## The Preparation of Some Antimalarials with Quaternary Carbon Side Chains

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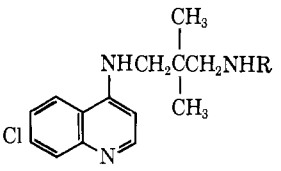
*Received March 7, 1967*

Possible nonbiodegradability of quaternary carbon side chains prompted us to insert such a chain in a typical antimalarial drug. Antimalarials of the following structure were synthesized.



**1**, R = H
**2**, R = $CONH_2$
**3**, R = $CO_2C_2H_5$

It is of interest that **1** and **3** were active in testing against *Plasmodium berghei*, **1** having a curative rating, while **2** was inactive. A similar relationship of the amine and corresponding ureide has been noted previously: 6-methoxy-8-(3-aminopropylamino)quinoline was 50 times more effective as an antimalarial than 6-methoxy-8-(3-ureidopropylamino)quinoline.[1]

Antimalarial compounds with quaternary side chains have been made previously but for the most part are based on the parent structure: 6-methoxy-8-(2,2-dimethyl-3-diethylaminopropylamino)quinoline.[2,3] This compound apparently is about equivalent to pamaquine in antimalarial activity[4] and in addition has some anesthetic action.

Nonbiodegradable side chains have been incorporated in antimalarial compounds previously, but they have been based on a tertiary carbon rather than quaternary carbon structure such as, for example, 7-chloro-4-(4-diethylamino-4-methylbutylamino)quinoline.[5]

### Experimental Section

**7-Chloro-4-(3-amino-2,2-dimethylpropylamino)quinoline (1).**—To 30 g (0.3 mole) of 3-amino-2,2-dimethylpropylamine (Aldrich Chemical Co.), held at 150° with stirring, 10 g (0.05 mole) of 4,7-dichloroquinoline, dissolved in 37 g (0.36 mole) of 3-amino-2,2-dimethylpropylamine, was added dropwise over a period of 8 hr. The excess diamine was removed by distillation at water aspirator pressure, and the residue was dispersed in dilute $NH_3$, filtered, and washed with water. Extraction from a Soxhlet cup with hexane yielded 7.6 g (58%) of white, disklike crystals: mp 94–95°; neutr equiv, 269 (calcd 263.5). The free base tended to react with $CO_2$ to form a high-melting, insoluble compound which could be reconverted to the free base by reextraction in a Soxhlet. The dihydrochloride salt was made by solution in 5% HCl, evaporation to dryness, and recrystallization from isopropyl alcohol to which a few drops of water were added, mp 280–290° dec.

*Anal.*[6] Calcd for $C_{14}H_{20}Cl_3N_3 \cdot H_2O$: Cl, 29.97; N, 11.90. Found: Cl, 29.91; N, 11.83.

**7-Chloro-4-(3-ureido-2,2-dimethylpropylamino)quinoline (2).**—The diamine **1** (2.15 g, 0.0064 mole), 5 g (0.083 mole) of urea, 40 ml of water and 5 drops of concentrated HCl were refluxed for 4 hr during which time crystals deposited. The crystals were recrystallized from alcohol as 1.3 g (37%) of white needles, mp 219–219.5° gas dec.

*Anal.* Calcd for $C_{15}H_{19}ClN_4O$: C, 58.73; H, 6.24; Cl, 11.56; N, 18.28. Found: C, 58.52; H, 6.24; Cl, 11.56; N, 18.26.

**7-Chloro-4-(3-ethylcarbamido-2,2-dimethylpropylamino)quinoline (3).**—To a stirred solution of 2 g (0.0074 mole) of **1** in 10 ml of pyridine, 2.2 g (0.02 mole) of ethyl chlorocarbonate was added dropwise. The contents were then heated to 60° for 15 min, cooled, poured into water, and neutralized carefully with $NH_3$. The precipitate was filtered, washed with water, and recrystallized from 75% aqueous ethanol yielding colorless needles, 1.6 g (65%), mp 161–162°.

*Anal.* Calcd for $C_{17}H_{22}ClN_3O_2$: Cl, 10.57; N, 12.51. Found: Cl, 10.50; N, 12.46.

**Pharmacology.**—Five mice were infected with a lethal dose of *P. berghei* 3 days prior to administration of the chemical at various dose concentrations (see Table I). The chemical was introduced subcutaneously in oil. Mean survival time of infected control mice is 6.5 ± 0.5 days. Extension in survival time of chemically treated mice is interpreted as evidence of antimalarial activity. Number of mice surviving (out of five) after 30 days is suggestive of curative rating.

TABLE I

| Compd | Dose level, mg/kg | Mean survival time, days | No. surviving at end of 30 days (cures) |
|---|---|---|---|
| 1[a] | 40 | 12.6 | |
| | 160 | ... | 1 |
| | 640 | ... | 2 |
| 2 | 160 | 6.6 | |
| | 640 | 9.4 | |
| 3 | 40 | 13.6 | |

[a] Tested as dihydrochloride hydrate.

**Acknowledgment.**—The authors are indebted to the U. S. Army Research and Development for Grant No. DA-49-193-MD-2752 in support of this work.

(1) G. W. Moersch, R. W. Gouley, H. T. Patterson, and H. S. Mosher, *J. Am. Chem. Soc.*, **69**, 2619 (1947).

(2) M. D. Bovet, *Arch. Intern. Pharmacodyn.*, **41**, 103 (1931); *Chem. Abstr.*, **26**, 4865 (1932); O. Y. Magidson and A. L. Midzhoyan, *J. Gen. Chem. USSR*, **7**, 1557 (1937); *Arch. Pharm.*, **272**, 74 (1934); S. Tatsuoka, *et al.*, *J. Pharm. Soc. Japan*, **69**, 33 (1949); **65B**, 52 (1945); *Ann. Rept. Takeda Res. Lab.*, **10**, 16 (1951); *Chem. Abstr.*, **47**, 4886 (1953); S. Tateoka, *J. Pharm. Soc. Japan*, **65**, 1 (1945).

(3) The compounds, 7-chloro-4-(2,2-dimethyl-3-piperazinopropylamino)-quinoline and the reaction product of this with 4,7-dichloroquinoline have been prepared and claimed to display antimalarial activity: Rhone-Poulenc S.A., Belgian Patent 618,068 (Nov 26, 1962); *Chem. Abstr.*, **59**, 6370 (1963).

(4) S. Kuroda, *J. Pharm. Soc. Japan*, **64**, 71 (1944).

(5) SN-10451. D. S. Breslow, M. S. Bloom, J. C. Shivers, J. T. Adams, M. J. Weiss, R. S. Yost, and C. R. Hauser, *J. Am. Chem. Soc.*, **68**, 1232 (1946).

(6) All analyses are by Galbraith Laboratories, Knoxville, Tenn.

## Nitrofuryl Heterocycles. VI.[1] 1-Alkyl- and 1-Aryl-5-(5-nitro-2-furyl)tetrazoles

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*Received January 25, 1967*

In a continuing search for new 5-nitro-2-furyl heterocycles which might possess useful antimicrobial activity, a series of 1-alkyl- and 1-aryl-5-(5-nitro-2-furyl)-tetrazoles was prepared. Syntheses and *in vitro* antibacterial data for these tetrazoles are reported.

**Chemistry.**—The unsubstituted 5-(5-nitro-2-furyl)-tetrazole (**1**) was prepared by the method of Finnegan,

(1) For paper V in this series see H. A. Burch, *J. Med. Chem.*, **10**, 91 (1967).