Antimalarials. 7. Bis(trifluoromethyl)-α-(2-piperidyl)-4-quinolinemethanols[1]

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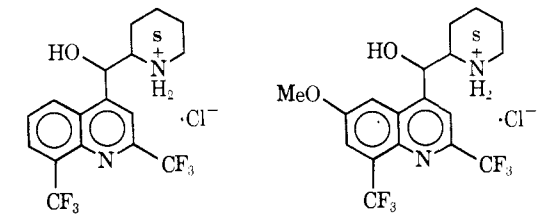
The 2,6-, 2,7-, and 2,8-bis(trifluoromethyl)-α-(2-piperidyl)quinolinemethanols, and the 6-methoxy derivative of the latter, have been synthesized from the appropriate 4-quinolones, through the 4-bromoquinolines, CO_2 carboxylations of the 4-Li derivatives, additions of 2-PyrLi, and H_2/Pt reductions of the resulting pyridyl ketones. An attempt to obtain the 2,5-bis(trifluoromethyl) analog utilized the corresponding 4-quinolone formed as a by-product in the synthesis of the 2,7 isomer; addition of the 4-Li derivative to 2-pyridaldehyde gave the α-pyridylmethanol, but subsequent H_2/Pt reduction of this gave only the 4-dihydroquinolone-α-(2-piperidyl)methanol.

The α-(2-piperidyl)-2-trifluoromethyl-4-quinolinemethanols carrying OCH_3, CH_3, or Cl in positions 6 or 8 have consistently shown only moderate or slight antimalarial activities against *Plasmodium berghei* in mice, and they were also moderately phototoxic.[3a] The synthesis of the 2,8-bis(trifluoromethyl) analog, **1**, begun before decision had been made to terminate work in this series, was nevertheless completed[1c] for comparison with the 9-phenanthrene amino alcohols where 3,6-disubstitution of CF_3 groups had brought a very considerable increase in antimalarial activity.[4] When this compd **1** proved to be curative at 20 mg/kg[1d,5] and relatively nonphototoxic,[1d,6] the synthesis of the 2,7 and 2,6 analogs **3** and **4** were undertaken to initiate evaluation of the pharmacological effects of different nuclear positions of 2 or more CF_3 groups with or without additional substituents.



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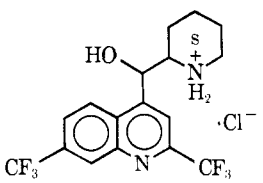

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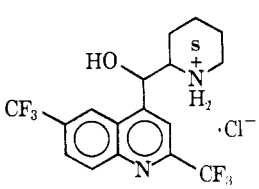

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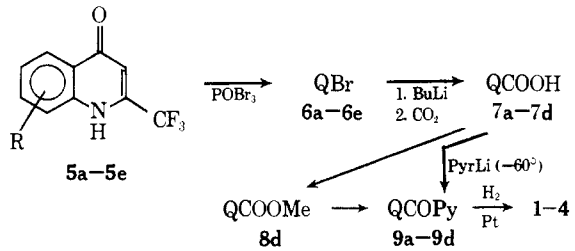
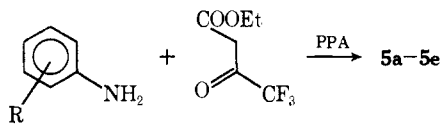
Four target drugs **1–4** were synthesized each in 4 steps from the corresponding 4-quinolones **5a–5d** by adaptations of known procedures,[3,7] as follows. Conversion by $POBr_3$ into the 4-bromoquinolines **6a–6d** and CO_2 carboxylation of the 4-Li derivative gave cinchoninic acids **7a–7d**. Addition of 2-PyrLi gave the pyridyl ketones **9a–9d**, but only **9a,b** were obtained in good yields; **9d** was best obtained through the ester **8d**. Reductions with H_2/Pt gave good yields of **1** and **2**, but mediocre yields of **3** and **4**.



Q = substituted 4-quinolyl; Pyr = 2-pyridyl; **a**, R = 8-CF_3; **b**, R = 8-CF_3-6-OMe; **c** R = 7-CF_3; **d**, R = 6-CF_3; **e**, R = 5-CF_3

The 4-quinolones **5a–5e** were obtained by PPA condensation of the appropriate trifluoromethylaniline (**10**) and ethyl 4,4,4-trifluoroacetoacetate in adaptation of previously described procedures.[3a,7] However, 3-trifluoromethylaniline gave a mixture of 2,7- and 2,5-bis-



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(trifluoromethyl)quinolones, **5c** and **5e**; this was best converted directly to a mixture of the 4-bromo derivatives, at which point it was separated into **6c** and **6e**.

