Table I—Maximum Values for the Aggregation Number of Micelles of *n*-Alkyl Surfactants Consistent with Spherical Shape

n	$d_{25°/25°}$[a]	$z_{max.}$[b]
10	0.791	29
12	0.802	42
14	0.811	58
16	0.818	77
18	0.823	98

[a] Of $CH_3(CH_2)_{n-1}$. [b] From Eq. 7.

Effect of Hydrocarbon Compressibility—If micelles have radii greater than the extended hydrocarbon chain length, spherical shape implies that some of the polar headgroups are buried inside the hydrocarbon core or that there is a hole in the center of the micelle, provided that the specific gravity of the core is that listed in Table I for atmospheric pressures. The possibility is now examined that compression of the oil droplet which constitutes the hydrocarbon core, resulting from its small radius of curvature, is capable of closing that hole.

According to the Laplace equation, the pressure within the spherical oil droplet exceeds the external pressure by a difference:

$$\Delta P = 2\gamma/R \qquad \text{(Eq. 11)}$$

where γ is the interfacial tension. The compressibility coefficient is defined as:

$$\beta = -(\Delta V/\Delta P)/V_0 \qquad \text{(Eq. 12)}$$

For surfactants derived from *n*-dodecane, $R_{max.} = (12)(1.27) = 15.24$ Å $= 15.24 \times 10^{-8}$ cm. By setting the oil–water interfacial tension at 50 dynes/cm., $\Delta P = 6.56 \times 10^8$ dynes/cm.[2] according to Eq. 11. For higher *n*-alkanes at low pressure, β is of the order of 100×10^{-6} atm.$^{-1}$ or 10^{-10} cm.[2]/dyne (13). By Eq. 12, $\Delta V/V_0 = -0.0656$; *i.e.*, the volume decreased and the specific gravity increased by 6.56%. The higher specific gravity is (0.802)(1.0656) = 0.855. By Eq. 7, the maximum value of z is now 45. This still falls short of the observed association numbers (7, 14, 15).

These estimates represent the upper limit. Actual compressions are certainly smaller because of the following reasons:

1. In selecting the values of γ and β, the fact that the outer ends of the hydrocarbon chains are connected to hydrophilic groups was neglected.

2. The Laplace equation was derived for the situation where R is large compared to the thickness of the interfacial layer (17). In the present situation, this is not true, so that ΔP is probably smaller.

3. The repulsion between ionized headgroups (18) or the crowding of polyoxyethylene chains reduces the core density somewhat, so that the specific gravity values of Table I are slightly high.

The conclusion for the surfactants examined, namely, those which have a single normal hydrocarbon chain for hydrophobic moiety, is the following: With very few exceptions, experimentally determined aggregation numbers of small micelles are too high to be consistent with spherical shape.

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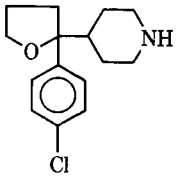
Received January 4, 1971.
Accepted for publication July 6, 1971.

Structure and Antimalarial Activity o Aminoalcohols and 2-(*p*-Chlorophenyl)-2-(4-piperidyl)tetrahydrofuran

Keyphrases □ Aminoalcohols—structure–antimalarial activity relationships □ 2-(*p*-Chlorophenyl)-2-(4-piperidyl)tetrahydrofuran—structure–antimalarial activity relationships □ Antimalarial agents—structure–activity relationships of aminoalcohols and 2-(*p*-chlorophenyl)-2-(4-piperidyl)tetrahydrofuran

Sir:

A series of substituted tetrahydrofuran derivatives synthesized by Marxer (1, 2) showed some interesting antimalarial activity (3, 4). The most active member of this series is 2-(*p*-chlorophenyl)-2-(4-piperidyl)tetra-



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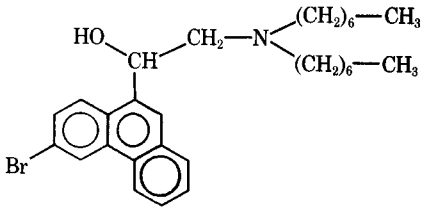

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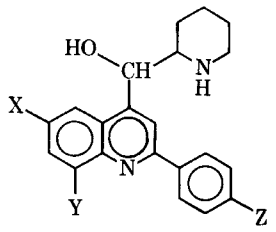


III

hydrofuran (I). Compound I has a marked antimalarial action against blood-induced infection with *Plasmodium berghei berghei* N strain in mice. It is also active against strains of *P. berghei* resistant to chloroquine, mepacrine, primaquine, cycloquanil, and dapsone, as well as against infections with *P. berghei yoelii* (Nigeria) in mice.

A preliminary structure *versus* antimalarial activity relationship study (4) of compounds of this series disclosed that: (*a*) the antimalarial activity is decreased when the piperidyl nitrogen atom is substituted, (*b*) change of the position of the piperidyl nitrogen from 4 to 2 or 3 decreases the activity, (*c*) no activity is found when the piperidine ring is replaced by a pyridine ring, and (*d*) decrease in activity results when the chlorine atom on the benzene ring is replaced by hydrogen, methyl, or methoxy groups.

