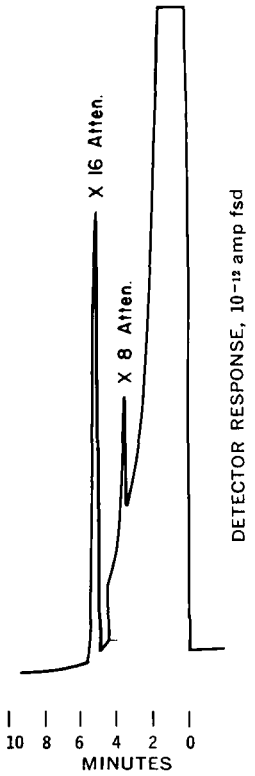

Figure 2—*Representative gas chromatogram obtained from a plasma sample containing 0.104 μg/ml meperidine (as base). Key: peak 1, meperidine (×8 attenuation); and peak 2, internal standard (×16 attenuation). Scale was expanded on first peak for more accurate measurement and to show lack of interference from other peaks.*

standard *versus* amount meperidine. The coefficient of variation of 2% was typical over the concentration range encountered. The limit of sensitivity attainable was approximately 0.005 μg/ml. A representative chromatogram is shown in Fig. 2.

Because procaine (and many ester-type local anesthetics) is susceptible to base-catalyzed hydrolysis with the general method, the following modifications were found useful. The plasma samples (previously treated with sodium arsenite to prevent enzymic hydrolysis) were made basic, where appropriate, with sodium carbonate solution (2 *M*, saturated with sodium chloride). Saturation with sodium chloride assisted the partition into the organic phase at the lower pH of the sodium carbonate (where the tertiary amine is still appreciably ionized). Final extraction was best accomplished with chloroform, which increased the partition of the basic drug.

The technique presented here offers the following advantages over that described by Goehl and Davison (1):

1. It is applicable, with appropriate choice of internal standard (*i.e.*, similar physiochemical properties to drug) and GC conditions, to most basic drugs and is routinely used in the authors' laboratories for the determination of lidocaine, mepivacaine, etidocaine, bupivacaine, ketamine, and, with small modifications, to base-labile ester-type local anesthetics such as procaine.
2. It has greater sensitivity.
3. It is an internal standard technique and hence is not dependent on volumes transferred, diluted, or injected.
4. No evaporation of solvent is required; therefore, there is no potential for drug loss by volatilization (3, 4).
5. Inclusion of hexamethyldisilazane, with its potential detector contamination problems, is not required.
6. Final solvent may be altered to chloroform for greater polarity or to carbon disulfide (centrifuged at 10,000 rpm for 10 min) for greater sensitivity (*i.e.*, reduced solvent peak size and larger injection volume permitted).
7. This technique may be combined with an alkali flame detector for even greater sensitivity[5].

(1) T. J. Goehl and C. Davison, *J. Pharm. Sci.*, 62, 907(1973).
(2) B. J. Hodshon, T. Ferrer-Allado, V. L. Brechner, and A. K. Cho, *Anesthesiology*, 36, 506(1972).
(3) J. Ramsay and D. B. Campbell, *J. Chromatogr.*, 63, 308(1971).
(4) G. T. Tucker, *Anesthesiology*, 32, 255(1970).

L. E. Mather[x]
G. T. Tucker
Department of Anesthesiology
University of Washington
Seattle, WA 98195

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[x] To whom inquiries should be directed.

[5] L. E. Mather, unpublished observations.

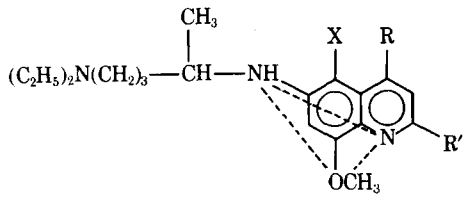
Novel Common Structural Feature among Several Classes of Antimalarial Agents

Keyphrases □ Antimalarial agents—discussion of common structural feature □ Structure-activity relationships—antimalarial agents, common structural feature of several classes discussed

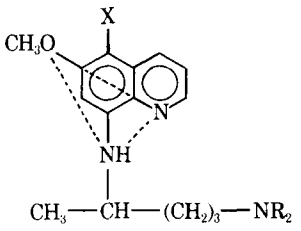
Sir:

A common triangular feature among certain antimalarial cinchona alkaloids, aminoalcohols, and 2-(*p*-chlorophenyl)-2-(4-piperidyl)tetrahydrofuran was recently proposed from this laboratory (1). The components as well as parameters involved in this pharmacophore are interestingly similar to those proposed for α-adrenergic receptor features (2).