The addition of 2-PyrLi to 2,6-bis(trifluoromethyl)-choninic acid (**7d**) gave, besides 27% of the pyridyl ketone **9d**, a 6% yield of a second product to which the structure **11** is assigned on the basis of anal. and ir, nmr, and mass spectra. The latter indicated formation of a fragment of relative intensity 100 corresponding to loss of Bu, and another of 32 corresponding to loss of Pyr.

The formation of **11** is reasonably interpreted in terms of reversible Michael addition of 2-PyrLi to the Li carboxylate of **7d** to give dianion **12**, subsequent loss of CO_2 giving the new dianion **13**, followed by C-alkylation by BuBr present in the reagent to give the monoanion of **11**. It may be significant that in the PyrLi reaction with ester **8d**, **11** was not detected as a product; and the pyridyl ketone **9d** was obtained in 55% yield.

In utilizing the limited amount of 2,5-bis(trifluoromethyl)-4-quinolone (**5e**), produced in the synthesis

(1) (a) This work was supported by the U. S. Army Medical Research and Development Command, Office of the Surgeon General; Contract No. DA-48-193-MD-2955, R. E. Lutz, Responsible Investigator. (b) Contribution No. 927 of the Army Research Program on Malaria. (c) Presented in part at the Southest Regional American Chemical Society Meeting, Richmond, Va., Nov 1969, Abstract 255. (d) Antimalarial test results were supplied by the Walter Reed Army Institute of Research.

(2) Postdoctoral Research Associates.

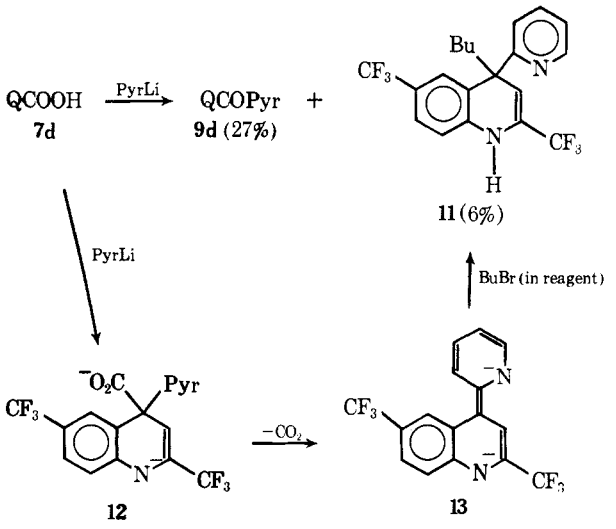
(3) (a) R. M. Pinder and A. Burger, *J. Med. Chem.*, **11**, 267 (1968); (b) A. R. Patel, C. J. Ohnmacht, D. P. Clifford, A. H. Crosby, and R. E. Lutz, *ibid.*, **14**, 198 (1971); (c) D. W. Boykin, A. R. Patel, and R. E. Lutz, *ibid.*, **11**, 273 (1968).

(4) E. A. Nodiff, *et al.*, in preparation.

(5) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

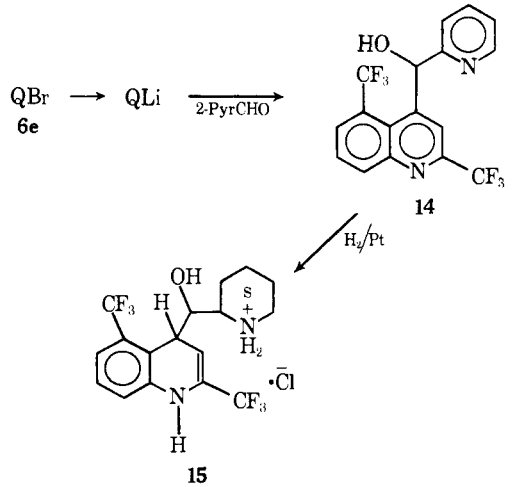
(6) W. E. Rothe and D. P. Jacobus, *ibid.*, **11**, 366 (1968).

