Antimalarials. II.[1a] α-(2-Piperidyl)- and α-(2-Pyridyl)-2-trifluoromethyl-4-quinolinemethanols[1b]

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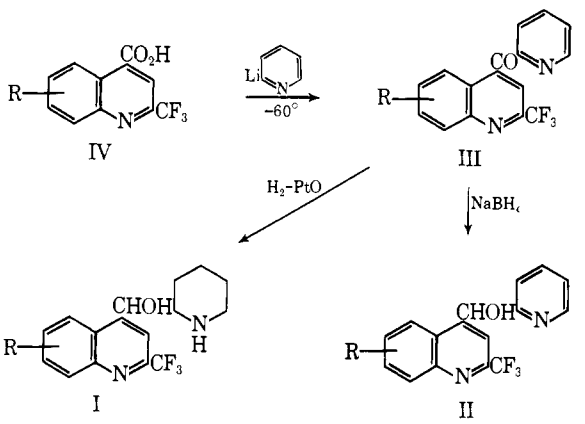
A series of α-(2-piperidyl)-2-trifluoromethyl-4-quinolinemethanols was synthesized in the hope that replacement of 2-aryl by 2-CF_3 would decrease the photosensitizing qualities of the 2-aryl analogs. All of the 2-trifluoromethyl derivatives carrying 6- or 8-CH_3, -CH_3O, or -Cl substituents increased the survival time of mice infected with *Plasmodium berghei*, but they retained photosensitizing properties, albeit less than the 2-aryl-substituted analogs.

A number of α-(2-piperidyl)-4-quinolinemethanols[1a,2,3] have high antiplasmodial activity in avian infections.[4] High activity is associated with a substituent in the 2 position of the quinoline nucleus, particularly phenyl, which will prevent oxidation at that position; the cinchona alkaloids and related compounds are rapidly biotransformed in man to the inactive carbostyril derivatives.[5] The most promising compound, 6,8-dichloro-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol, was eighty times more active than quinine against *Plasmodium cathemerium* in the duck,[4] but it produced severe photosensitivity and did not find clinical use in man.[6] There is renewed interest in this type of antimalarial, both because it is firmly bound to host tissues and slowly released and therefore has repository properties, and because it has shown one of the highest recorded activities against *Plasmodium berghei* in mice.[7] It has been theorized that phototoxicity arises because of the increased resonance conjugation from the 2-aryl group;[7] a trifluoromethyl group in lieu of a 2-aryl group may modify this property and still prevent oxidation to the carbostyril. We are therefore reporting the synthesis and antimalarial activity of a series of α-(2-piperidyl)-2-trifluoromethyl-4-quinolinemethanols (I) and of the corresponding α-(2-pyridyl) compounds (II) which represent a new type of analog.

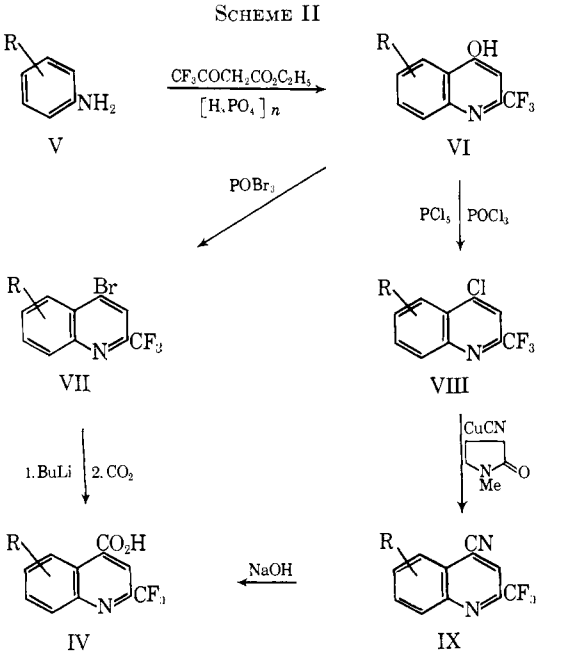
The synthetic approach to amino alcohols of types I and II, starting from the corresponding quinoline-4-carboxylic acids (IV), is outlined in Scheme I and reduces the number of steps from six[2,3] to two.[1a] Addition of 2-lithiopyridine to the acids at −60°, followed by hydrolysis, gave the pyridyl ketones (III). Catalytic hydrogenation of III selectively reduced the carbonyl group and the pyridine nucleus without attacking the qunoline nucleus, giving the amino alcohols of type I, while reduction with sodium borohydride gave amino alcohols of type II.