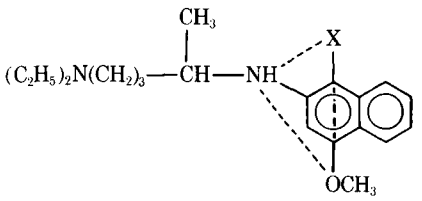
In connection with a structural modification study of some 6-aminoquinolines (I) (3–6) and 8-aminoquin-



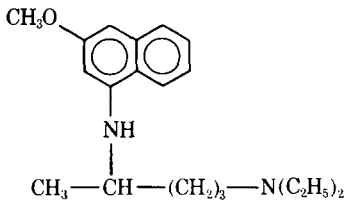
I



II



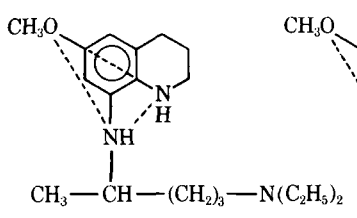
IIIa: X = H
IIIb: X = OCH_3



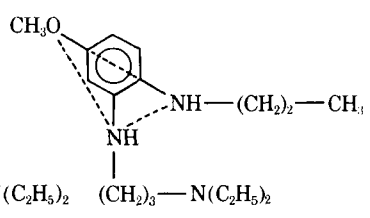
IV

olines (II) (3, 7–17), three deaza analogs, 3-(4-diethylamino-1-methylbutylamino)-1-methoxynaphthalene (IIIa), 2-(4-diethylamino-1-methylbutylamino)-1,4-dimethoxynaphthalene (IIIb), and 1-(4-diethylamino-1-methylbutylamino)-3-methoxynaphthalene (IV), were synthesized and their antimalarial activity was evaluated (18). Compounds IIIa and IV were devoid of antimalarial activity, but some antimalarial activity was observed with Compound IIIb (18).

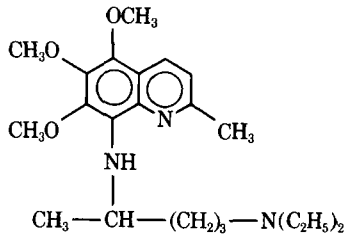
A comparative study of the structures of the active *versus* the inactive compounds revealed an interesting pattern. The active compounds (I, II, and IIIb) possess *three* electronegative elements, each containing one or two lone pairs of electrons (N, O, *etc.*), substituted on a benzene (planar) ring at the 1-, 2-, and 4-positions; the inactive compounds (IIIa and IV) lack such an arrangement. One of the three substituents in the active compounds consists of a substituted aminoalkylamino side chain. The same



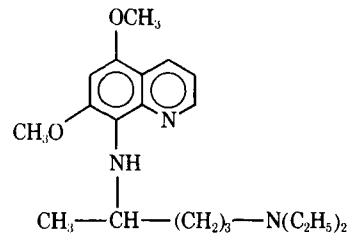
V



VI



VII

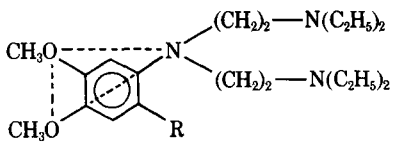


VIII

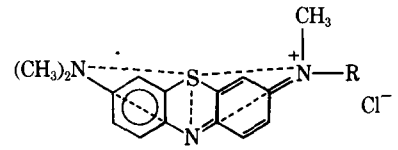
pattern can also be extended to 1,2,3,4-tetrahydro-8-aminoquinolines such as V (19–21) as well as to the corresponding open chain *o*-phenylenediamines such as VI (22, 23), both of which have demonstrated antimalarial activity.

