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NEW ANTIMALARIAL AGENTS

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Final Report

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BACKGROUND:

The number of papers dealing with the synthesis and study of antimalarial agents is indeed legion.¹ This extensive amount of work has led to certain conclusions regarding the types of peripheral substituents on quinoline-like compounds which are necessary for antimalarial activity.

No <u>definitive</u> work has yet been described concerning the structural requirements of the aromatic moiety of the antimalarial drugs (this excludes the "quinone" theory).

The general structural requirements for antimalarial activity appear to be the following:

(CH₂) 5^{NR}2

 $H-(CH_2)_n(C_2H_5)_2$

1) For "quinine-like" compounds:

2) For 8-aminoquinolines:

3) For 4-aminoquinolines:

STATEMENT OF PROBLEM:

It has been shown that the oxidation of the quinoline nucleus at position 4 is involved in the antimalarial activity of these compounds.²

- 1 -

¹"Medicinal Chemistry", ed. A. Burger, Interscience Publishers, Inc. New York, 1960, pp/814 ff.

²W. Schulemann, Proc. Roy. Soc. Med., <u>25</u>, 897 (1932).

Consequently, if one could prepare structurally related compounds which are more readily oxidized at the 4-position of quinoline-like compounds (to form quinones, for example), and if these compounds have the "active" peripheral substituents described in the introduction, one might well obtain improved antimalarial agents.

Furthermore, the introduction of another hydrogen-bonding site of low chemical reactivity might well enable larger amounts of the drug to be retained at the "active-site" without interfering with the chemical reactions involved.

Published preliminary molecular orbital calculations from our laboratories³ and unpublished data of polarographic reduction potentials indicate, that the above goals can be achieved by two, as yet untested, classes of compounds:

1) Naphthyridines:

2) Polyazaindenes:





³W. W. Paudler and H. L. Blewitt, Tetrahedron <u>21</u>, 353 (1965).

- 2 -

A) Naphthyridines:

1) Hydroxy-naphthyridines:

The following compounds of this type were prepared by the general method outlined in the "synthetic section" of this report and the activities indicated have been established:

Code No. 79319A



OH .CO2H

CO2Et

HC

- a) negative in rodent
- antimalarial screen
 b) 23% toxic deaths in mosquito test (0.1% concentration)
- a) negative in rodent entimalarial screen
- b) 11% toxic deaths in mosquito test (0.1% concentration)
- a) negative in rodent antimalarial screen
- b) 11% toxic deaths in mosquito test (0.1% concentration)

79321A

79322A

OH CO2Et

- a) negative in rodent antimalarial screen
- b) 94-100% toxic deaths in mosquito test (0.1% concentration)
 57% toxic deaths in mosquito test (0.1% concentration)
 Partial sporozoite supp.

- 3 -

BNAC 30570



9% toxic deaths in mosquito test (0.1% concentration)

79323A



3% toxic deaths in mosquito test (0.1% concentration)

2) A mo-naphthyridines:

7932¹1A

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34% toxic deaths in mosquito test No cures

79325A

-MH2

3% toxic deaths in mosquito test No cures

79320A

OH Et02C MI2

Of toxic deaths in mosquito test Partial sporozoite supp. (0.1% concentration) No cures

- 4 -

CUL3-CH(CH2)2N(Et)2 ŃН

reported as "active" (BNAC 30552)



No report

3) "Other" Naphthyridines:

BNAC 30561

BNAC 30552

Cl

29% toxic deaths in mosquito test (0.1% concentration) Inactive

No report (Will be resubmitted if lost)

B) Polyazaindenes:

These heteroderivatives of the indenyl carbonion, in the opinion of this writer, should definitely be studied in further detail. The following screening results are available:

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BNAC 29595



100% toxic deaths in mosquito test complete sporozoite supp. (0.1% concentration)

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Ц % toxic deaths in mosquito
test
(0.1% concentration) BNAC 29602 CH3 C1 сііз BNAC 29620 9% toxic deaths in mosquito test (0.1% concentration) СНз CH3 BNAC 29639 43% toxic deaths in mosquito ٩I test (0.1% concentration) I СНз СНЗ CH3 100% toxic deaths in mosquito BNAC 29657 test (0.1% concentration) 100% toxic deaths in mosquito ANAF 92664 test (0.1% concentration)