SCHEME I



The 2-trifluoromethylcinchoninic acids (IV) were prepared by the route outlined in Scheme II. Condensation of a substituted aniline (V) with ethyl 4,4,4-trifluoroacetoacetate[8] in the presence of polyphosphoric

SCHEME II



(1)(a) Paper I: D. W. Boykin, Jr., A. R. Patel, R. E. Lutz, and A. Burger, *J. Heterocycl. Chem.*, **4**, 459 (1967). (b) This work was supported by the U. S. Army Medical Research and Development Command, Contract No. DA-49-193-MD-2955, Contribution No. 297, A. Burger and R. E. Lutz co-responsible investigators.

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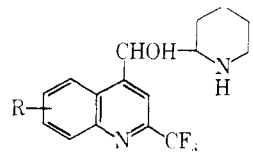
TABLE I

ANTIMALARIAL ACTIVITY OF α-(2-PIPERIDYL)-2-TRIFLUOROMETHYL-4-QUINOLINEMETHANOLS[a]



R	Dose, mg/kg (no. cured out of 5 mice)	Increase in mean survival time, days
6-OCH_3	80 (1)	...
	160 (1)	...
	320 (2)	...
	640 (4)	...
6-CH_3	160 (0)	7.1
	320 (0)	7.5
	640 (0)	8.5
8-CH_3	160 (0)	7.3
	320 (1)	...
	640 (5)	...
6,8-$(CH_3)_2$	160 (0)	8.3
	320 (2)	...
	640 (3)	...
6-Cl	160 (0)	7.5
	320 (0)	8.7
	640 (1)	...

[a] Tests were carried out in mice infected with *P. berghei*.[12] Test results were supplied by Walter Reed Army Institute of Research, Washington, D. C. Enhancement in survival time of treated animals is regarded as evidence of antimalarial activity. A compound is considered active if the mean survival time of the treated group is more than double the mean survival time (7.0 ± 0.5 days) of the control group; it is said to be curative when the animal survives up to 60 days.

acid gave only the 4-quinolinols (VI). This reaction with ethyl acetoacetate itself gives a mixture of the 2- and 4-quinolinols, depending upon whether the amine reacts with the ester or the β-keto group.[9] The electron-withdrawing power of the trifluoromethyl group apparently leads to exclusive reaction of the (now) electronegative β-keto group with the amine.[10] The 4-quinolinols were brominated[11] or chlorinated[10] with phosphorus oxybromide or oxychloride in excellent yields. The 4-bromoquinolines (VII) reacted readily with *n*-butyllithium at −35°, and treatment of the resulting lithioquinolines with dry CO_2 gave the required cinchoninic acids (IV). The 4-chloroquinolines (VIII) were converted to the corresponding nitriles by reaction with cuprous cyanide in N-methylpyrrolidone,[12] and the nitriles were then hydrolyzed to the cinchoninic acids.

Biological Data.—The antimalarial test[13] data for the α-(2-piperidyl)-2-trifluoromethyl-4-quinolinemethanols are listed in Table I. These compounds possessed moderate antimalarial activity but were photosensitizing. The unsubstituted α-2-piperidyl-2-trifluoromethyl-4-quinolinemethanol, however, was inactive. The corresponding α-(2-pyridyl) compounds were inactive, but did not cause photosensitization.