Apparently, substitution of an additional electron-donating group, such as a methoxyl, at the 5-position of the benzene nucleus does not destroy and may even enhance the original antimalarial activity. This is illustrated by the activity exhibited by Compounds I (X = OCH_3; R, R′ = H or CH_3) (5) and II (X = OCH_3; R = H or C_2H_5) (3). However, additional substitution at the 3-position of the benzene nucleus with an electron-donating group gave deleterious results, as shown by the lack of antimalarial activity of Compounds VII and VIII (3).

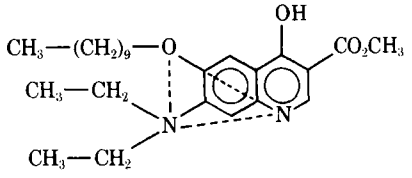
Certain aminopyrocatechol antimalarials (24–31), represented by 1,2-dimethoxy-4-[bis(diethylami-



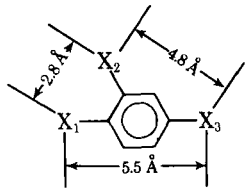
IXa: R = Br
IXb: R = H



Xa: R = CH_3
Xb: R = $(CH_2)_2$—$N(C_2H_5)_2$
Xc: R = CH—CH—CH_2—$N(C_2H_5)_2$ (CH_3 CH_3)



XI

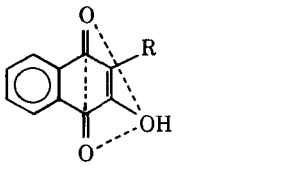


Scheme I

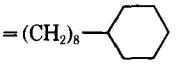
noethyl)amino]-5-bromobenzene (IX*a*, RC-12) and its debrominated derivative dimeplasmin (IX*b*), also possess a similar structural feature. Again, one substituent is a substituted aminoalkylamino side chain, which is probably necessary for secondary binding with certain biopolymers such as with mitochondria (32, 33) *in vivo*. The trisubstitution feature can also be visualized with the antimalarial methylene blue (X*a*) (34, 35) and related compounds (X*b* and X*c*) (36, 37). However, the dibasic side chain is absent in Compound X*a*. This chain is also absent in another antimalarial, methyl 6-decyloxy-7-diethylamino-4-hydroxy-3-quinolinecarboxylate (XI) (38), which does, however, possess the substitution pattern noted in other active compounds.

Thus, a common triangular feature (Scheme I) is proposed for the aforementioned antimalarials. The substituents X_1, X_2, and X_3 represent lone pair electron-containing electronegative atoms such as nitrogen, oxygen, or sulfur. Minimum distances between each of the atoms were obtained through measurements of Dreiding molecular models (39).

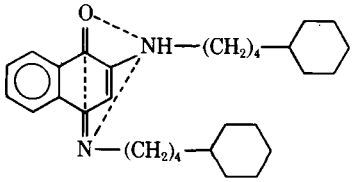
Lapinone (XII*a*), other 2-hydroxy-3-alkyl-1,4-naphthoquinones (XII*b* and XII*c*) (40–42), and some quinone imines (*e.g.*, XIII) and 4-amino-1,2-naphthoquinones (43–45) showed most antimalarial activity in prophylactic tests. The absence of the dibasic side chain probably necessitates different secondary structure–activity requirements. Nevertheless, introduction of an amino function at the 3-position (XII*d* and XII*e*) still led to inactive compounds (46, 47).



XII*a*: R = $(CH_2)_8$—C(OH)[$(CH_2)_4$—CH_3]$_2$
XII*b*: R = CH_2—CH(CH_3)—$(CH_2)_5$—CH_3



XII*d*: R = NH—NH—COR′



XIII

Although the 4-aminoquinolines (such as chloroquine) and the 9-aminoacridines (such as mepacrine) contain functional groups similar to those of 6-aminoquinolines and 8-aminoquinolines, they do not possess the proposed triangular pattern. Differences in structural features between these two types of compounds and their structural dissimilarity with the earlier reported aminoalcohols (1) may explain the variance in the mode of action (47–50) as well as the rarity in occurrence of cross-resistance between these three types of antimalarials (51, 52). Compounds possessing the presently postulated feature that may participate in biological redox reactions, such as on the energy-producing pathways of oxidative phosphorylation and the electron transport system (3, 53, 54), may have a closer relationship to causal prophylactic or radical curative agents rather than schizonticidal or suppressive agents. The antimalarial test results of the compounds were obtained from various literature sources and different test systems. The proposed structural feature serves only as a working hypothesis for classifying certain types of antimalarials without consideration of drug transport, distribution, and metabolism. Additional attention may be focused on the redox potential and partition coefficient studies (54, 55) as well as on the nature of side-chain substituents for designing more effective and less toxic antimalarial agents.