(7) A. S. Dey and M. M. Jouillé, *J. Heterocycl. Chem.*, **2**, 113 (1965).



of the isomers from 3-trifluoromethylaniline, it was feared that the PyrLi addition might be impeded by steric effects of the 5 substituent. Consequently this quinolone was converted through the 4-bromoquinoline **6e** to the Li derivative which was added successfully to 2-pyridaldehyde, giving the pyridyl alcohol **14** (37%) after tedious chromatographic work-up. Unfortunately, catalytic hydrogenation of this gave the dihydroquinoline which is presumed to be α-(2-piperidyl)-2,5-bis(trifluoromethyl)-1,4-dihydro-4-quinolinemethanol·HCl (**15**; nmr; 4 H, exchangeable by D_2O). Possibly this overreduction was facilitated by the appreciable release of steric strain in the quinoline 4,5-group nonbonded interaction which, conversely, would in some degree oppose the otherwise facile oxidation of the dihydroquinoline to the quinoline.

It is noteworthy that all of the reductions, of the four 2-pyridyl ketones **9a–9d** and also the 2-pyridylmethanol **14**, were in the main stereospecific, giving in each case as the isolated pure product one only of the theoretically possible diastereoisomers (racemates). It is hoped that the stereoisomer of **1** will be isolated in the large scale synthesis now under way,[8] and that ir and nmr study will lead to configurational and conformational assignments, both here and, by analogy, in other cases where only one form has been obtained.



Biological Activities.[1d,5] Antimalarial tests[1d,5] (Table I) showed target compounds **1–4** to be curative against

(8) E. E. Hamel, Aerojet Solid Propulsion Co., work in progress.

TABLE I[e]

ANTIMALARIAL ACTIVITIES[a] AGAINST *P. berghei* IN MICE

	Antimalarial act. Dose, mg/kg				
Compd	10	20	40	80	160
1[c]	12.5[a]	4 C[b]	5 C		
2[d]	11.5	1 C	2 C	5 C	
3	1.9	10.9	3 C	5 C	
4	0.7	7.7	14.3	2 C	5 C

[a] Expressed as increases in mean survival times, in days, and [b] numbers of cures [C = cures], in 5 mice. A compd is considered to be active if the mean survival time of the treated group is more than double that of the control group (7.0 ± 0.5 days); and it is said to be curative when the animal survives up to 6 days. [c] Also active at 120 mg/kg against *P. gallinacium* in chicks.[1d,5] [d] The corresponding 2-pyridyl ketone was inactive at 640 mg/kg. [e] See ref **1d** and ref **5**.

P. berghei in mice at 160 mg/kg or lower, and to compare very favorably with the 3,6-disubstituted 9-phenanthrene amino alcohols.[4] Furthermore, the phototoxicities of these compds were relatively low.[1d,6] The most active of these, the 2,8-bis(trifluoromethyl) compd, **1**, which was curative at 20 mg/kg, has now been prepared on a large scale[8] and is being evaluated further with promising results.

The one dihydroquinoline α-(2-piperidyl)methanol (**15**) with 2,5-bis(trifluoromethyl) groups obtained, proved to be inactive toward *P. berghei* in mice.[1d,5]

Because of the suspicion formerly held[6,9] that there might be a relation between phototoxicity and uv absorptivities, these values have been assembled in Table II.

TABLE II

UV ABSORPTIVITIES OF AMINO ALCOHOLS 1–4 IN MeOH

Uv absorptivities Compd							
1		**2**		**3**		**4**	
nm	ϵ^{-3}	nm	ϵ^{-3}	nm	ϵ^{-3}	nm	ϵ^{-3}
222	46.7	236	52.5	226	46.0	225	42.1
283	6.6	284	5.8	281	5.4	279	5.8
304	4.0	294	5.3	304[a]	3.0	309	3.2
318	3.1	326	7.4	318	1.6	322.5	3.1
		338	8.5				

[a] Shoulder.

Experimental Results[10]

5-Methoxy-2-nitrobenzotrifluoride, mp 30–32° (lit.,[11] mp 39°), was prepd in 89% yield by refluxing a soln of 5-chloro-2-nitrobenzotrifluoride in KOH–MeOH soln (4 hr).[11]

5-Methoxy-2-aminobenzotrifluoride (**10b**) was prepd by hydrogenation of the above nitro compd (43.25 g, 0.195 mole) with 10% Pd/C (0.15 g) in 200 ml of MeOH (5 hr). The yield of distd product was 33.2 g (89%), bp 97–98° (9 mm). The hydrochloride was recrystd from EtOH; mp 229–231° dec. *Anal.* ($C_8H_9ClF_3NO$) C, H, N.

Quinolones 5a–5e, bromoquinolines 6a–6e, cinchoninic acids 7a–7d, pyridyl ketones 9a–9d, and **α-(2-pyperidyl)methanols 1–4,** and **15** were prepd by adaptations of previously described procedures.[3,7] Specific minor variances are listed in Table III and in the following paragraphs.

