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Antimalarials. 7. 2,8-Bis(trifluoromethyl)-4-quinolinemethanols

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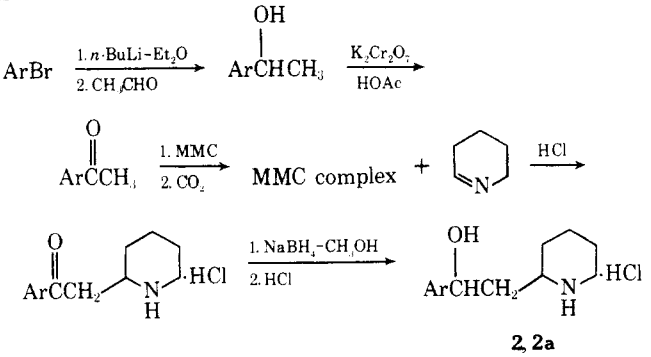
Based on the high antimalarial activity of α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol, ten additional 2,8-bis(trifluoromethyl)-4-quinolinemethanols were prepared in which the amino alcohol side chain was structurally varied. Synthesis of the compounds is described and antimalarial activity data against *Plasmodium berghei* are presented and discussed in terms of the structure variations.

α-(2-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol (**1**) was reported in 1971 by Ohnmacht et al.[1] to possess a high degree of antimalarial activity against *Plasmodium berghei* in mice.[2] This prompted the synthesis of ten additional analogs in which the amino alcohol group was variously altered. These included (a) variation in the alkyl group attached to nitrogen, (b) the preparation of homo analogs of the conventional α-alkylaminomethyl compound, and (c) the preparation of compounds bearing the α-alkylaminoisopropyl group. The homo analogs, i.e., ethanols as opposed to methanols, have been significantly more active in the case of certain quinoline, phenanthrene, and pyridinecarbinols.[3]

Chemistry. The target carbinolamines prepared in this work are tabulated in Table I. In all synthesis schemes, Ar is the 2,8-bis(trifluoromethyl)-4-quinolyl group. Compound **2**, the homo analog of **1**, was prepared from 2,8-bis(trifluoromethyl)-4-bromoquinoline according to Scheme I. The

Scheme I

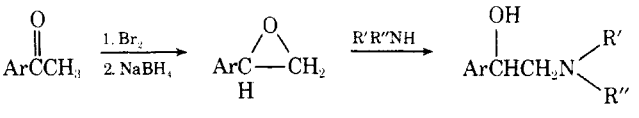


2, 2a

4-bromoquinoline was converted to the 4-lithioquinoline and condensed with acetaldehyde to form the 4-methylcarbinol (69–76%). The latter was oxidized with dichromate in acetic acid to yield the 4-acetylquinoline (87–88%). The acetyl compound was successfully converted to the required precursor, 2-piperidylmethyl 4-quinolyl ketone, using an interesting procedure reported recently by Claxton et al.[4] as follows. A standardized solution of magnesium methyl carbonate (MMC) in DMF was prepared by the method of Finkbeiner and Wagner.[5] 4-Acetylquinoline was added and the mixture was heated at 120° under N_2. After cooling, a separately prepared tripiperidine[6] was added to the MMC solution to give the 2-piperidylmethyl ketone in 50% yields based on acetylquinoline consumed. The conversions, however, were low, ranging from 33 to 43%. The 2-piperidylmethyl ketone was reduced with sodium borohydride to give the target carbinol, mp 257–261°, in 76% yield. The product was a mixture of two pairs of enantiomers (ca. 3:1). Recrystallization gave the predominant isomer, henceforth designated racemate A (**2**), mp 266–268°. Racemate B (**2a**), mp 261–263°, was isolated in low recovery from the mother liquors. A mixture of **2** and **2a** (1:1) melted at 248–255°. Initially, the preparation of **2** was attempted by more conventional routes without success. For example, 2,8-bis(trifluoromethyl)quinoline-4-carboxaldehyde (see below) was condensed with 2-picolyllithium. A four-component mixture (one major and three minor) was obtained with the desired intermediate 2-picolylcarbinol as a minor component (isolated in low yield).

