Antimalarial Activity and Conformation of *erythro*- and *threo*-α-(2-Piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol†

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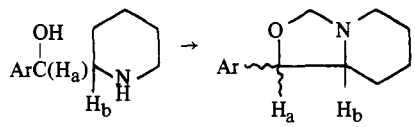
A convenient route to antimalarials containing a 2-piperidinemethanol group involves, as the final reaction step, a catalytic hydrogenation of a 2-pyridyl ketone,[1] thus producing a racemic mixture of erythro and threo amino alcohols. Previous piperidinemethanol preparations were accomplished either by a different synthetic scheme,[2] usually yielding only one isolated diasteromeric form,‡ or on a scale insufficient to permit isolation and characterization of the isomer formed in lesser amounts. There thus appears to be limited data available as to the effect of conformation on the antimalarial activity of piperidinemethanols.

2-Pyridyl 3,6-bis(trifluoromethyl)-9-phenanthryl ketone was prepared by the procedure of Nodiff, *et al.*,[5] and hydrogenated at atm pressure to give about an 85:15 mixture (analysis *via* nmr and tlc) of epimeric piperidinemethanols. The hydrochloride of the major epimer (I) was sparingly MeOH soluble and was obtained in pure form after 2 evaporative recrystallizations; concn of the mother liquors gave a residue containing roughly equal amounts of the diastereomers. Upon conversion to the TsOH salt, the minor epimer (II) could be isolated in pure form after 2 recrystallizations from MeOH. The amino alcohols were treated with methanolic CH_2O and converted to the corresponding 1-[3,6-bis(trifluoromethyl)-9-phenanthryl]hexahydro-3*H*-oxazolo[3,4-*a*]pyridine derivative (I → III, II → IV).



I II III IV

Ar = 3,6-Bis(trifluoromethyl)-9-phenanthryl

The difference in chemical shift between the two C_3CH_2 of 1-substituted-hexahydro-3*H*-oxazolo[3,4-*a*]pyridines and the geminal coupling constant for the same 2 protons can be employed to assign configuration to the amino alcohol precursors.[6] Thus, by examination of the nmr spectra of III and IV, we have assigned the configuration of I and II as erythro and threo, respectively. The data for III and IV are shown in Table I; for comparative purposes, data[6] for the racemic epimers of 1-phenylhexahydro-3*H*-oxazolo-[3,4-*a*]pyridine are included.

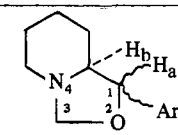
An nmr study of I and II and their protonated forms was conducted since it is possible their pharmacological activities are related to conformational preferences. The erythro (I) and threo (II) amino alcohols can lie in 3 possible staggered conformations (A, B, and C) with the vicinal coupling constant, J_{AB}, giving an estimate of the rotamer populations. In similar compounds, the pure gauche and trans coupling constant values have been suggested as 2.8 and 10.5[9] and 2.6 and 10.3 Hz.[10] The J_{AB} values for I and II and their HCl salts in solvents of differing polarity are shown in Table II.

These data suggest that in nonpolar solvents the erythro epimer resides almost entirely in the gauche forms IA and IB, with IA favored over IB since on inspection of molecular models the latter shows severe nonbonded interactions. Based on these steric interactions alone, IC should be the preferred rotamer. But in view of J_{AB} values, intramolecular H bonding must significantly influence the conformational preferences. The increase in J_{AB} of 1.39 and 1.96 Hz (compared with the $CDCl_3$ value), respectively, in Me_2CO and DMSO are consistent with the importance assigned to intramolecular H bonding as in these solvents, one would expect an increase in intermolecular H bonding[11] [OH---O=C$(CH_3)_2$ and OH---O=S$(CH_3)_2$] with a decrease in intramolecular H bonding (OH---N).

In the threo amino alcohol, in which nonbonded interactions enhance intramolecular H bonding, the J_{AB} values did not show as marked a solvent dependence. It is expected the population of IIC would be minimal, since it is incapable of intramolecular H bonding and has a high degree of nonbonded interaction. The nmr data indicates that II exists as a mixture of IIA and IIB, with IIA favored as it has the lesser steric interactions. The increase in J_{AB} observed in Me_2CO and DMSO (compared to $CDCl_3$) is consistent with the increased importance of steric factors in these solvents.