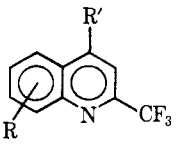
(9) E. R. Arkinson and A. J. Puttick, **13**, 537 (1970), and refs cited.

(10) Satisfactory spectra were obtained, where required for structural determination, and randomly in other cases. Instruments used were Thomas-Hoover apparatus for mp; ir, Perkin-Elmer 337; nmr, Hitachi-P.E. R-20; mass spectrograph, Hitachi P.E. RMU 6E. Microanalyses (Galbraith Lab, Inc.) were correct within ±0.4%.

(11) J. H. Brown, C. W. Suckling, and W. B. Whalley, *J. Chem. Soc.*, 895 (1949).

TABLE III

2-TRIFLUOROMETHYL-4-QUINOLINE DERIVATIVES[a]



Compd	R	R′	Mp, °C	% yield	Analysis[p]
5a[d,e]	8-CF_3	OH	128–132	75[k]	$C_{11}H_5F_6NO$[q]
5b[d,f]	6-OMe-8-CF_3	OH	172–174	31	$C_{12}H_7F_6NO_2$
5c[b,c]	7-CF_3	OH	289–290	*l*	$C_{11}H_5F_6NO$[q]
5d[c,d]	6-CF_3	OH	279–283	70	$C_{11}H_5F_6NO$[q]
5e[c,b]	5-CF_3	OH	319–321 dec	*l*	$C_{11}H_5F_6NO$[q]
6a[b,d]	8-CF_3	Br	62–64	95	$C_{11}H_4BrF_6N$[q]
6b[b,d]	6-OMe-8-CF_3	Br	164–166	91	$C_{12}H_6BrF_6NO$
6c[b,d]	7-CF_3	Br	106–108	67[m]	$C_{11}H_4BrF_6N$[q]
6d[d]	6-CF_3	Br	73–75	77	$C_{11}H_4BrF_6N$[q]
6e[d,g]	5-CF_3	Br	49–51	18[m]	$C_{11}H_4BrF_6N$[q]
7a[h]	8-CF_3	COOH	228–230.5	86	$C_{12}H_5F_6NO_2$[q]
7b[d,h]	6-OMe-8-CF_3	COOH	246–248	57	$C_{13}H_7F_6NO_3$
7c[h]	7-CF_3	COOH	199–200.5	90	$C_{12}H_5F_6NO_2$[q]
7d[h]	6-CF_3	COOH	216–218	87	$C_{12}H_5F_6NO_2$[q]
8d[d,i]	6-CF_3	COOMe	130–131.5	100	$C_{13}H_7F_6NO_2$[q]
9a[b,d]	8-CF_3	COPyr	128–129.5	61	$C_{17}H_8F_6N_2O$
9b[b,d]	6-OMe-8-CF_3	COPyr	164–165	90	$C_{18}H_{10}F_6N_2O_2$
9c[b,d]	7-CF_3	COPyr	124.5–125.5	27	$C_{17}H_8F_6N_2O$[q]
9d[b,e]	6-CF_3	COPyr	138.5–140	13[n], 55[o]	$C_{17}H_8F_6N_2O$[q]
14[d,e]	5-CF_3	CHOHPyr	107–109	37	$C_{17}H_{10}F_6N_2O$
1[c]	8-CF_3	CHOHPip·HCl	259–260 dec	53	$C_{17}H_{17}ClF_6N_2O$
2[b]	6-OMe-8-CF_3	CHOHPip·HCl	298–300 dec	86	$C_{18}H_{19}ClF_6N_2O_2$
3[b]	7-CF_3	CHOHPip·HCl	244–245 dec	24	$C_{17}H_{17}ClF_6N_2O$
4[c]	6-CF_3	CHOHPip·HCl	197–199 dec	22	$C_{17}H_{17}ClF_6N_2O$
1,4-Dihydroquinolines					
15[j]	5-CF_3	H, CHOHPip·HCl	193 dec[r]	27	$C_{17}H_{17}ClF_6N_2O$
11[b]	6-CF_3	Pyr, Bu	170–171	6	$C_{20}H_{18}F_6N_2$

[a] Pyr = 2-pyridyl; Pip = piperidyl. Recrystn solvent, or other purification methods are indicated: [b] EtOH. [c] MeCN. [d] Sublimed. [e] Hexane. [f] C_6H_6. [g] Column chromatog. [h] PhMe. [i] MeOH. [j] Me_2CO. [k] Yield of crude reaction product which was used directly in the next step. [l] Could not be fully sepd; total yield of mixt after crystn from EtOH, 70%. [m] Yield of pure material from a mixt of **5c** and **5e**. [n] Yield from the acid **7d**. [o] Yield from the ester **8d**. [p] Anal. were within ±0.2% for C, H, N or [q] for C, H. [r] nm 227, 242, 354 (ϵ^{-3} 2.14, 6.0, 3.1).