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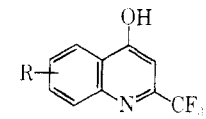
Experimental Section

Melting points were determined in a capillary melting point bath and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

In accordance with previous observations[11] regarding the properties of 2-trifluoromethylquinolines, the compounds described herein did not form salts due to the decreased basicity of the quinoline nitrogen atom. The 2-trifluoromethyl-4-quinolinols (Table II) and 2-trifluoromethyl-4-chloroquinolines (Table III) were prepared according to Dey and Joullié.[10]

TABLE II

2-TRIFLUOROMETHYL-4-QUINOLINOLS

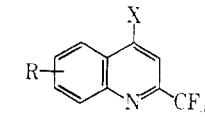


R	Yield, %[a]	Mp, °C[a]	Formula[b]
6-Cl	70	274–275	$C_{10}H_5ClF_3NO$[c]
8-Cl	55	134–135	$C_{10}H_5ClF_3NO$
6,8-Cl_2	58	180–181	$C_{10}H_4Cl_2F_3NO$
6,8-$(CH_3)_2$	65	150–151	$C_{12}H_{10}F_3NO$

[a] Recrystallized from EtOH. [b] All compounds were analyzed for C, H, N. Their ir spectra were as expected. [c] N: calcd, 5.32; found, 5.82.

TABLE III

2-TRIFLUOROMETHYLQUINOLINE DERIVATIVES



R	X	Yield, %[a]	Mp, °C[a]	Formula[b]
H	Br	80	38–39	$C_{10}H_5BrF_3N$
H	CN	63	130–131	$C_{11}H_5F_3N_2$[c]
6-CH_3	Br	91	70–71	$C_{11}H_7BrF_3N$
6,8-$(CH_3)_2$	Br	95	115–116	$C_{12}H_9BrF_3N$
6,8-$(CH_3)_2$	Cl	95	99–101	$C_{12}H_9ClF_3N$
6,8-$(CH_3)_2$	CN	76	126–127	$C_{13}H_9F_3N_2$
8-CH_3	CN	65	80–81	$C_{12}H_7F_3N_2$
6-Cl	Br	90	119–120	$C_{10}H_4BrClF_3N$
6-Cl	Cl	92	103–104.5	$C_{10}H_4Cl_2F_3N$[d]
6-Cl	CN	51	142–143	$C_{11}H_4ClF_3N_2$
8-Cl	Cl	84	58.5–59.5	$C_{10}H_4Cl_2F_3N$
8-Cl	CN	42	167–169	$C_{11}H_4ClF_3N$
6,8-Cl_2	Br	97	75–76	$C_{10}H_3BrCl_2F_3N$
6,8-Cl_2	Cl	88	75–76	$C_{10}H_3Cl_3F_3N$
6-OCH_3	Br	92	124–125	$C_{11}H_7BrF_3NO$

[a] Recrystallized from EtOH. [b] All compounds were analyzed for C, H, N. Their ir spectra were as expected. [c] N: calcd, 12.61; found, 12.20. [d] C: calcd, 45.13; found, 45.56.

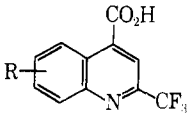
2-Trifluoromethyl-4-bromoquinolines (Table III).—In a typical preparation, a mixture of 2-trifluoromethyl-4-quinolinol (30 g, 0.14 mole) and $POBr_3$ (57 g, 0.2 mole) was stirred at 140° for 3 hr. The warm mixture was poured into ice-water (600 ml), and the solid material was filtered off and recrystallized from EtOH, yield 31 g.