(1) C. C. Cheng, *J. Pharm. Sci.*, **60**, 1596(1971).
(2) B. Pullman, J.-L. Coubeils, P. Courrière, and J.-P. Gervois, *J. Med. Chem.*, **15**, 17(1972).
(3) F. Schönhöfer, *Z. Physiol. Chem.*, **274**, 1(1942).
(4) F. Schönhöfer and W. Schulemann, British pat. 970,949 (1962); through *Chem. Abstr.*, **61**, 1329h(1964).
(5) E. Fink, P. Nickel, and O. Dann, *Arzneim.-Forsch.*, **20**, 1775(1970).
(6) E. F. Elslager, M. P. Hutt, and L. M. Werbel, *J. Heterocycl. Chem.*, **6**, 99(1969).
(7) E. Fourneau, J. Tréfouel, B. D. Tréfouel, and G. Benoit, *Ann. Inst. Pasteur*, **46**, 514(1931); *ibid.*, **50**, 731(1933).
(8) D. C. Quin and R. Robinson, *J. Chem. Soc.*, **1943**, 555.
(9) J. Crum and R. Robinson, *ibid.*, **1943**, 561.
(10) R. C. Elderfield, L. C. Craig, W. M. Lauer, R. T. Arnold, W. J. Gensler, J. D. Head, T. H. Bembry, H. R. Mighton, J. Tinker, J. Galbreath, A. D. Holley, L. Goldman, J. T. Maynard, and N. Picus, *J. Amer. Chem. Soc.*, **68**, 1516(1946).
(11) R. C. Elderfield, W. J. Gensler, J. D. Head, H. A. Hageman, C. B. Kremer, J. B. Wright, A. D. Holley, B. Williamson, J. Galbreath, L. Wiederhold, III, R. Frohardt, S. M. Kupchan, T. A. Williamson, and O. Birstein, *ibid.*, **68**, 1524(1946), and references cited therein.
(12) F. Y. Wiselogie, "A Survey of Antimalarial Drugs, 1941–1945," Edwards, Ann Arbor, Mich., 1946.
(13) J. Greenberg, D. Taylor, and E. S. Josephson, *J. Infec. Dis.*, **88**, 163(1951).
(14) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, "Survey of Antimalarial Agents," Public Health Service Publication No. 9, Washington, D.C., 1953.
(15) M. B. Braude and V. I. Stavrovskaya, *Zh. Obshch. Khim.*, **26**, 878(1956).
(16) J. Hill, in "Experimental Chemotherapy," R. J. Schnitzer and F. Hawking, Eds., Academic, New York, N.Y., 1963, p. 513.
(17) D. A. Berberian, F. Coulston, H. P. Drobeck, H. W. Freele, and E. W. Dennis, *Antibiot. Chemother.*, **12**, 103(1962).
(18) D. J. McCaustland, P.-L. Chien, C. C. Cheng, J. Novotny, W. L. Schreiner, and F. W. Starks, *J. Med. Chem.*, **16**, 1311(1973).
(19) H. J. Barber and W. R. Wragg, *J. Chem. Soc.*, **1946**, 610.
(20) K. S. Topchiev and M. B. Braude, *C. R. Acad. Sci., Russ.*, **52**, 593(1946).

