centrated to an oil, which was distilled under high vacuum. Compound **6** solidified after the reaction mixture was poured into 2 *N* NaOH and left overnight and was crystallized from EtOH–H_2O. The same was the case with **14**, which was crystallized from DMF–H_2O. Compounds **10** and **11** solidified after the dried Et_2O extract was concentrated and were crystallized from EtOAc and petroleum ether (bp 30–60°), respectively.

7-Chloro-1,3-dimethyl-4-(3-diethylaminomethyl-4-hydroxyanilino)-1H-pyrazolo[3,4-*b*]quinoline (15).—A solution of 3-diethylaminomethyl-4-hydroxyaniline (5.7 g, 0.02 mol) in a minimum amount of H_2O was neutralized with dilute NaOH to congo red paper. To this was added 4,7-dichloro-1,3-dimethyl-1H-pyrazolo[3,4-*b*]quinoline (5.0 g, 0.02 mol) and 100 ml of ethoxyethanol. The mixture was refluxed for 4 hr. A clear solution formed after 2 hr and then a yellow solid separated. The reaction was cooled, and the yellow solid was filtered and crystallized from Me_2CO–H_2O.

Acknowledgment.—This work was supported by the U. S. Army Medical Research and Development Command under Research Contract No. DA-49-193-MD-2869. This is Contribution No. 487 from the Army Research Program on Malaria.

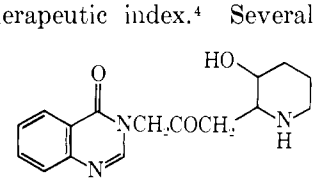
Febrifugine Antimalarial Agents. I. Pyridine Analogs of Febrifugine

MORRIS FISHMAN AND PHILIP A. CRUICKSHANK

Central Research Department,
Chemical Research and Development Center,
FMC Corporation, 8, Princeton, New Jersey 08540

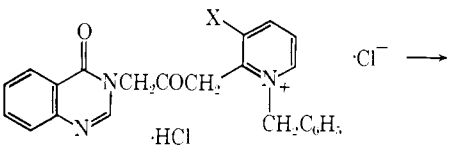
Received September 12, 1969

The alkaloid febrifugine (**1**) has been shown to be the active ingredient of the ancient antimalarial preparation Ch'ang Shan.[1] Although **1** is effective against avian malarias,[2] *Plasmodium cynomolgi* in monkeys,[3] and *Plasmodium berghei* in mice,[4] it has poor activity against *Plasmodium falciparum* and *Plasmodium vivax*;[4-6] in addition, it is a powerful emetic and has a low chemotherapeutic index.[4] Several analogs of **1**[7] showed an improved chemotherapeutic index against *Plasmodium lophurae* in ducks;[2] one analog was tested in limited clinical trails, but was ineffective against *P. vivax* and *P. falciparum*.

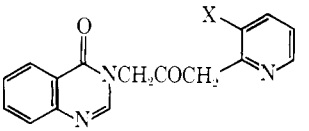


1

We have now prepared 3-[β-keto-γ-(3-hydroxy-2-pyridyl)propyl]-4-quinazolone (**3c**) (Table I), in which the piperidine ring of the side chain has been replaced by pyridine. Baker and McEvoy[8] synthesized the



2



3

a, X = H
b, X = OCH_3
c, X = OH

pyridinium derivative **2b**, and described hydrogenolysis of the corresponding free base to the methyl ether **3b** using Raney Ni catalyst. However, no attempt to prepare **3c** by cleavage of the MeO group was reported.

Working with the desoxy analog **2a**[8] as a model compound, we found that hydrogenolysis of the benzyl group could be effected smoothly over Pd–C, affording 3-[β-keto-γ-(2-pyridyl)propyl]-4-quinazolone (**3a**). The MeO derivative **2b** gave **3b** under identical conditions.

TABLE I
3-[β-KETO-γ-(3-SUBSTITUTED 2-PYRIDYL)PROPYL]-4-QUINAZOLONES

Compd	X	Yield, %	Mp, °C	Formula[c]
3a	H	59	209–212[a]	$C_{16}H_{13}N_3O_2 \cdot 2HCl \cdot H_2O$
3b	OCH_3	41	151–155[b]	$C_{17}H_{15}N_3O_3$
3c	OH	53	211–214 dec[a]	$C_{16}H_{13}N_3O_3 \cdot 2HCl \cdot 1.5H_2O$

[a] Washed with AcMe, Et_2O. [b] Recrystallized from MeOH; lit.[7] mp 157–158°. [c] All compounds were analyzed for C, H, N.

For the preparation of **3c**, the intermediate 1-benzyl-3-hydroxy-2-[β-keto-γ-(4-quinazolon-3-yl)propyl]pyridinium chloride hydrochloride (**2c**) was hydrogenolyzed over Pd–C.

