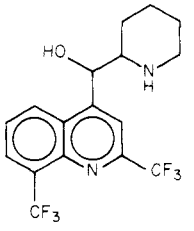

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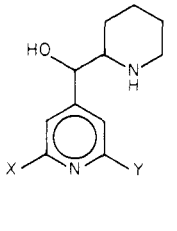
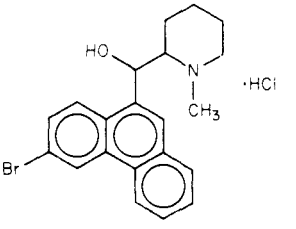
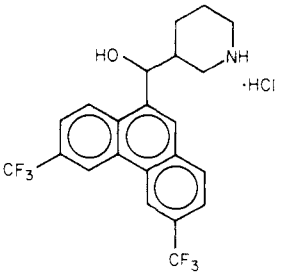


IV

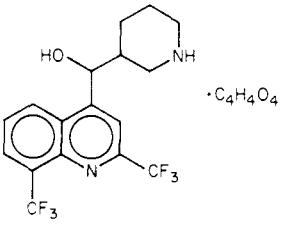
It was therefore rather surprising to note that the diastereomers of 6-bromo-α-[2-(1-methylpiperidyl)]-9-phenanthrenemethanol[6] (V) and of α-(3-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol[7] (VI) prepared in this laboratory exhibited strikingly different biological activity—one isomer being active against *P. berghei* and the other being either toxic or inactive. In order to confirm the validity of our observation, the diastereomers of still another 3-piperidyl derivative, α-(3-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol (VII), were prepared and tested in the *P. berghei* system.



Va (mp 272–274° dec)
b (mp 191–193° dec)



VIa (mp 293–295°)
b (mp 189–191°)

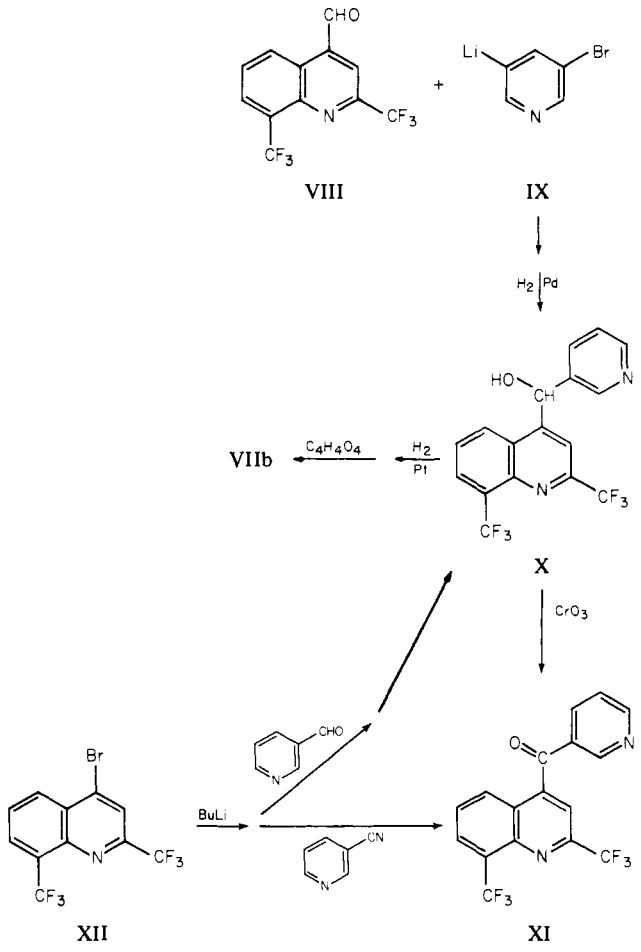


VIIa (mp 252–256°)
b (mp 218–220°)