2-Trifluoromethylcinchoninic Acids (Table IV). A.—In a typical example, a solution of 4-bromo-2-trifluoromethylquinoline (55 g, 0.2 mole) in dry ether (600 ml) was added over 15 min to an Et_2O solution of *n*-BuLi (prepared from 3.5 g of Li wire and 35 g, 0.25 mole, of *n*-BuBr), stirred under N_2 at −35° for 20 min, and was then poured, with vigorous stirring, onto powdered solid CO_2. After removal of ether, the residue was dissolved in H_2O and the acid precipitated by careful acidification with AcOH. The collected solid was recrystallized from EtOAc, yield 31 g.

B.—The 4-chloroquinolines were converted to the 4-cinchoninonitriles (Table III) by the method of Newman and Boden.[12] In a typical hydrolysis, a mixture of 8-methyl-2-

TABLE IV

2-TRIFLUOROMETHYLQUINOLINECARBOXYLIC ACIDS

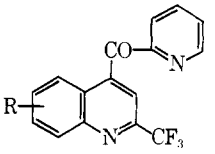


R	Method	Yield, %[a]	Mp, °C[b]	Formula[c]
H	A, B	65, 51	196–197	$C_{11}H_6F_3NO_2$
6-CH_3	A	67	215–216	$C_{12}H_8F_3NO_2$
8-CH_3	B	51	199–200	$C_{12}H_8F_3NO_2$
6,8-$(CH_3)_2$	A, B	62, 65	224–226	$C_{13}H_{10}F_3NO_2$
6-Cl	A, B	72, 74	226–227	$C_{11}H_5ClF_3NO_2$[d]
8-Cl	B	18	210–212	$C_{11}H_5ClF_3NO_2$[e]
6-OCH_3	A	63	238–239	$C_{12}H_8F_3NO_3$

[a] Yield from sequence B is based on the starting 4-chloroquinolines. [b] Recrystallized from EtOAc. [c] See footnote *b*, Table III. [d] C: calcd, 47.93; found, 47.36. [e] No N analysis.

TABLE V

2-TRIFLUOROMETHYL-4-PYRIDOYLQUINOLINES



R	Yield, %	Mp, °C[a]	Formula	Analyses
H	63	130–132	$C_{16}H_9F_3N_2O$	C, H, N
6-CH_3	60	125–126	$C_{17}H_{11}F_3N_2O$	C, H
8-CH_3	64	98–99	$C_{17}H_{11}F_3N_2O$	C, H, N
6,8-$(CH_3)_2$	73	119–120	$C_{18}H_{13}F_3N_2O$	C, H
6-Cl	48	152–153	$C_{16}H_8ClF_3N_2O$	C, H
8-Cl	31	116–117	$C_{16}H_8ClF_3N_2O$	C, H
6,8-Cl_2	34	138–139	$C_{16}H_7Cl_2F_3N_2O$	C, H, N
6-OCH_3	67	132–133	$C_{17}H_{11}F_3N_2O_2$	C, H, N

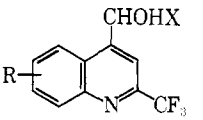
[a] Recrystallized from EtOH.

trifluoromethylcinchoninonitrile (23.6 g, 0.1 mole) and a solution of NaOH (12 g, 0.3 mole) in H_2O (50 ml) and EtOH (120 ml) was stirred under reflux for 12 hr. The solution was evaporated to dryness, and the residue was dissolved in H_2O and filtered through Celite. The clear filtrate was acidified by dropwise addition of AcOH, and the white precipitate was collected and recrystallized from EtOAc, yield 20 g.

2-Pyridyl 4-Quinolyl Ketones (Table V).—To an ethereal solution of *n*-butyllithium (0.05 mole) at −60° was added rapidly 2-bromopyridine (8 g, 0.05 mole), and the brown mixture was stirred at −60° for 1 hr. Finely powdered 6-methoxy-2-trifluoromethylcinchoninic acid (5.4 g, 0.02 mole) was added all at once and the mixture was stirred at −60° for 2 hr. It was allowed to warm to room temperature and then hydrolyzed by addition of H_2O. The ether layer was dried ($MgSO_4$) and distilled to give a yellow solid, which was recrystallized from EtOH as yellow needles, yield 4.7 g.