Compounds **3a–c** were assayed against *P. berghei* in mice and *Plasmodium gallinaceum* in chicks.[9] No antimalarial activity was observed.

Experimental Section

Melting points were determined on a Thomas–Hoover "Uni-Melt" capillary melting point apparatus and are not corrected. The ir and nmr spectra were as expected.

1-Benzyl-3-hydroxy-2-[β-keto-γ-(4-quinazolon-3-yl)propyl]-pyridinium Chloride Hydrochloride (2c).—A solution of **2b** (13.7 g, 0.029 mole) in 573 ml of 48% aqueous HBr was refluxed for 18 hr. After cooling, the solution was evaporated to dryness *in vacuo*. A saturated solution of $NaHCO_3$ was added to the residue; the resulting mixture was extracted ($CHCl_3$), and the

(1) J. B. Koepfli, J. A. Brockman, Jr., and J. Moffat, *J. Am. Chem. Soc.*, **72**, 3323 (1950).
(2) R. Hewitt, E. R. Gill, W. S. Wallace, and J. H. Williams, *Am. J. Trop. Med. Hyg.*, **1**, 768 (1952).
(3) F. G. Henderson, C. L. Rose, P. H. Harris, and K. K. Chen, *J. Pharmacol. Exptl. Therap.*, **95**, 191 (1949).
(4) R. N. Chaudhuri, B. N. Dutta, and N. K. Chakravarty, *Indian Med. Gaz.*, **89**, 660 (1954).
(5) G. R. Coatney, W. C. Cooper, W. B. Culwell, W. C. White, and C. A. Imboden, Jr., *J. Natl. Malaria Soc.*, **9**, 183 (1950).
(6) V. A. Trevino, L. A. Reyes, and M. F. Mendoza, *Rev. Inst. Salubridad Enfermedades Trop.* (Mex.), **13**, 253 (1953).
(7) B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.*, **17**, 141, 149, 157, 164 (1952); **18**, 133, 138 (1953).
(8) B. R. Baker and F. J. McEvoy, *ibid.*, **20**, 118 (1955).
(9) The screening tests were carried out at the University of Miami, Miami, Fla., under the direction of Dr. L. Rane. Details of the mouse screen with *P. berghei* have been published [T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967)].

extracts were dried ($MgSO_4$) and concentrated *in vacuo*. An HCl salt of the residue was prepared; yield 3.80 g (24%), mp 178–180°. *Anal.* ($C_{23}H_{20}ClN_3O_3 \cdot HCl \cdot 2H_2O$) C, H, N.

3-[β-Keto-γ-(3-hydroxy-2-pyridyl)propyl]-4-quinazolone (3c).—A solution of **2c** (1.91 g, 0.004 mole) in 100 ml of distilled H_2O was hydrogenated over 0.3 g of 5% Pd–C at atmospheric pressure and temperature. After 18 hr the catalyst was removed, a saturated solution of $NaHCO_3$ was added, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was converted to an HCl salt.

Acknowledgments.—The authors wish to thank Mr. Harold Jarrow for his technical assistance and Miss Christine Miles for help in interpreting the nmr spectra. This work was supported by a research contract with the U. S. Army Medical Research and Development Command (DA-49-193-MD-3020). This is Contribution No. 677 to the Army Research Program on Malaria.

Synthesis and Antimalarial Activity of Amodiaquine Analogs[1]

NED D. HEINDEL AND JAMES MOLNAR[2]

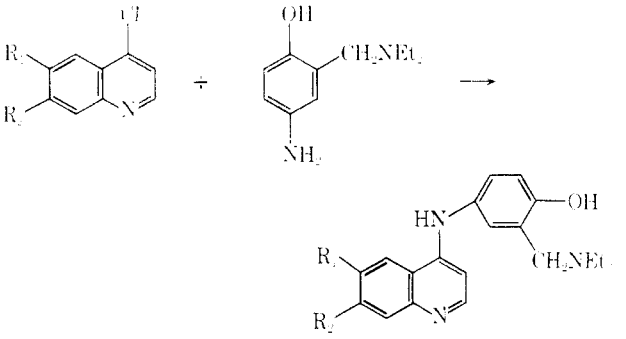
Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania 18015

Received August 15, 1969

Ever since the initial discovery that certain α-dialkylamino-*o*-cresols possessed antimalarial activity,[3] chemists have tried to incorporate this moiety in a host of candidate drugs. One such agent, 7-chloro-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline or amodiaquine, was first prepared by Burckhalter's group.[4] Today, amodiaquine is one of the most widely used drugs for the strains of parasites susceptible to its schizontocidal properties. It displays gametocytocidal action against *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae* but not against *Plasmodium falciparum*.[5] Substituted analogs of amodiaquine have been prepared, but virtually none of these appeared to be superior to the parent compound.[4,6]

We wish to report the synthesis of three related 4-aminoquinolines bearing the same pendant phenolic Mannich base at C-4 as amodiaquine. In primary mouse screens against *Plasmodium berghei* and in *Plasmodium gallinaceum* infected chicks, these materials displayed impressive antimalarial acitivity.