(21) A. Gray and J. Hill, *Ann. Trop. Med. Parasitol.*, **43**, 32(1949).
(22) H. J. Barber, F. W. Major, and W. R. Wragg, *J. Chem. Soc.*, **1946**, 613.
(23) V. I. Stavrovskaya and K. S. Topchiev, *Dokl. Akad. Nauk SSSR*, **58**, 237(1947).
(24) R. Green, *Lancet*, **217**, 1137(1929).
(25) W. Schulemann and W. Kropp, U.S. pat. 1,757,394 (1930).
(26) J. A. Sinton, *Indian J. Med. Res.*, **17**, 815(1930).
(27) F. Schönhöfer, "Chemotherapy," *Office Tech. Services Rept.*, PB-85033 (1948); FIAT, *Rev. German Sci.*, 43.
(28) L. J. Bruce-Chwatt, *Trans. Roy. Soc. Trop. Med. Hyg.*, **59**, 105(1965).
(29) L. H. Schmidt, R. N. Rossan, R. Fradkin, J. Woods, W. Schulemann, and L. Kratz, *Bull. WHO*, **34**, 783(1966).
(30) L. M. Werbel, E. F. Elslager, M. P. Hutt, and J. M. Vandenbelt, *J. Pharm. Sci.*, **56**, 1335(1967).
(31) E. L. Stogryn, *J. Med. Chem.*, **12**, 185(1969); *ibid*, **13**, 864, 1106(1970); *ibid.*, **14**, 171(1971).
(32) R. L. Beaudoin, C. P. A. Strome, and W. G. Clutter, *Mil. Med.*, **134**, 979(1969).
(33) M. Aikawa and R. L. Beaudoin, *ibid.*, **134**, 986(1969).
(34) P. Ehrlich and P. Guttman, *Klin. Wochenschr.*, **28**, 953(1891).
(35) A. J. Ewins, *J. Chem. Soc.*, **1944**, 351.
(36) W. Schulemann, A. Wingler, and F. Mietzch, U.S. pat. 1,766,403 (1930); through *Chem. Abstr.*, **24**, 4166(1930).
(37) P. B. Russell, in "Medicinal Chemistry," 2nd ed., A. Burger, Ed., Wiley-Interscience, New York, N.Y., 1960, p. 814.
(38) R. L. Clark and M. H. Fisher, German pat. 1,908,262 (1969); through *Chem. Abstr.*, 72, 3394d(1970).
(39) L. F. Fieser, *J. Chem. Educ.*, **40**, 457(1963); *ibid.*, **42**, 408(1965).
(40) L. F. Fieser, M. Z. Nazer, S. Archer, D. A. Berberian, and R. G. Slighter, *J. Med. Chem.*, **10**, 517(1967).
(41) D. Berberian and R. G. Slighter, *J. Parasitol.*, **54**, 999(1968).
(42) D. Berberian, R. G. Slighter, and H. W. Freele, *ibid.*, **54**, 1181(1968).
(43) F. J. Bullock, J. F. Tweedie, D. D. McRitchie, and M. A. Tucker, *J. Med. Chem.*, **13**, 97(1970).
(44) *Ibid.*, **13**, 550(1970).
(45) R. M. Pinder, in "Progr. Med. Chem.," vol. 8, G. P. Ellis and G. B. West, Eds., Butterworths, London, England, 1971, p. 231.
(46) F. I. Carroll, K. H. Dudley, and H. W. Miller, *J. Med. Chem.*, **12**, 187(1969).
(47) K. H. Dudley and H. W. Miller, *ibid.*, **13**, 535(1970).
(48) R. D. Powell, *Clin. Pharmacol. Ther.*, **7**, 48(1966).
(49) D. J. Halbrook, Jr., L. P. Whichard, C. R. Morris, and L. A. White, in "Progress in Molecular and Subcellular Biology," vol. 2, F. E. Hahn, Ed., Springer-Verlag, Heidelberg, Germany, 1971, p. 113.
(50) P. E. Thompson and L. M. Werbel, "Antimalarial Agents, Chemistry and Pharmacology," Academic, New York, N.Y., 1972.
(51) D. C. Warhurst, C. A. Homewood, W. Peters, and V. C. Baggaley, *Proc. Helmintol. Soc.*, **39**, 271(1972).
(52) C. D. Fitch, *ibid.*, **39**, 265(1972).
(53) E. Fink, P. Nickel, and O. Dann, *Arzneim-Forsch.*, **20**, 1775(1970).
(54) C. Hansch, in "Drug Design," vol. I, E. J. Ariens, Ed., Academic, New York, N.Y., 1971, p. 271.
(55) Y. C. Martin, T. M. Bustard, and K. R. Lynn, *J. Med. Chem.*, **16**, 1089(1973).

C. C. Cheng

Midwest Research Institute
Kansas City, MO 64110

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