TABLE VI

2-TRIFLUOROMETHYLQUINOLINE-4-METHANOL DERIVATIVES



R	X[a]	Yield, %	Mp, °C	Recrystn solvent	Formula[b]
H	Pip	50	254–255	EtOH	$C_{16}H_{17}F_3N_2O \cdot HCl$
H	Pyr	80	115–116	MeOH	$C_{16}H_{11}F_3N_2O$
6-CH_3	Pip	66	254–256	EtOH	$C_{17}H_{19}F_3N_2O \cdot HCl$
6-CH_3	Pyr	91	139–140	EtOH	$C_{17}H_{13}F_3N_2O$
8-CH_3	Pip	60	284–286	EtOH	$C_{17}H_{19}F_3N_2O \cdot HCl$
8-CH_3	Pyr	100	120–122	MeOH–C_6H_6	$C_{17}H_{13}F_3N_2O$
6,8-$(CH_3)_2$	Pip	55	279–280	EtOH	$C_{18}H_{21}F_3N_2O \cdot HCl$
6,8-$(CH_3)_2$	Pyr	86	128–129	MeOH–C_6H_6	$C_{18}H_{15}F_3N_2O$
6-Cl	Pip	45	265–266	EtOH	$C_{16}H_{16}ClF_3N_2O \cdot HCl$
6-Cl	Pyr	89	149–150	EtOH–petr ether[d]	$C_{16}H_{10}ClF_3N_2O$
8-Cl	Pip	28	248–250	EtOH	$C_{16}H_{18}ClF_3N_2O \cdot HCl$[c]
8-Cl	Pyr	78	124–125	MeOH–C_6H_6	$C_{16}H_{10}ClF_3N_2O$
6,8-Cl_2	Pip	33	262–264	EtOH	$C_{16}H_{15}Cl_2F_3N_2O \cdot HCl$
6,8-Cl_2	Pyr	82	138–139	EtOH–petr ether[d]	$C_{16}H_9Cl_2F_3N_2O$
6-OCH_3	Pip	52	241–242	EtOH	$C_{17}H_{19}F_3N_2O_2 \cdot HCl$
6-OCH_3	Pyr	100	172–173	MeOH	$C_{17}H_{13}F_3N_2O_2$

[a] Pip = 2-piperidyl; Pyr = 2-pyridyl. [b] See footnote *b*, Table III. [c] N: calcd, 7.35; found, 7.80. [d] Bp 30–60°.

α-(2-Piperidyl)-2-trifluoromethyl-4-quinolinemethanols (Table VI).—A solution of 6-methoxy-2-trifluoromethyl-4-quinolyl 2-pyridyl ketone (4 g) in EtOH (300 ml) containing 1 molar equiv of HCl was shaken with PtO_2 (200 mg) at 2.8 kg/cm² under H_2. The reduction was stopped when 4 equiv of H_2 had been absorbed; the catalyst was filtered off, and the residue was concentrated until crystallization began. Recrystallization from EtOH gave white needles, yield 2.2 g.

α-(2-Pyridyl)-2-trifluoromethyl-4-quinolinemethanols (Table VI).—$NaBH_4$ (0.26 g, 0.007 mole) was added portionwise to a stirred solution of 6-methoxy-2-trifluoromethyl-4-quinolyl 2-pyridyl ketone (2.2 g, 0.007 mole) in MeOH (200 ml), and the mixture was stirred at room temperature for 2 hr. MeOH was removed under reduced pressure and the residue was taken up in ether, washed (H_2O), and dried ($MgSO_4$). The ether was distilled, and the residue was recrystallized from MeOH, yield 2.3 g.

Acknowledgment.—This study has profited from frequent and helpful discussions with Professor R. E. Lutz and Drs. D. W. Boykin, Jr., and A. R. Patel of the University of Virginia.