The coupling constants for the HCl salts of I and II (Table II) indicate the preferred protonated rotamers are IA and a mixture of IIA and IIB. It is of interest to compare the J_{AB}

Table I. Nmr Data for 1-Aryl-hexahydro-3*H*-oxazolo[3,4-*a*]pyridines[a]

Ar	Configuration of H_aH_b	Chemical shift C_3 protons[b]		$\Delta_{H_3H_3'}$	J_{H_3Gem}[c]
					
Phenyl[5]	Cis[d]	3.78	4.70	0.92	−1.3
e (III)		4.17	5.09	0.92	−1.5
Phenyl[5]	Trans[d]	4.21	4.64	0.43	−2.7
e (IV)		4.52	4.95	0.43	−2.6

[a]Spectra obtd on a Varian Model DP-60 high-resolution spectrometer in $CDCl_3$ at room temp at 10% concn. [b]In δ values, relative to TMS. [c]An average of 6 runs. [d]Confign of phenyl 2-piperidylmethanols has also been established by Dudas and Weisz[7] and by Kovar, *et al.*[8] [e]3,6-Bis(trifluoromethyl)-9-phenanthryl.

Table II. J_{AB} Values for Epimeric α-(2-Piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol and Their HCl Salts[a]

Solvent	Temp, °C	J_{AB}, Hz[b] I	II	I·HCl	II·HCl
DMSO-d_6	100	4.66[c]	7.31	2.65[c]	7.55
TFA[d]	60			2.69	6.98
Acetone-d_6	50	4.09	6.91		
$CDCl_3$	50	2.70[e]	6.58		
C_6D_6	50	2.68[e]	6.41		

[a]Spectra were obtd at indicated temp on a Varian Model DP-60 high-resolution spectrometer at a concn of 10%. [b]An average of 6–10 runs; values accurate to an estimated ±0.2 Hz. [c]OH resonance eliminated by addn of D_2O. [d]F_3CCO_2H. [e]Exchangeable protons replaced with D by shaking overnight with D_2O.

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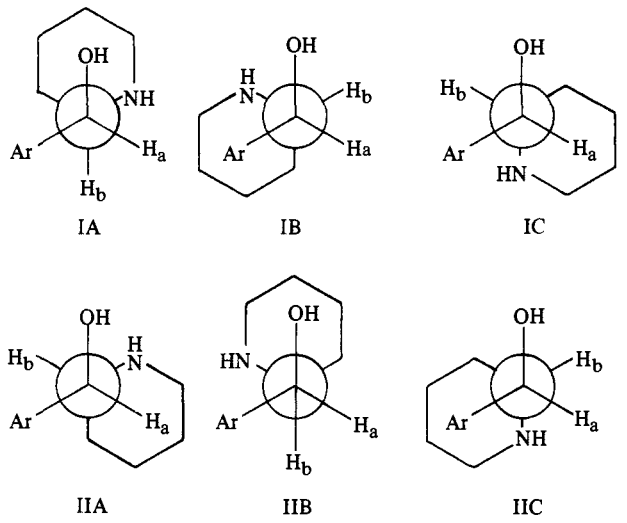
‡H. Sargent[3] reported the isolation of both piperidinemethanol epimers from the catalytic reduction of 2-piperidyl 6-methoxy-4-quinolyl ketone. The materials were tested as SN2157 and SN8279 against *P. lophurae* in ducks and found to be of comparable activity.[4]



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coupling constants observed in DMSO for the free bases and their protonated forms. Evidently, on protonation, the bulk of the solvated quaternary N in I · HCl is significantly increased by H bonding with DMSO. This would enhance the population of IA at the expense of IB and IC. Similarly, protonation of II should increase the population of IIA with a concomitant decrease in IIB, due to the increased steric requirements of the solvated ammonium group.