Chemistry. Condensation of 2,8-bis(trifluoromethyl)quinoline-4-carboxaldehyde[8] (VIII) with lithiopyridine IX at −74° followed by hydrogenation gave the pyridylcarbinol X in 20% yield. Oxidation of X with CrO_3 afforded the ketone XI. In contrast to the isomeric distribution of the phenanthrene analog,[7] catalytic reduction of both the ketone XI and the carbinol X gave predominantly VIIb, the isomer with lower melting point (in the phenanthrene series,[7] hydrogenation of the corresponding ketone afforded mainly the higher melting isomer VIa; while in the catalytic reduction of the carbinol, the lower melting isomer VIb predominated). These results are apparently due to different stereochemical control during the catalytic reduction process. The fumarate salt of the lower melting isomer VIIb separated readily when the Et_2O solution of the neutralized reduction product was treated with a saturated solution of fumaric acid in Me_2CO (the HCl salt of this product did not readily solidify). The higher melting isomer VIIa was only obtained in very low yield from the mother liquor of the reduction of the ketone XI. Once isolated, the higher melting isomer is, however, much less soluble in CH_3OH than the other isomer VIIb.

The carbinol X was also prepared by a more efficient route; conversion of 4-bromo-2,8-bis(trifluoromethyl)-quinoline[9] (XII) to the lithio compound followed by treatment with 3-pyridinecarboxaldehyde gave the carbinol X in good yield. Carbinol X, in turn, was converted to XI. A one-step reaction of the 4-lithioquinoline with 3-cyanopyridine to form the ketone XI directly was also

† This paper is dedicated to the memory of Professor Edward E. Smissman.



studied, but the yield was unsatisfactory.

Numerous attempts to improve the yield of the higher melting isomer VIIa by varying the reaction conditions during the catalytic reduction of the ketone XI were of no avail. From a total of 60 g of the ketone, only 0.5 g of pure VIIa was isolated.

The diastereomers VIIa and VIIb have been characterized by various analytical and spectroscopic means. Among these, the mass spectra of these diastereomers showed the same characteristic fragmentation pattern as those of the corresponding phenanthrene diastereomers VIa and VIb. In the high mass region, a peak of $M^+ - 19$ was present in the spectrum of VIIa in addition to the molecular ion peak, while both the $M^+ - 17$ and $M^+ - 16$ peaks were shown in that of VIIb. The same behavior was observed in the spectra of the phenanthrene isomers VIa and VIb. The difference in the fragmentation pattern may be explained by the varying degree of H bonding in these two *dl* pairs. As expected, the ir spectra of VIIa and VIIb were also different.

Biological Results and Discussion. The antimalarial screening of VII against *P. berghei* revealed, once again, that the higher melting isomer VIIa (mp 252–256°) showed increasing in mean survival time of +5.9, +10.1, +11.2, and +15.2 at single sc doses of 40, 80, 160, and 320 mg/kg, respectively, and had four cures at 640 mg/kg whereas the lower melting isomer VIIb (mp 218–220°) was inactive.

The difference in the antimalarial activity profile between the first group (I–IV) and the second group of compounds (V–VII) may possibly be explained as follows. It has been postulated that active antimalarials of this type possess a common structural feature[10] wherein the distance between the oxygen and the nonaromatic nitrogen atom is approximately 3 Å. The possible minimum N–O distance of compounds of the first group, as measured by the Dreiding models, is 2.5 Å, whereas the maximum distance between these two atoms is 3.5 Å. Since, within a reasonable range, the matching of distances between the active sites of a bioreceptor and the pharmacophore of a drug need not necessarily be exact,[11] any structural isomer of the first group should have a proper N–O distance to match the receptor and therefore should be active. The toxic N-methylated compound Vb also showed some activity at lower doses; the addition of the methyl group may sterically interfere or enhance a secondary binding, much like the difference in toxicity of the natural and the unnatural dihydroquinidines noted by Brossi and associates.[2] Based on Dreiding model measurements, the minimum N–O distance of the 3-piperidyl compounds VI and VII is 2.6 Å, but the maximum distance can be as much as 5 Å. Isomers sterically favoring the conformation with the latter distance can no longer fit the same "active site", hence are inactive.

