# Electronic Structure, Antimalarial Activity, and Phototoxicity of Selected Quinolinemethanol Derivatives and Analogs[1]

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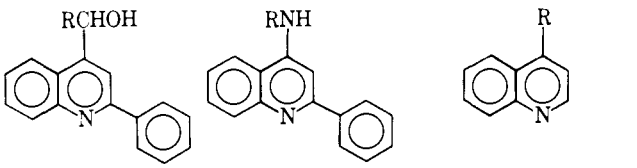
The electronic structures of eighteen derivatives and analogs of quinolinemethanol were calculated by the Hückel molecular orbital method. The results were searched for possible correlations among the electronic indices and phototoxicity and/or antimalarial activity. A parameter, $E_{HOMO} + E_{LEMO}$, is introduced as a measure of molecular "electronegativity." The 2 position was found to be the most positive in all the molecules calculated except those which have a 4-amino group. This observation may be related to the fact that chloroquine, which has a 4-amino moiety, is not metabolically attacked at the 2 position but the quinolinemethanols are.

Derivatives of quinolinemethanol of type I are reported to be both active against *Plasmodium berghei* in mice and phototoxic.[2] The 2-phenyl group is believed to contribute to the high activity by preventing oxidation to carbostyril.[3] The activity decreases markedly and phototoxicity is not observed, however, when an >NH moiety replaces >CHOH (derivatives of type II) *or* if the 2-phenyl group is removed (derivatives of type III).[4] Several laboratories, including ours, have as their target a molecular modification of quinolinemethanol which would preserve the high activity of the 2-phenyl derivatives and reduce the phototoxicity.




R = R'CHOH or R'NH

I II III

Chloroquine (VII, Figure 1) is also a derivative of quinoline and serves as an interesting compound for comparison. It undergoes metabolic attack on the amino side chain[5] rather than at the 2 position as is found in quinolinemethanols of type III. Also, since 2-phenyl analogs of chloroquine of type II are not phototoxic,[4] the phototoxicity of the quinolinemethanols of type I seems to depend on both the presence of a phenyl group at the 2 position *and* a methanol moiety at the 4 position.

With the idea that the electronic structures of these molecules are at least partially responsible for the activities and phototoxicities, Hückel molecular orbital (HMO) calculations were performed on variations of the quinoline ring system. The aim is to use the results to assist in the rational design of molecules having maximum antimalarial activity and minimum phototoxicity.

(1) This research is being supported by the U. S. Army Medical Research and Development Command (DA-49-193-MD-2779), the National Science Foundation (GB-7383), and a grant from Eli Lilly and Company. This paper is Contribution No. 441 from the Army Research Program on Malaria. Computer facilities were provided through Grant HE-09495 from the National Institutes of Health.

(2) D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz, *J. Med. Chem.*, **11**, 273 (1968).

(3) R. M. Pinder and A. Burger, *ibid.*, **11**, 267 (1968).

(4) W. E. Rothe and D. P. Jacobus, *ibid.*, **11**, 366 (1968).

(5) R. T. Williams, "Detoxication Mechanisms," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1959, p 652.

## Methods

All of the calculations were in the simple Hückel approximation.[6,7] The semiempirical parameters[8] are those recommended by Streitwieser[6] and are given in Table I.

TABLE I

SEMIEMPIRICAL PARAMETERS[a] USED IN THE HÜCKEL CALCULATIONS

| Atom | $h$ | $k^b$ | No. of $\pi$ electrons donated |
|---|---|---|---|
| C | 0.00 | 1.00 | 1 |
| Cl | 2.00 | 0.40 | 2 |
| N (aromatic) | 0.50 | 1.00 | 1 |
| N (amino) | 1.50 | 0.80 | 2 |

[a] Taken from ref 6, p 135. [b] Bonded to carbon.

## Results and Discussion

Figure 1 gives the moieties which were calculated and is purposely arranged so that molecules next to one another differ by only one substitutional or structural variation. This facilitates convenient and the most meaningful comparisons of the data since, in the HMO approximation, relative values in a series of closely related molecules are more significant than the absolute values. Several electronic indices were calculated (bond order, free valence, etc.), but just those which are believed to be important to the interpretation of the biological data are presented here.

Since the methanol moiety and saturated side chains are not considered as part of the conjugated $\pi$-electron systems in the HMO method, quinolinemethanol will be considered equivalent to quinoline (IV), and chloroquine will be considered equivalent to 4-amino-7-chloroquinoline (VII).