Compounds **3, 5,** and **7** were prepared from the above intermediate, 2,8-bis(trifluoromethyl)quinolyl methyl ketone, by well-developed procedures as shown in Scheme II.[7]

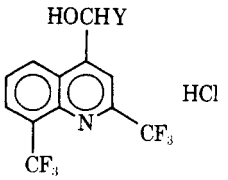
Scheme II



3, R′ = *t*-Bu; R″ = H
5, R′ = *n*-Pr; R″ = H
7, R′ = R″ = *n*-Pr

Bromination yielded the bromo ketone as an oil which, without purification, was reduced with $NaBH_4$ to give the epoxide in 65–73% yield based on the starting methyl ketone. The epoxide was treated with the appropriate amine to yield compounds **3, 5,** and **7** in 74, 63, and 84% yields, respectively.

Table I. 2,8-Bis(trifluoromethyl)-4-quinolinemethanols

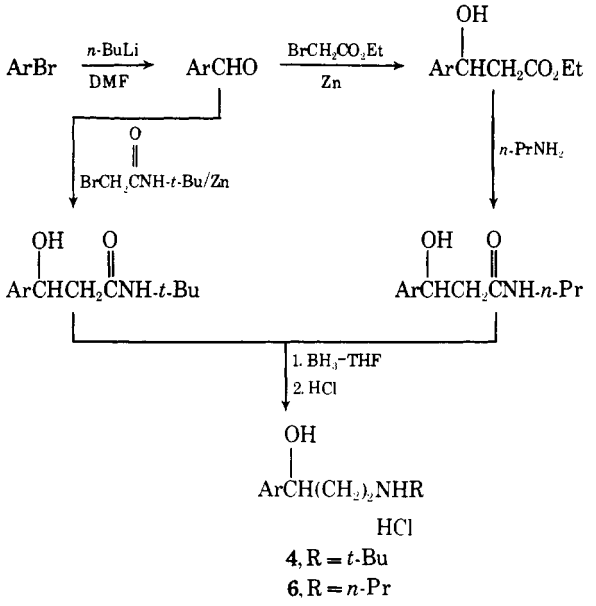


No.	Y	Mp, °C	Solvent	Yield, %	Formula	Analyses[a]
2	CH_2-2-NC_5H_{10}[b]	266–268	MeOH–Et_2O	76[c]	$C_{18}H_{19}ClF_6N_2O$	Cl, F
2a	CH_2-2-NC_5H_{10}[d]	261–263	EtOH	*d*	$C_{18}H_{19}ClF_6N_2O$	Cl, F
3	CH_2NH-*t*-Bu	265–267 dec	EtOH	74	$C_{17}H_{19}ClF_6N_2O$	Cl, F
4	$(CH_2)_2NH$-*t*-Bu	231.8–233.1	EtOH	60	$C_{18}H_{21}ClF_6N_2O$	Cl, F
5	CH_2NH-*n*-Pr	232–235 dec	CH_3CN	63	$C_{16}H_{17}ClF_6N_2O$	Cl, F
6	$(CH_2)_2NH$-*n*-Pr	180–180.5	EtOH	64	$C_{17}H_{19}ClF_6N_2O$	Cl, F
7	CH_2N(*n*-Pr)$_2$	225–227 dec	*i*-PrOH	84	$C_{19}H_{23}ClF_6N_2O$	Cl, F
8	CH_2NH-*n*-Bu	232–233	CH_3CN	31	$C_{17}H_{19}ClF_6N_2O$	Cl
9	CH_2N(*n*-Bu)$_2$	167–169	EtOAc–petr ether	39	$C_{21}H_{27}ClF_6N_2O$	Cl
10	$C(CH_3)_2NH$-Et	239–241	*i*-PrOH	65	$C_{17}H_{19}ClF_6N_2O$	
11	$C(CH_3)_2NH$-*n*-Bu	238–240	*i*-PrOH	81	$C_{19}H_{23}ClF_6N_2O$	

[a] In addition to C, H, and N. [b] Racemate A. [c] Yield as racemic mixture; 59% yield as racemate A. [d] Racemate B from mother liquors of A.