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ANAF 92673



11% toxic deaths in mosquito
test
(0.1% concentration)
(abnormal cocytes)

C) Synthetic Sequences:

A) NAPHTHYRIDINES:





NH2 NH2 EMAE EtO2C NN NH2



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POC13





B) POLYAZAINDENES

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EXPERIMENTAL:

The following will serve to indicate the transformations in the naphthyridine series. The syntheses of the different naphthyridines have been described by W. W. Paudler and T. J. Kress, in Advances in Heterocyclic Chemistry, Vol. 12, Academic Press, New York, N. Y., 1970.

4-Hydroxy-1, 6-Naphthyridine:

4-Hydroxy-1, 6-naphthyridinc-3-carboxylic acid (6.0 g.; 0.031 mole) was placed in a pyrex test tube (2-1/2 x 20 cm.), connected to a vacuum (0.05 mm) and the test tube was lowered into an oven (10 cm deep) at 310°. The tube was kept in the oven for 5-10 min. On cooling, 3.1 g (68°/o theory) of 4-hydroxy-1, 6-naphthyridine (B) was collected from the upper walls of the tube, m.p. 297-301°. The test tube was again placed in the oven and heated at 200°C/0.05 mm for 2 hours; on cooling 0.5 g of additional B was collected. A small sample of B was sublimed and submitted for elemental analysis.
Anal Calcd. for: C₀H₆N₂O: C, 65.74 H, 4.14 N, 19.17 Found: C, 65.60 H, 4.04 N, 21.50

4-Chloro-1, 6-Naphthyridine:

4-Hydroxy-1,6-naphthyridine (0.635 g (0.0043 mole)) and POCL₃ (5 ml) were heated on a steam bath for 1 hour, and the mixture was poured on an excess of crushed ice with vigorous stirring. Sodium acetate was added until solution was neutral to Congo red paper. The solution was then extracted with 300 ml of diethyl ether. The ether solution was washed (twice) with a saturated solution of NaHCO₃, dried over NaSO₄, and evaporated to dryness to yield 0.4 g 4-chloro-1,6-naphthyridine (B) (m.p. 87-89). Some of the material (B) had sublimed out of the reaction mixture and 0.1 g was recovered, giving a total yield of 0.5 g (70°/o of theory), m.p. 87-89° C. and the state of the second second

4-(5-dicthylamino-2-pentylamino)-1,6-Naphthyridino:

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4-Hydroxy-1,6-naphthyridine (0.5 g) dissolved in 5 g of 5-diethylaminopentylamine was heated under reflux for 12 hours. The reaction mixture was then subjected to vacuum distillation to remove the unreacted amine. This material was dissolved in 15 ml of water and extracted with CHCl₃ ($3 \times 125 \text{ ml.}$). The dried (Na₂CO₃) chloroform extracts were evaporated to dryness. The residue was fractionally vacuum distilled. The high-boiling fraction (1.8 g.) (220°C/0.005 nm. Hg) crystallized upon cooling and gave the correct elemental analysis for 4-(5-diethylamino-2-pentylamino)-1,6-naphthyridine.

The following exemplifies the reaction conditions involved in the polyazaindene transformations:

The appropriate chloro-polyazaindene (2 g.) in 6 g of the selected amine (e.g. 1-diethylaminc-4-aminopentane) was heated under reflux for 18 hours. The reaction mixture was diluted with water and extracted with CHCl₃. After removal of the chloroform, the residue was vacuum distilled (1 mm. Hg), affording the unreacted amine. The remainder was then distilled at 0.09 mm. Hg. The high-boiling fraction (140-160°, depending upon the particular polyazaindene employed) was examined by mass spectroscopy and by elemental analysis.

CONCLUSIONS AND RECOMMENDATIONS

An examination of the test data appears to imply that a more extensive investigation of the polyazaindene quarternary salts may well be worthwhile. These ring systems which are relatively new and have been subjected to limited examination only should be readily biodegradable.

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If this is indeed the case, these compounds could then be used as mosquito repellents or as spray agents to control the mosquito population.

I believe such an investigation would be of greater potential use than further study of these compounds as potential antimalarial drugs.

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