Table II gives the net $\pi$-electron charge-density distributions at the atomic sites for the moieties in Figure 1. Table III gives the energies of the highest occupied and lowest empty molecular orbitals (HOMO and LEMO) and the sums and differences of these energies. The difference of the HOMO and LEMO energies corresponds to the lowest $\pi$-electronic excita-

(6) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists, John Wiley and Sons, Inc., New York, N. Y., 1961.

(7) C. A. Coulson and A. Streitwieser, Jr., "Dictionary of $\pi$-Electron Calculations," W. H. Freeman and Co., San Francisco, Calif., 1965.

(8) W. P. Purcell and J. A. Singer, *J. Chem. Eng. Data*, **12**, 235 (1967).

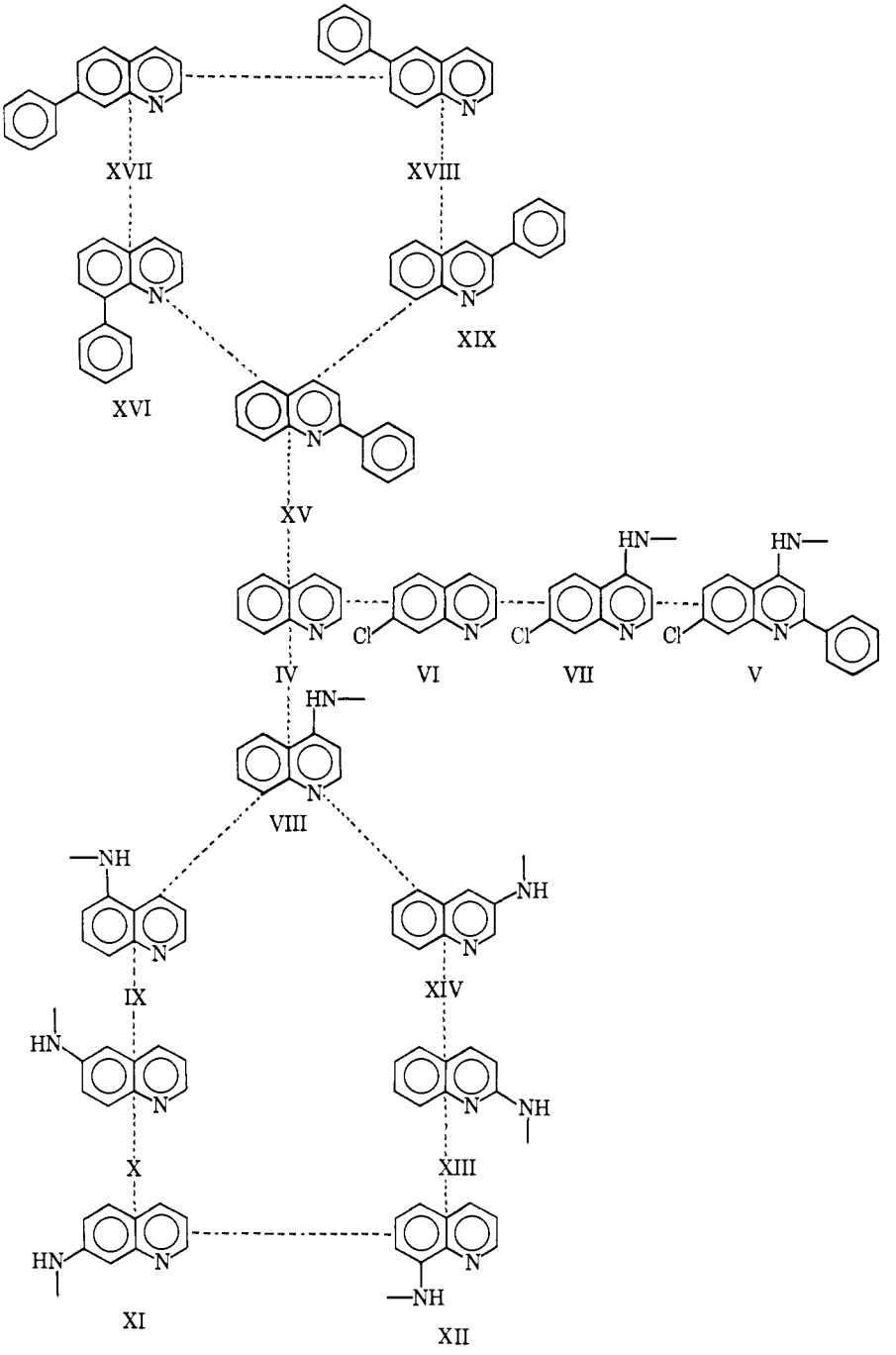



Figure 1.—Quinoline moieties for which the HMO electronic structures were calculated.