Compounds **4** and **6**, representing homologs of compounds **3** and **5**, respectively, were prepared according to Scheme III. 2,8-Bis(trifluoromethyl)-4-bromoquinoline was converted by a one-step procedure to the 4-aldehyde with *n*-butyllithium and DMF by the method of Sainsbury et al.[8] in 63% yield. A Reformatsky condensation[9] on the 4-carboxaldehyde produced the 3-hydroxypropionate ester in 89% yield. Aminolysis of the ester (79% yield), followed by borane reduction of the amide,[10] produced target compound **6** in 64% yield. The route shown on the left-hand side of Scheme III was utilized for the preparation of compound **4** inasmuch as *tert*-butylamine would not react appropriately with the 3-hydroxypropionate ester. Instead, the 3-hydroxypropionamide was obtained in 62% yield directly from the 4-carboxaldehyde by a Reformatsky condensation[9] with α-bromo-*N*-(*tert*-butyl)acetamide, prepared from bromoacetyl bromide and *tert*-butylamine by the method of Weaver and Whaley.[11] Reduction with borane[10] gave the target compound **4** in 60% yield.

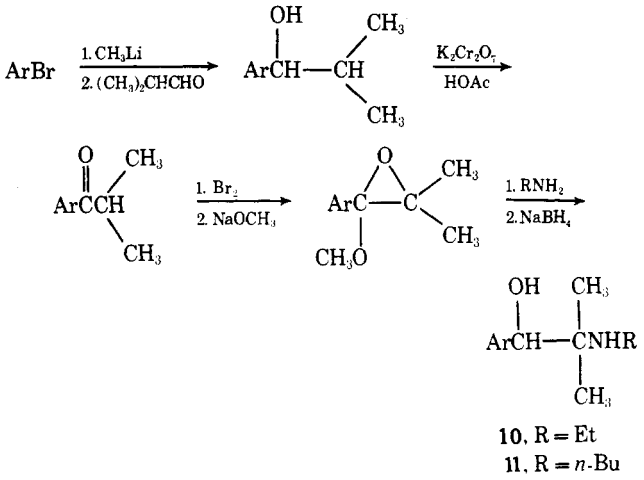
Scheme III



Compounds **8** and **9** were prepared from 2,8-bis(trifluoromethyl)-4-quinolinic acid by the well-known diazomethane route of Lutz and coworkers.[7]

Compounds **10** and **11**, bearing a *gem*-dimethyl group in the side chain, were prepared by the method of Stevens and Chang[12] as shown in Scheme IV. The 4-bromoquinoline was converted to the isopropyl-4-quinolylcarbinol (56%) via the lithio salt and treatment with isobutyraldehyde. Oxidation with potassium dichromate in acetic acid gave the 4-quinolyl isopropyl ketone (90%). Bromination in chloroform containing a trace of hydrobromic acid gave the α-bromoisopropyl 4-quinolyl ketone (66%). Treatment with methoxide gave the epoxy ether (80%). The epoxy ether was refluxed with the appropriate alkylamine in ethanol to yield the corresponding amino ketones isolated as hydrochloride salts (R = Et, 70%; R = *n*-Bu, 65%). Reduction with $NaBH_4$ gave target compounds **10** (65%) and **11** (81%).

Scheme IV



Biological Activity. Antimalarial activity data against *P. berghei* in mice were obtained by the Rane Laboratory, University of Miami, as described elsewhere[2] and are presented in Table II. Compound **1** is shown for reference purposes. The data for **1** are those reported by Ohnmacht et al.[1] for the major isomer, later shown to be erythro. The threo, or minor, isomer was isolated first by Olsen.[13] The optical antipodes of both racemates were prepared by Carroll and Blackwell, but no significant difference in antimalarial activity between racemates or the antipodes was observed in the Rane test.[14]

Table II. Antimalarial Activity against *Plasmodium berghei*

	Rane data,[a] ΔMST, days at mg/kg (C = cure; T = toxic death)						
No.	10	20	40	80	160	320	640
1[b]	12.5	4C	5C	5C	5C	5C	5C
2		4.9	15.9	16.7	17.9	3C	4C
2a		6.9	1C	2C	3C	3C	4C
3		0.3	11.3	12.1	15.1	15.3	15.9
4	9.3	13.1	15.1	17.1	3C	3C/2T	2C/3T
5		6.9	11.7	13.9	1C	2C	3C/2T
6	0.7	5.7	10.1	13.3	15.9	16.9	18.1
7		2.9	10.7	11.5	14.3	15.9	3C
8	0.3	5.1	13.5	2C	5C	5C	5C
9	0.7	1.1	11.5	14.3	5C	5C	
10			0.7	3.9	10.5	11.3	11.7
11			1.1	4.1	7.9	5C	5C