6-Methoxy-2,8-bis(trifluoromethyl)-4-quinolone (5b) was purified by recrystn from C_6H_6 rather than the often less effective soln in base and pptn by acid.[3,5]

2,5- and 2,7-Bis(trifluoromethyl)-4-bromoquinolines (6e,c.)—A mixture of 2,5- and 2,7-bis(trifluoromethyl)-4-quinolones (39.2 g, 0.14 mole; recrystd from EtOH), and $POBr_3$ (57 g, 0.2 mole), was stirred at 140° for 3 hr and poured into ice H_2O. The product was extd with CH_2Cl_2 and recrystd from EtOH, giving pure **6c** (30.17 g, 63%), mp 104–106°. The residue obtd upon evapn of the EtOH liquors (15.13 g, 32%), was chromatogd on a 5-cm column of 1 kg of Woelm neutral alumina (activity no. 1). Eluting with hexane and 1, 2, 5, and 10% benzene–hexane gave 1.84 g of addnl **6c** (total yield 67%), 8.79 g (18%) of **6e**, mp 47–50°, and a small quantity of a mixt of these.

6-Methoxy-2,8-bis(trifluoromethyl)cinchoninic Acid (7b).—The required 4-Li derivative was prepd by addn of the very slightly Et_2O-sol 4-Br deriv **6b** to a slight excess of BuLi in anhyd Et_2O and stirring for 2.5 hr. Pouring the reaction mixt onto dry powdered CO_2 gave **7b** (57%), mp 246–248°. A decrease in the prepn time of the Li compd led to a decrease in the yield of **7b** and a corresponding increase in recovered **6b**.

Methyl 2,6-bis(trifluoromethyl)cinchoninate (8d) was prepd in quant yield by 45-min refluxing of a MeOH soln of crude acid chloride which had been prepd by the reaction of **7d** with $SOCl_2$ (2 hr).

α-(2-Pyridyl)-2,6- and -2,7-bis(trifluoromethyl)-4-quinolyl ketones (9c,d) were isolated by column chromatog (Florisil, $CHCl_3$ as eluent) and recrystd from EtOH. Concn of recrystn liquors from **9d** yielded **11** (6%), pale yellow: ir (KBr) 3175 cm^{-1} (NH); nmr ($CDCl_3$–DMSO-d_6): δ 9.00 (s, 1, NH), 8.60 (m, 1), 7.61 (m, 1), 7.12 (m, 5), 5.00 (s, 1, H-3), 2.2 (m, 2), 0.95 (m, 7); mass spec (70 eV) *m/e* (rel intensity) 400 (2), 381 (5), 343 (100), 322 (32), 303 (4), 273 (16), 78 (20).

α-(2-Pyridyl)-2,5-bis(trifluoromethyl)-4-quinolinemethanol (14).—A soln of 6.4 g (0.06 mole) of 2-pyridaldehyde in 40 ml of anhyd Et_2O was added dropwise at −70° under N_2 to a stirred Et_2O soln (150 ml) of 2,5-bis(trifluoromethyl)-4-quinolyllithium [from 7.93 g (0.023 mole) of **6e** and 17.2 g (0.05 mole) of 22% BuLi in hexane soln], with stirring for an addnl 2 hr. After hydrolysis the Et_2O layer was evapd to dryness, and the residue was chromatogd on 400 g of Florisil (C_6H_6 as eluent). The crude oil obtd was recryst from hexane, 3.64 g of **14** (tan), mp 95–103°. Sublimation at 70° (0.05 mm) returned 3.19 g (37%), mp 102–105°.

The Bis(trifluoromethyl)-α-(2-piperidyl)-4-quinolinemethanols (1–4) and the 5-Trifluoromethyl-1,4-dihydro Derivative (15).—The catalytic hydrogenations of **9a–9d** and of **14** were carried out by published procedure in EtOH with PtO_2.[3] After filtration through Celite, the EtOH was vacuum evapd. Crude **3** and **4** were initially purified by trituration of the residue with Et_2O and filtration.