tion energy of the molecule. The sum of HOMO and LEMO energies is a parameter which has not been used previously; it may be considered as a measure of the "electronegativity" of the molecule. The corresponding theoretical expression for the electronegativity of an atom was derived by Mulliken.[9] Based on the concept that the energy expended in going from the covalent molecule A–B to the ionic states $A^+B^-$ and $A^-B^+$ is equal if A and B have the same electronegativity, Mulliken concluded[10] that the electronegativity of an atom is proportional to the sum of its appropriate valence-state ionization potential and electron affinity. The parameter $E_{\mathrm{HOMO}} + E_{\mathrm{LEMO}}$ corresponds to the sum of the ionization potential and electron affinity of a *molecule* in the Hückel approximation.[11]

Some generalizations may be made about the results of the calculations. (1) The amino group makes the molecule (IV, VIII–XIV) a better electron donor and a worse electron acceptor. It makes the molecule easier to excite electronically; one exception to this is the 2-amino derivative XIII, which has the same excitation energy as the parent compound IV. The amino group makes $E_{\mathrm{HOMO}} + E_{\mathrm{LEMO}}$ smaller. (2) Phenyl group substitution makes the molecule a better electron donor and a better electron acceptor. It makes the molecule easier to excite electronically. The sum of $E_{\mathrm{HOMO}} + E_{\mathrm{LEMO}}$ becomes smaller with the single exception of the

(9) R. S. Mulliken, *J. Chem. Phys.*, **2**, 782 (1934).
(10) R. S. Mulliken, *ibid.*, **46**, 497 (1949).
(11) W. P. Purcell, J. A. Singer, K. Sundaram, and G. L. Parks in "Medicinal Chemistry," A. Burger, Ed., 3rd ed, John Wiley and Sons, Inc., New York, N. Y., in press.

TABLE II

NET $\pi$ CHARGES FOR THE MOIETIES IN FIGURE 1

| Atom | IV | V | VI | VII | VIII | IX | X | XI | XII | XIII | XIV | XV | XVI | XVII | XVIII | XIX |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $N_1$ | −0.216 | −0.283 | −0.218 | −0.268 | −0.267 | −0.225 | −0.214 | −0.228 | −0.207 | −0.286 | −0.210 | −0.233 | −0.215 | −0.218 | −0.215 | −0.214 |
| $C_2$ | +0.104 | +0.088 | +0.104 | +0.103 | +0.103 | +0.105 | +0.091 | +0.103 | +0.091 | +0.141 | +0.075 | +0.089 | +0.102 | +0.104 | +0.103 | +0.108 |
| $C_3$ | −0.008 | −0.076 | −0.010 | −0.077 | −0.075 | −0.021 | −0.008 | −0.021 | −0.006 | −0.036 | +0.041 | −0.005 | −0.008 | −0.009 | −0.008 | −0.007 |
| $C_4$ | +0.069 | +0.114 | +0.069 | +0.119 | +0.119 | +0.074 | +0.056 | +0.069 | +0.059 | +0.067 | −0.003 | +0.064 | +0.067 | +0.067 | +0.067 | +0.064 |
| $C_5$ | +0.012 | +0.018 | +0.013 | +0.019 | +0.018 | +0.069 | −0.058 | +0.016 | −0.041 | +0.012 | −0.001 | +0.011 | +0.010 | +0.011 | +0.011 | +0.011 |
| $C_6$ | −0.003 | −0.023 | −0.009 | −0.021 | −0.015 | −0.071 | +0.046 | −0.033 | +0.002 | −0.015 | −0.003 | −0.004 | −0.003 | −0.002 | −0.002 | −0.003 |
| $C_7$ | +0.016 | +0.029 | +0.029 | +0.029 | +0.016 | +0.020 | −0.014 | +0.063 | −0.054 | +0.015 | +0.003 | +0.016 | +0.010 | +0.014 | +0.017 | +0.015 |
| $C_8$ | −0.012 | −0.038 | −0.027 | −0.035 | −0.022 | −0.064 | −0.008 | −0.082 | +0.047 | −0.025 | −0.011 | −0.015 | −0.010 | −0.015 | −0.012 | −0.012 |
| $C_9$ | −0.001 | −0.030 | −0.005 | −0.029 | −0.026 | −0.026 | +0.000 | −0.018 | −0.001 | −0.018 | −0.000 | −0.003 | −0.002 | −0.001 | −0.002 | −0.002 |
| $C_{10}$ | +0.044 | +0.045 | +0.044 | +0.043 | +0.042 | 0.044 | +0.026 | +0.044 | +0.020 | +0.044 | +0.025 | +0.045 | +0.046 | +0.042 | +0.044 | +0.041 |
| $Cl_7$ | | +0.016 | +0.016 | +0.016 | | | | | | | | | | | | |
| N (amino) | | +0.105 | | +0.106 | +0.106 | +0.095 | +0.084 | +0.088 | +0.091 | +0.101 | +0.084 | | | | | |