[a]These data, obtained by the Rane Laboratory, University of Miami, using a method described by Osdene, Russell, and Rane,[2] were supplied by Drs. Thomas R. Sweeney, Richard E. Strube, and Bing T. Poon of the Walter Reed Army Institute of Research. Untreated animals die within 6–8 days with a mean survival time of 6.2 days. An increase of 100% in mean survival time is considered the minimum response for a candidate compound. Treated animals are kept under observation for 60 days. Survivors at the end of this period are considered to be cured. Groups of five mice have been used at each dose level of the drugs. [b]From ref 1; for additional data, see ref 14.

The data of Table II indicate that none of the ten new analogs of **1** is more active than **1** in the Rane test.

Compound **4** is curative at 160 mg/kg and **8** is curative at 80 mg/kg; compound **4** retains activity through 10 mg/kg, however. Further, compound **4** has demonstrated promising activity against *Plasmodium falciparum* in the Aotus monkey[15b] and has been prepared in large quantities for advanced testing. As stated earlier, the insertion of an additional methylene group in the conventional mono- or dialkylaminomethyl side chain has been shown to improve antimalarial activity significantly in certain of the 4-quinolinemethanols, 9-phenanthrenemethanols, and 4-pyridinemethanols.[3] In the present work, however, compound **2** (and **2a**), the homo analog of **1**, was found to be less active than **1**. Similarly, in the case of **5** and **6** for compounds bearing the *N*-(*n*-propyl) group, the homo analog **6** is less active than **5** at least at the higher dose levels; at lower dosages, there is no difference in activity between the two compounds. A comparison of **3** with **4**, both of which bear an *N*-(*tert*-butyl) group, indicates that, in this case, the homo analog **4** is markedly more active than **3**. Compound **4** is active at 10 mg/kg and curative at 160 mg/kg, whereas **3** is inactive below 40 mg/kg and noncurative through 640 mg/kg.

A comparison of the effect of monoalkylaminomethyl groups and dialkylaminomethyl groups fails to reveal major differences in antimalarial activity. Thus, **5** and **7** give comparable results as do **8** and **9**, where the alkyl groups are *n*-propyl and *n*-butyl, respectively. Among the monoalkylaminomethyl analogs **3** (*tert*-butyl), **5** (*n*-propyl), and **8** (*n*-butyl), there is no difference in activity at a dose level of 40 mg/kg; all three compounds are active. At higher dose levels, however, marked differences are observed. Compound **8** (*n*-butyl) is curative at 80 mg/kg, whereas **5** is curative at 160 mg/kg and **3** fails to yield cures even at 640 mg/kg.

Compounds **10** and **11** with a unique *gem*-dimethyl configuration in the side chain are active only at high dose levels. Somewhat better results with this configuration were obtained in 2,6-bis(4-chlorophenyl)-4-pyridinemethanols, viz., the NH-*n*-Bu analog gave 2/5C at 40 mg/kg,[16] comparable to the best results in that series.[17]

Experimental Section

Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind., and by Galbraith Laboratories, Inc., Knoxville, Tenn. Analyses indicated by element symbols agree with calculated values within ±0.3%. Melting points were taken in open capillary tubes and are uncorrected. 2,8-Bis(trifluoromethyl)-4-bromoquinoline and the corresponding 4-quinolinic acid were prepared by Dr. Robert E. Olsen, Cordova Chemical Division, Aerojet Chemical Co., and provided by the Walter Reed Army Institute of Research.