Dreiding models also indicate that, in order to attribute the differences in activities to the O–N internuclear distance, one isomer would have to bind to the active site with its aryl group in an axial conformation (the isomer which allows for hydrogen bonding between the piperidine and the carbinol function). The other isomer, with its aryl group equatorial, would not bind effectively. The mass spectral data also substantiate the fact that one *dl* pair exists with its aryl group axial and the other equatorial.

It is of interest to note that among three sets of diastereomers prepared in the laboratory, in each case it is the higher melting isomer that exhibited antimalarial activity.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

α-(3-Pyridyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol (X). Method A. Compound X was prepared from 7.1 g (0.03 mol) of 3,5-dibromopyridine, 0.03 mol of 2.2 *M* BuLi, and 2.93 g (0.01 mol) of 2,8-bis(trifluoromethyl)quinoline-4-carboxaldehyde[8] (VIII) in 20% yield by a procedure essentially identical with the synthesis of α-(3-pyridyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol,[7] mp 223–225°. Anal. ($C_{17}H_{10}F_6N_2O$) C, H, N.

Method B. To an Et_2O solution (100 ml) of 0.05 mol of BuLi in hexane was added, with stirring, a solution of 17.2 g (0.05 mol) of 4-bromo-2,8-bis(trifluoromethyl)quinoline[9] (XII) in 100 ml of the same solvent at −74° in 1 hr. Stirring was continued for 30 min at the same temperature. The dark-colored mixture was then treated with 5.35 g (0.05 mol) of pyridine-3-carboxaldehyde in 30 ml of Et_2O. The mixture was allowed to warm to −10° in 1.5 hr. It was poured into 500 ml of cold H_2O, and the solvents were evaporated under a stream of air. The precipitated solid was collected by filtration and washed (H_2O) to furnish 17 g (92% yield) of the desired product, mp 212–215°. On recrystallization from MeOH, it melted at 223–225° and was proved to be identical with the product previously prepared by method A. In several parallel runs the yield ranged from 80 to 94%.

2,8-Bis(trifluoromethyl)-4-quinolyl 3-Pyridyl Ketone (XI). This compound was obtained in 81% yield from 6.0 g (0.16 mol) of X and 5 g (0.05 mol) of CrO_3 in 150 ml of AcOH by a procedure identical with that for the preparation of 3,5-bis(trifluoromethyl)-9-phenanthryl 3-pyridyl ketone:[7] mp 78–81°.

α-(3-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol Fumarate. Lower Melting Isomer VIIb. Method A. The carbinol X, 3.8 g (0.01 mol), was hydrogenated in a mixture of 100 ml of EtOH and 2 ml of HCl in the presence of PtO_2 at 3.5 kg/cm² for 8 hr. The catalyst was separated and the solution evaporated under reduced pressure to dryness. The residue, though crystalline, could not be recrystallized and was neutralized with aqueous NaOH. The free base was extracted with Et_2O (200 ml) and the Et_2O extract was washed (H_2O), dried ($MgSO_4$), and

treated with a saturated Me_2CO solution of fumaric acid. The precipitate was filtered after 2 hr to furnish 2.8 g of the desired product, mp 209–212° dec. The presence of the other isomer VIIa was not detected. Anal. ($C_{21}H_{20}F_6N_2O_5$) C, H, N.

Method B. A solution of 4.8 g of the ketone XI in 120 ml of EtOH and 3 ml of HCl was hydrogenated in the presence of PtO_2 at 4.2 kg/cm² for 8 hr. After removal of the catalyst, the solution was evaporated to dryness. The residue was made basic with aqueous NaOH and the base was taken into 300 ml of Et_2O. The Et_2O solution was washed (H_2O), dried ($MgSO_4$), and treated with fumaric acid solution in Me_2CO. There was obtained 1.7 g of the product (mp 209–212°) which was shown to be identical with the lower melting isomer VIIb obtained in the preceding experiment.