The synthetic route in all cases involved displacement upon the corresponding 4-chloroquinoline by the deacetylated, *in situ* generated 4-hydroxy-3-diethylaminomethylaniline. The requisite 4-chloroquinolines were prepared by standard methods from the 2-carbomethoxy-4(1H)-quinolones[7] by saponification, decarboxylation, and chlorination. The selection of the 6-



1, $R_1 = OCH_3$; $R_2 = Cl$
2, $R_1 = OCH_3$; $R_2 = F$
3, $R_1 = OCH_3$; $R_2 = CF_3$
amodiaquine, $R_1 = H$; $R_2 = Cl$

methoxy- and 7-halo-containing functions for incorporation in these candidate materials was predicted by their demonstrated potency in many other aminoquinoline antimalarials.

Biological Activity.—Shown in Table I are comparison data for amodiaquine[8] and our synthetic analogs in the Rane mouse and chick profiles. From this primary screening it would appear that **1** and **2** are somewhat more active against *P. berghei* than amodiaquine itself. These substances effected four cures out of five test animals at the 160-mg/kg level *vs.* three for amodiaquine. Comparison at the 40-mg/kg level in the mouse screen permitted the same conclusion. The trifluoromethyl analog **3** is *less active than the comparison* compounds.

Experimental Section[9]

Melting points were obtained in microcapillaries on a Mel-Temp apparatus and are uncorrected. Nmr spectra were obtained on a Varian A-60 spectrometer and are reported in δ ppm units *vs.* TMS standard.

6-Methoxy-7-trifluoromethyl-4(1H)-quinolone.—A solution of 0.04 mole of methyl 6-methoxy-7-trifluoromethyl-4(1H)-quinolone-2-carboxylate[7] in 40 ml of 10% (w/w) aqueous NaOH was refluxed for 1.5 hr, filtered while hot, cooled to ice-bath temperatures, and neutralized with 6 *N* HCl. The precipitated acid was collected, washed well (H_2O), vacuum dried, and added as a powder in small portions to 50 ml of boiling Ph_2O. After the addition process, which required approximately 1 hr to minimize frothing, the medium was heated for an additional 10 min, cooled, diluted with 800 ml of 30–60° petroleum ether, and filtered. The crude product (7.3 g or 75%) was purified by thorough washing with hot petroleum ether and double vacuum sublimation, mp 256–264° dec. *Anal.* ($C_{11}H_8F_3NO_2$) C, H, N.

4-Chloro-6-methoxy-7-trifluoromethylquinoline.—A mixture of 0.46 mole of 6-methoxy-7-trifluoromethyl-4(1H)-quinolone and 200 ml of $POCl_3$ was refluxed for 2 hr. Excess $POCl_3$ was removed by vacuum distillation and the residue was cooled and poured over 300 g of chopped ice. After 1 hr, the solution was adjusted to pH 9 with aqueous NH_3 and the precipitated halo heterocycle was isolated by filtration, yield 106 g (88%). An analytical sample was prepared by vacuum sublimation, mp 153–155°. *Anal.* ($C_{11}H_7ClF_3NO$) C, H, N.

4-Chloro-6-methoxy-7-fluoroquinoline.—A solution of 0.16

(1) Supported in part by Contract DA-49-193-MD-3011 from the U. S. Army Medical Research and Development Command. This publication represents Contribution No. 698 from the Army Research Program on Malaria.

(2) NDEA Predoctoral Fellow 1968–1969.

(3) J. H. Burckhalter, F. H. Tendick, E. M. Jones, W. F. Holcomb, and A. L. Rawlins, *J. Am. Chem. Soc.*, **68**, 1894 (1946). For recent work in this area see W. G. Duncan and D. W. Henry, *J. Med. Chem.*, **12**, 711 (1969).

(4) J. H. Burckhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Holcomb, and A. L. Rawlins, *J. Am. Chem. Soc.*, **70**, 1363 (1948).

(5) "Chemotherapy of Malaria," World Health Organization Technical Report No. 375, Geneva, 1967, p 25.

(6) J. H. Burckhalter, W. H. Edgerton, and J. A. Durden, *J. Am. Chem. Soc.*, **76**, 6089 (1954), and references cited therein.

(7) N. D. Heindel, I. S. Bechara, P. D. Kennewell, J. Molnar, C. J. Ohnmacht, S. M. Lemke, and T. F. Lemke, *J. Med. Chem.*, **11**, 1218 (1968).

(8) Testing data in the Rane mouse screen for amodiaquine (Camoquin® or SN 10,751 are equivalent names) was provided by Dr. Bing T. Poon of the Walter Reed Army Institute of Research.

(9) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within ± 0.4% of the theoretical values.