1-[2,8-Bis(trifluoromethyl)-4-quinolyl]ethanol. 2,8-Bis(trifluoromethyl)-4-bromoquinoline (68.8 g, 0.2 mol) in dry ether (400 ml) was added over 90 min to a cold (−75°) solution of *n*-butyllithium (214 ml, 0.35 mol) in dry ether (700 ml) maintained under a dry nitrogen atmosphere. The solution was stirred at −75° for 30 min and treated dropwise with a solution of acetaldehyde (44 g, 1.0 mol) in dry ether (250 ml). The reaction mixture was stirred for 30 min at −75°, allowed to warm gradually to room temperature, and stirred for an additional 30 min. The mixture was cooled to 0° and 1 *N* HCl (350 ml) was added. The organic layer was separated, washed with water, and dried ($MgSO_4$). Removal of solvent gave a brown oil which slowly crystallized. Recrystallization from benzene–petroleum ether afforded a first crop, 44 g, mp 105–108°, and a second crop, 2.7 g, mp 105–108°. The combined yield was 76%. Anal. ($C_{13}H_9F_6NO$) C, H, N.

4-Acetyl-2,8-bis(trifluoromethyl)quinoline. A mixture of the above carbinol (50 g, 0.162 mol), potassium dichromate (26 g, 0.088 mol), and glacial acetic acid (150 ml) was heated on a steam bath for 90 min. The reaction mixture was cooled, treated with water (300 ml), and extracted with ether. The ether layer was washed with water, dried ($MgSO_4$), and concentrated to give a crystalline product. Recrystallization from EtOH–H_2O afforded 43.3 g (87%) of the title ketone, mp 85–88°. Anal. ($C_{13}H_7F_6NO$) C, H, N.

2,8-Bis(trifluoromethyl)-4-quinolyl 2-Piperidylmethyl Ketone. A solution of magnesium methyl carbonate (MMC)[5] (approximately 1.3 mol in 1.3 l. of dry DMF) was heated to 120° under CO_2. 4-Acetylquinoline (80 g, 0.26 mol) was added and the mixture was heated at 120° for 4 hr under N_2 while allowing MeOH to evaporate. The mixture was allowed to cool to room temperature under CO_2 and treated with tripiperidine[6] (26.1 g, 0.315 mol as monomer, mp 58–61°). The mixture was stirred under CO_2 at room temperature for 24 hr and poured carefully with vigorous stirring into 3.2 l. of cold (ice bath) 2 *N* HCl. The mixture was stirred for 4 hr, during which time the oily product solidified. After standing overnight, the solid product was collected, washed with a small amount of cold water, and dried (vacuum oven). The brown solid was dissolved in MeOH (100 ml). Ether (500 ml) was added and the solution was placed in a refrigerator. The crude product, 20 g, mp 195–200°, was collected by filtration. The filtrate was taken to dryness, treated with MeOH (150 ml), and held at 5° overnight. Starting material (40 g, mp 82–85°) was recovered by filtration. The mother liquor was concentrated, treated with ether (200 ml), and cooled to 5° to remove another 4 g of crude product, mp 195–200°. Additional starting material (6 g) was recovered by concentrating the mother liquor and treating with methanol (100 ml). The combined yield (24 g) of the title ketone was 50% based on 4-acetylquinoline consumed; the conversion was 43%. In a second run using 120 g of the 4-acetylquinoline, the yield was again 50% and the conversion was 33%. The crude product was recrystallized from MeOH–ether to yield pure ketone, mp 219–222°. Anal. ($C_{18}H_{17}ClF_6N_2O$) C, H, N.

1-[2,8-Bis(trifluoromethyl)-4-quinolyl]-2-(2-piperidyl)-ethanol Hydrochloride (2). $NaBH_4$ (4.69 g, 0.2 mol) in water (30 ml) was added slowly to the above ketone (mp 219–222°, 47 g, 0.11 mol) suspended in MeOH (900 ml). The resulting homogeneous solution was stirred for 30 min. Excess borohydride was destroyed with dilute HCl (pH 3). The mixture was made alkaline with dilute NaOH, diluted with water (900 ml), and extracted with $CHCl_3$ (250 ml, three times). The extracts were washed with water, dried ($MgSO_4$), and evaporated. The residual oil was treated with ethereal HCl to pH 2. The precipitated HCl salt was collected and dissolved in hot MeOH (200 ml). The MeOH solution was filtered and concentrated to 100 ml and diluted with ether (250 ml). After refrigeration overnight, 35 g (76%) of product, mp 257–261°, was collected. The product was a racemic mixture by TLC (benzene–

$CHCl_3$). One additional precipitation from MeOH with ether gave 27 g (59%) of compound **2**, mp 266–268°, containing predominantly one racemate (ca. 95%, TLC) designated A.