α-(3-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol Fumarate. Higher Melting Isomer VIIa. From the mother liquor of the preceding experiment, there was isolated 0.2 g of a solid product, mp 230–235°. On recrystallization from MeOH, a pure sample was obtained as white crystals, mp 264–266° dec, which was shown to be totally different from the other isomer VIIb. Anal. ($C_{21}H_{20}F_6N_2O_5$) C, H, N.

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Synthesis and Antiinflammatory Properties of N-Substituted 4,5-Dioxopyrrolidine-3-carboxanilides*

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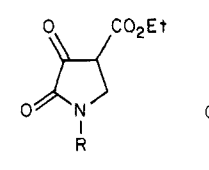
The synthesis and physical properties of a series of *N*-methyl- and *N*-phenyl-4,5-dioxopyrrolidine-3-carboxanilides are described. Unlike previously reported carboxanilides derived from 1,3(2*H*,4*H*)-dioxoisoquinoline and 2-oxobenzofuran, the currently described agents exist solely as the enol tautomers and, as a result, do not display comparable acidic properties. None of the newly reported compounds exhibited activity equal to that of aspirin in the carrageenin-induced rat foot edema assay.

The finding that certain carboxylic acid amides bearing suitably acidic protons at a position α to the amide carbonyl group also exhibit antiinflammatory properties was first reported in 1969[1] and has since been the subject of a detailed review.[2] The ready availability of 4,5-dioxopyrrolidine-3-carboxylic acid esters[3,4] (I) prompted the synthesis and pharmacologic examination of related amides having structural features in common with previously reported anilides displaying antiinflammatory activity.[1,2] Although Beckett et al.[5] reported that no important pharmacologic properties were manifested by N-substituted 4,5-dioxopyrrolidine-3-carboxylic acid esters, they failed to prepare any of the corresponding amide derivatives.

When ethyl N-substituted-4,5-dioxopyrrolidine-3-carboxylates (I) were allowed to react with aniline and substituted anilines in refluxing xylene, generally excellent yields of the respective anilides II were obtained (Table I). Like the esters (I) utilized as starting materials, reported by Beckett et al.[5] to exist in solution solely in the enolic form, but unlike previously reported anilides derived from 1,3(2*H*,4*H*)-dioxoisoquinoline[6] and 2-oxobenzofuran,[7] compounds of type II also exist in the enolic configuration. For example, the NMR spectrum of II (R_1 = CH_3, R_2 = H) exhibits, in addition to the aromatic and *N*-methyl signals, singlets at δ 9.2 (1 H), disappearing upon the addition of D_2O, and at δ 4.02 (2 H). The fact that neither of these signals, the former due to the enolic proton and the latter to the methylene hydrogens of the pyrrolidine ring, is split is consistent with the assignment of the enolic configuration III.



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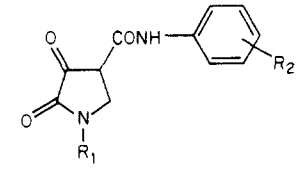

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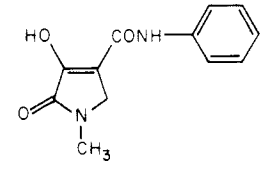

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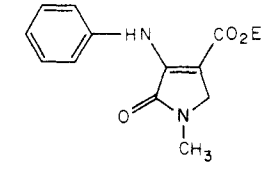

IV

In comparison to those carboxanilides derived from 1,3(2*H*,4*H*)-dioxoisoquinoline[6] and 2-oxobenzofuran,[7] the anilides described in Table I displayed only moderately acidic properties despite the activation afforded the ionizing group by the presence of an adjacent carbonyl function and a vinylogous amide moiety. The reason for

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