TABLE III

MOLECULAR ORBITAL ENERGIES (IN UNITS OF $\beta^0$) FOR THE MOIETIES IN FIGURE 1

| | IV | V | VI | VII | VIII | IX | X | XI | XII | XIII | XIV | XV | XVI | XVII | XVIII | XIX |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $E_{HOMO}$ | 0.703 | 0.593 | 0.695 | 0.603 | 0.607 | 0.562 | 0.613 | 0.635 | 0.552 | 0.672 | 0.621 | 0.667 | 0.566 | 0.632 | 0.614 | 0.621 |
| $E_{LEMO}$ | −0.527 | −0.548 | −0.532 | −0.600 | −0.595 | −0.572 | −0.541 | −0.548 | −0.567 | −0.561 | −0.545 | −0.464 | −0.468 | −0.487 | −0.499 | −0.496 |
| $E_{HOMO} - E_{LEMO}$ | 1.230 | 1.111 | 1.227 | 1.203 | 1.202 | 1.134 | 1.154 | 1.183 | 1.119 | 1.233 | 1.164 | 1.131 | 1.031 | 1.119 | 1.113 | 1.117 |
| $E_{HOMO} + E_{LEMO}$ | 0.176 | 0.075 | 0.163 | 0.003 | 0.012 | −0.010 | 0.072 | 0.087 | −0.015 | 0.111 | 0.078 | 0.203 | 0.098 | 0.145 | 0.115 | 0.125 |

2-phenyl derivative XV, which has the largest value, 0.203 $\beta$, of all the molecules calculated.

Another interesting observation is that the 2 position is the most positive in all the molecules except those which have a 4-amino group. This is thought provoking since chloroquine which has a 4-amino moiety is not metabolically attacked at the 2 position but the quinolinemethanols are. A similarly unique property associated with the 2 position is that substitution there results in marked changes in $E_{HOMO} + E_{LEMO}$ when compared with substitution at other positions (Table III, moieties V, XIII, and XV). One might conclude that the changes in electronic structure associated with the 2 position parallel the metabolic and phototoxic properties.

Perhaps the most striking observation in Table III is the large value, 0.203 $\beta$, for the sum of the energies for the HOMO and LEMO of 2-phenylquinoline (XV). This result sets the derivative apart from its analogs and suggests the hypothesis that the parameter may be related to phototoxicity, since a corresponding compound, $\alpha$-(2-piperidyl)-2-phenyl-4-quinolinemethanol, has the largest phototoxic potency (minimum effective dose = 50 mg/kg ip in mice) compared to other compounds[4] corresponding to the moieties in Table III. Confirming evidence for the hypothesis is found in the low value, 0.075 $\beta$, obtained for the parameter for V in spite of the presence of a phenyl group in the 2 position. This result is consistent with the observation that the corresponding 2-phenyl analog of chloroquine does not elicit a phototoxic response in mice.[4] It may be then that $E_{HOMO} + E_{LEMO}$ increases with increasing phototoxicity, and that, in designing a drug which is not phototoxic, one should search for molecules with low values of $E_{HOMO} + E_{LEMO}$. In connection with our interpretation of this parameter as a measure of the electronegativity of a molecule, it is interesting that the phototoxic potency of 2-substituted quinolinemethanols has been observed to vary with different functional groups in a manner that may suggest an association with their relative electronegativities.[4] An observation which offers another opportunity to test the hypothesis that large values of $E_{HOMO} + E_{LEMO}$ parallel phototoxicity is the fact that



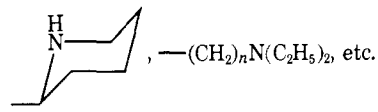

XX XXI

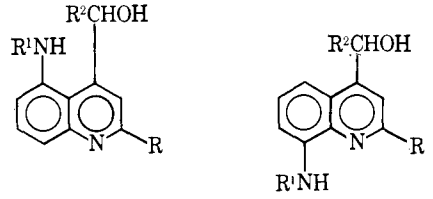
XX is phototoxic whereas XXI is not.[12] Subsequent HMO calculations of the two analogs gave values for $E_{HOMO} + E_{LEMO}$ of 0.396 and 0.463 $\beta$ for XX and XXI, respectively. These results negate the hypothesis indicating that one cannot say categorically that the higher the value of $E_{HOMO} + E_{LEMO}$, the greater the phototoxicity.