To obtain racemate B (**2a**), the combined crystallization mother liquors were concentrated to give 12 g of product, mp 250–255°, containing racemate B as the major component by TLC. This material was recrystallized from EtOH to give 4.9 g, mp 257–260°, of nearly pure racemate B. TLC showed a trace of racemate A. A second recrystallization gave 3.2 g of TLC pure **2a**, mp 261–263°. A mixture (1:1) melting point between racemate A (mp 266–268°) and racemate B (mp 261–263°) exhibited a depression, mp 248–255°.

1-[2,8-Bis(trifluoromethyl)-4-quinolyl]oxirane. The above 4-acetylquinoline (130 g, 0.423 mol) was dissolved in $CHCl_3$ (1.1 l.) containing hydrobromic acid (2 ml, 48%). A portion of a solution of Br_2 (67.8 g, 0.423 mol) in $CHCl_3$ (150 ml) was added, and the reaction was initiated by warming the solution (steam bath). The remainder of the Br_2 solution was added in portions at room temperature, allowing the bromine color of the mixture to disappear after each addition. The reaction solution was washed with 5% $NaHCO_3$ and water and dried ($MgSO_4$). The solvent was evaporated to give 162 g of oil, one spot on TLC (benzene). The NMR spectrum was consistent with 2,8-bis(trifluoromethyl)-4-quinolyl bromomethyl ketone. This compound was prepared also from 2,8-bis(trifluoromethyl)-4-quinolinic acid via the diazoketone route.[7] The α-bromo ketone (162 g) in EtOH (1.5 l.) and 2-ethoxyethanol (0.5 l.) was cooled to −25°. $NaBH_4$ (16.06 g) in water (100 ml) was added. The mixture was allowed to warm to room temperature and stirred for 1.5 hr. KOH (16.06 g) in EtOH (80 ml) was added. After stirring for 30 min, water (2 l.) was added and the mixture was extracted with $CHCl_3$ (750 ml, twice). The extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was crystallized from EtOH–H_2O to afford the title compound: first crop, 80 g, mp 80–84°; second crop, 14 g, mp 79–83°. The combined yield was 72%. Recrystallization from EtOH–H_2O gave an analytical sample, mp 82–84°. Anal. ($C_{13}H_7F_6NO$) C, H, N.

α-(*tert*-Butylamino)methyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol Hydrochloride (3). A mixture of the oxirane (28 g, 0.091 mol), *tert*-butylamine (70 ml, 0.661 mol), and EtOH (150 ml) was refluxed overnight. The solution was evaporated to dryness in vacuo. The residual amine was removed by azeotropic evaporation with benzene (aspirator). The solid residue was recrystallized from EtOH–H_2O to afford 34 g of the title amino alcohol as white crystals, mp 114–118°. The amino alcohol (34 g) in ether (500 ml) was made acidic with HCl gas. The precipitate was collected and washed with ether. Recrystallization from ethanol gave 28 g (74%) of pure **3** as white crystals, mp 265–267° dec.

α-(*n*-Propylamino)methyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol Hydrochloride (5). A mixture of the above oxirane (45 g, 0.147 mol), *n*-propylamine (120 ml, 1.47 mol), and EtOH (200 ml) was refluxed 5 hr. Work-up, as described for compound **3**, gave 38 g of the title free base, mp 140–143°. The product (38 g) was converted to the HCl salt which was recrystallized from CH_3CN to give 37 g (63%) of the title compound **5**, mp 232–235° dec.

2,8-Bis(trifluoromethyl)cinchoninaldehyde. This was prepared from 2,8-bis(trifluoromethyl)-4-bromoquinoline and DMF via the lithium salt according to the general method of Sainsbury et al.[8] The product (63%), recrystallized from petroleum ether (bp 60–75°), was pure by TLC, mp 91–92° (lit.[15c] mp 88–90°). Anal. ($C_{12}H_5F_6NO$) C, H, N.