Biological Data. The *dl*-erythro and *dl*-threo isomers of α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol were tested[12] for antimalarial activity as their HCl and TsOH salts and as their oxazolopyridine derivatives against *Plasmodium berghei* in mice and *P. gallinaceum* in chicks by Dr. Leo Rane at the University of Miami. The test results, furnished to us through the Walter Reed Army Institute of Research, show these materials to be highly active against *P. berghei*, giving 5 cures out of 5 infected mice at dosages of 40 mg/kg for the threo epimers and 5 cures at 80 mg/kg for the erythro compds.§ No toxic deaths were reported up to dosages of 640 mg/kg. Against *P. gallinaceum*, the minimum dosage showing activity was 20 and 160 mg/kg for the threo and erythro compds, respectively.

To attempt a general correlation of epimer conformation with antimalarial activity on the above limited data is premature.

Experimental Section#

***dl-erythro*-α-(2-Piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol Hydrochloride (I · HCl).** H_2 was passed through a mixt of 115 g (0.275 mole) of 2-pyridyl 3,6-bis(trifluoromethyl)-9-phenanthryl ketone, 5.0 g of PtO_2 (Engelhard 85%), 4.2 l. of MeOH, and 40 ml of concd HCl for 16 hr. Darco was added and, after filtration, the filtrate was evapd *in vacuo* to 10% the original vol, pptg a mass of white crystals. The solids were dissolved in MeOH (Darco) and again concd to 10% the original vol to give 96.0 g (82.3%) of I · HCl, mp 331–332° dec. *Anal.* ($C_{22}H_{19}NOF_6$ · HCl) C, H, Cl, N.

***dl-threo*-α-(2-Piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol Hydrochloride (II · HCl).** The mother liquors from the above recryst were concd to dryness, treated with dil K_2CO_3 soln, and dried. The mixt of I and II (15.0 g, 35 mmoles) in 200 ml of MeOH was treated with 4.9 g (25 mmoles) of TsOH · H_2O, refluxed for 5 min, and cooled to ppt II · TsOH. Recrystn (2x, MeOH, Darco) gave an analytical material, mp 269–270°. *Anal.* ($C_{29}H_{27}NO_4F_6S$) C, H, N, F.

II · TsOH (50 g, 0.1 mole) was neutralized by stirring overnight with dil aq NaOH soln. II was dissolved in anhyd Et_2O and satd with HCl gas to ppt II · HCl. Refluxing with CCl_4 removed a yellow impurity to leave II · HCl as a white powder, mp 284–285° (44.2 g, 95%). *Anal.* ($C_{22}H_{21}NOF_6$ · HCl) C, H, N, Cl.

1-[3,6-Bis(trifluoromethyl)-9-phenanthryl]hexahydro-3*H*-oxazolo[3,4-*a*]pyridine. III. A mixt of 4.9 g (11 mmoles) of I, 2 ml of $(CH_2O)_3$ soln, and 50 ml of MeOH was refluxed 8 hr. Addl $(CH_2O)_3$ soln (2 ml) was added, the reflux was contd overnight. The mixt was cooled and filtered, and the product was recrystd (EtOH, Darco) to give 3.0 g (63%) of III as white flakes, mp 167–168°. *Anal.* ($C_{23}H_{19}NOF_6$) C, H, N.

IV. A similar reaction of II gave 4.5 g of crude product. The solid was dissolved in $CHCl_3$, poured onto a silica gel H column (75 g), and eluted with $CHCl_3$. Recrystn (MeOH–H_2O) gave 4.0 g (84%) of IV as a white powder, mp 181–182°. *Anal.* ($C_{23}H_{19}NOF_6$) C, H, N.

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§The synthesis and activity of I · HCl has been previously reported by Nodiff, *et al.*[5]

#All melting point (uncorr) were taken on a Büchi apparatus. Instruments employed were: Beckman IR-9 infrared spectrophotometer, Varian Model DP-60 high-resolution nmr spectrophotometer and Beckman DK-2 uv spectrophotometer. Elemental anal. were correct (±0.3%) and were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

N-Demethylation of Morphine and Structurally Related Compounds with Chloroformate Esters†

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Hundreds of modifications of morphine and structurally related compounds have been performed and the compounds tested in an effort to analyze the relationship between structure and analgetic activity.[1,2] The most common of these modifications is replacement of the Me group attached to the basic N with some other substituent. Thus,

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