In designing a molecule with desirable properties, however, it seems reasonable to suggest (1) a quinolinemethanol for activity, (2) a substituent other than

(12) D. P. Jacobus, personal communication, May 17, 1968.

phenyl in the 2 position to block metabolic attack, and (3) an NH moiety in the 5 or 8 position to give a low $E_{HOMO} + E_{LEMO}$ or low phototoxicity. Derivatives which might be worthy of synthesis and evaluation include those of type XXII and XXIII where $R^1$ and $R^2$ are the commonly employed moieties in antimalarial drug design such as




XXII XXIII

Such syntheses are in progress.

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# Antimalarial Activity of Guanylhydrazone Salts of Aromatic Ketones. I. Primary Search for Active Substituent Patterns[1]

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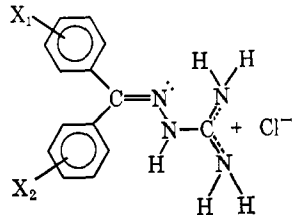
Thirty two guanylhydrazones of aromatic ketones were synthesized and tested in the primary antimalarial screen in mice infected with *Plasmodium berghei*. Biological data have been received on 30 compounds. Nine compounds showed significant activity and seven of these gave a high percentage of cures. The biological results and structure–activity correlation are discussed as well as drug design and the synthetic problems involved. Activity of some of these compounds on L1210 leukemia in mice is described.

In 1962 a small group of substituted benzophenone guanylhydrazones (I) was synthesized specifically to study their action on L1210 leukemia in mice.[2,3] Several of these compounds displayed significant activity.




I

However, the dose–response relations and therapeutic indices were so poor that the project was abandoned. In 1965 and 1966 we sent 17 of these compounds (Table I) to the Walter Reed Army Institute of Research for testing in the primary antimalarial screen (*Plasmodium berghei* in mice). One compound, 4-fluoro-4′-trifluoromethylbenzophenone guanylhydrazone hydrochloride (**15**), was quite active and caused some cures. As a consequence a contract was activated to pursue this lead.

Referring to structure I, one can introduce one or more substituents in either or both rings and insert various substituents in place of hydrogen on the aminoguanidine moiety. Considering the limited biological data available (Table III) a simple series was generated wherein the guanidine group was unchanged, a 4-$CF_3$ group was maintained on one ring, and a variety of substituents were placed on the 4′ position. These groups were chosen with the usual considerations. A range of electronic effects and influences on solubility-distribution behavior could be studied relatively easily. While this work was in progress information was received on the moderate activity of **7** and the high activity of **17**. Consequently, attention was focused on bromo, iodo, and additional trifluoromethyl substituents. The resultant series of compounds is shown in Table II.

**Biological Data and Correlations.**—An inspection of the data in Table III and a consideration of ancillary toxicity data make it apparent that there are two correlations involved in the structure–activity relationships: a toxicity correlation and an antimalarial activity correlation. Any activity which might conceivably have been displayed by compounds substituted only in one ring with fluoro, chloro, or trifluoromethyl is masked by high host toxicity. The same limitation applies when both rings bear fluoro or chloro substituents. For monosubstitution the toxicity decreased in the order: $CF_3 > I > F > Br$. When bromo and/or trifluoromethyl substituents are present in both rings toxicity is quite low.

The only monosubstituted compounds showing antimalarial activity in the primary screen were the 4-bromo and particularly the 4-iodo derivatives. In the new series of 4-trifluoromethyl-4′-halo derivatives the order of activity cannot be stated precisely at this time. However, incomplete advance biological data show that both the 4′-chloro and 4′-iodo derivatives are active. Curiously enough, the 4,4′-dibromo derivative is inactive but it has the expected low toxicity. In contrast, both the 4,4′-ditrifluoromethyl and the 4-bromo-

(1) This investigation was conducted under Contract DA-49-193-MD-3016 from the U. S. Army Research and Development Command. This is Contribution No. 313 to the Army Research Program on Malaria.

(2) F. A. French, E. J. Blanz, Jr., and C. C. Cheng, *Proc. Am. Assoc. Cancer Res.*, **4**, 20 (1963).

(3) This work was supported by Grant CA-03287 from the National Cancer Institute.