The structure–activity pattern of compounds of Type I bears a close resemblance to that of another series of antimalarials—the aminoalcohols (5) [for example, compounds of Type II (6) and compounds of Type III (7, 8)]. Each series of compounds is composed of three parts: a planar (aromatic or heteroaromatic) ring, an oxygen-containing portion, and a nonplanar nitrogen-containing portion.

Examination and comparison of molecular models of these compounds revealed that the distances between the oxygen atom, the nitrogen atom, and the aromatic ring (the ring to which the side-chain substituent is attached) are approximately the same in both series under certain conformations. By using Dreiding molecular models (9–11), when the center ring of II or the pyridine ring of III is placed directly over the benzene ring of I and the carbon atoms attached to the rings are superimposed on one another, the oxygen and the nitrogen atoms of either II or III can be turned along their axes in such a way that they can be superimposed on the oxygen and the nitrogen atoms of I, respectively. The same relationship naturally exists when the phenanthrene ring or the quinoline ring of II or III is replaced with other planar aromatic or heteroaromatic ring systems. It is possible that compounds of both series, although displaying antimalarial activity of a different nature, might bind to the same pertinent receptor sites of certain biopolymers of malarial parasites. In this regard, it would seem that, since all of these compounds contain planar ring systems as their components, the antimalarials may intercalate with the parasite deoxyribonucleic acid double helix. Intercalation with deoxyribonucleic acid by other groups of antimalarials [chloroquine and its analogs (12–24) and primaquine and its analogs (25, 26)] is well known and has been investigated in detail.

A close study of Dreiding (9–11) and Briegleb–Stuart (27, 28) molecular models of these compounds revealed that the oxygen and the nitrogen atoms are in close proximity to each other in these molecules and that they are linked by hydrogen bonding (the H-atom can be contributed by either O or N) to form a five-membered ring, as shown in IV*a* or IV*b* (n = 1). The interatomic distance between the oxygen atom and the nitrogen atom and the distance of each atom to the center of the aromatic ring (to which the side chain is attached) were measured and is presented in Scheme I.

From the aforementioned information, it can be readily visualized that:

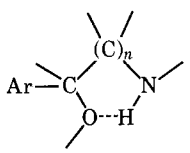
1. Antimalarial activity is abolished when the piperidine ring on the side chain of Compound I or III is replaced by a planar pyridine ring (7, 8, 29).

2. In the case of Compound III, the interatomic distance between N and O remains the same when these two atoms are chemically bound through a —CH_2— linkage. Larger substituents on the nitrogen atom sterically distort the shape of the original five-membered ring, which may affect the antimalarial activity. The nitrogen atom of Compound II is not affected by this restriction since it is attached to free-rotating aliphatic chains.

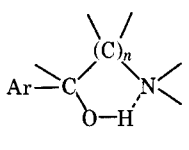
3. Insertion of a —CH_2— linkage between the carbinol carbon and the nitrogen atom transforms the five-membered ring into a six-membered ring (IV, n = 2). However, the interatomic distance between N and O remains approximately the same, which does not affect the antimalarial activity[1].

4. Reduction of the planar aromatic or heteroaromatic ring markedly affects the antimalarial activity (30, 31) since intercalation with deoxyribonucleic acid would be less probable with nonplanar rings.

5. π-Deficient heterocyclic ring systems such as quinoline or electron-withdrawing groups (CF_3, Br,

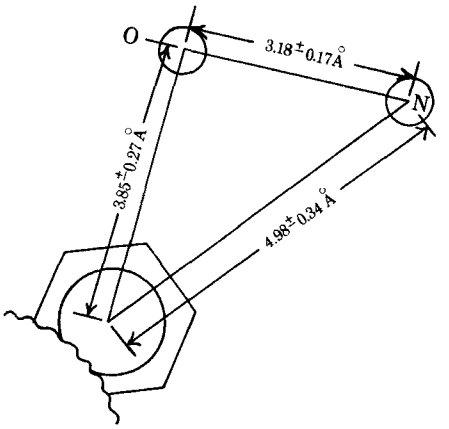


IV*a*



IV*b*

[1] Unpublished data from Midwest Research Institute laboratory.



Scheme I

Cl, *etc.*) substituted on the aromatic rings may act as acceptors in the formation of charge-transfer complexes with deoxyribonucleic acid; hence, they contribute to antimalarial activity.

The preceding account, which may also be intercorrelated with quinine (32, 33) and related cinchona alkaloids, is subject to confirmation or correction by molecular orbital calculations and other studies. The general approach may be regarded as a working hypothesis in studying the mode of action of certain antimalarials and in designing more effective agents for malarial chemotherapy.

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Received April 23, 1971.
Accepted for publication July 16, 1971.
Supported by Contract DA-49-193-MD-2749 with the U. S. Army Medical Research and Development Command. This paper is contribution No. 928 from the Army Research Program on Malaria.
The author thanks Dr. Richard E. Strube for his interest, information, and encouragement.