Ethyl 3-[2,8-Bis(trifluoromethyl)-4-quinolyl]-3-hydroxypropionate. To a refluxing, stirred suspension of acid-washed Zn (0.737 g, 0.011 mol), benzene (50 ml), and the above aldehyde (2.93 g, 0.010 mol) was added ethyl bromoacetate (1.84 g, 0.011 mol) in benzene (15 ml) over a 30-min period. The mixture was refluxed 30 min and filtered. The filter cake was washed with benzene. The filtrates were combined and washed consecutively with 3 *N* HCl and saturated Na_2CO_3. The combined extracts were concentrated in vacuo to give 3.75 g (89%) of a yellow solid suitable for further transformation. Product pure by TLC was obtained by recrystallization from 1 l. of petroleum ether (bp 60–75°), mp 98.4–100.4°. Anal. ($C_{16}H_{13}F_6NO_3$) C, H, N.

α-Bromo-*N*-(*tert*-butyl)acetamide was prepared in 71% yield by the method of Weaver and Whaley.[11] Recrystallization from petroleum ether (96–105°) gave product, mp 98–99° (sealed tube). Anal. ($C_6H_{12}BrNO$) C, H, N. This compound was reported by Nyquist[18] but no preparative details or physical constants were given.

3-[2,8-Bis(trifluoromethyl)-4-quinolyl]-3-hydroxy-*N*-(*tert*-butyl)propionamide. To a stirred, refluxing suspension of acid-washed Zn (280 g, 0.428 mol) and 2,8-bis(trifluoromethyl)cinchoninaldehyde (35.0 g, 0.120 mol) in dry benzene (1.5 l.) was slowly added a solution of α-bromo-*N*-(*tert*-butyl)acetamide (23.5 g, 0.132 mol) in dry benzene (400 ml). The reaction mixture was refluxed 2 hr. The suspended material was collected on a filter and then dried. The filter cake was dissolved in 6 *N* HCl (1 l.) and the extracted with CH_2Cl_2. The extracts and the original benzene filtrate were combined, washed with 3 *N* HCl, saturated Na_2CO_3, and H_2O, dried ($MgSO_4$), and then concentrated in vacuo to a white solid suitable for further transformation. Recrystallization from petroleum ether (96–105°) gave 66 g (62%) of the title amide, mp 168°. Anal. ($C_{18}H_{18}F_6N_2O_2$) C, H, N.

3-(*tert*-Butyl)amino-1-[2,8-bis(trifluoromethyl)-4-quinolyl]propanol Hydrochloride (4). The crude amide (38.0 g, 0.092 mol) was reduced with borane in THF as described for compound **6** below. Pure **4** (TLC) was obtained by recrystallization from absolute EtOH: yield 24.0 g (60%); mp 231.8–233.1°.

3-[2,8-Bis(trifluoromethyl)-4-quinolyl]-3-hydroxy-*N*-(*n*-propyl)propionamide. A solution of the ethyl 3-hydroxypropionate (5.0 g, 0.014 mol) was refluxed in *n*-propylamine (100 ml) for 4 hr. Excess amine was removed by spin evaporation in vacuo. The residue was recrystallized from absolute ethanol to produce 4.4 g (79%) of the title amide, mp 152.5–153°. Anal. ($C_{17}H_{16}F_6N_2O_2$) C, H, N; H: calcd, 4.09; found, 3.63.

3-(*n*-Propyl)amino-1-[2,8-bis(trifluoromethyl)-4-quinolyl]propanol Hydrochloride (6). A solution of hydroxyamide (36.6 g, 0.093 mol) in THF (500 ml) was added dropwise to a stirred, cold (−6°) solution of borane (0.3 mol) in THF (1.3 l.). The low temperature was maintained for 0.5 hr longer and then slowly raised. The reaction mixture was refluxed for 1.5 hr, cooled to 30°, and diluted with water (500 ml) followed by concentrated HCl (100 ml). This mixture was refluxed 15 min, cooled to 30°, and then concentrated in vacuo. The product that precipitated was stirred with water (500 ml) and the suspension was basified with solid KOH to pH 12. The resulting solution was extracted with ether. The ether extracts were washed with water, dried (Na_2SO_4), and then treated with anhydrous HCl (7.0 g, 0.2 mol) before being concentrated in vacuo. Pure **6** (TLC) was obtained by recrystallization from absolute ethanol: yield 24.8 g (64%); mp 180–180.5°.

α-(Di-*n*-propylamino)methyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol Hydrochloride (7). The above oxirane (35 g, 0.114 mol), dipropylamine (120 ml, 0.88 mol), and ethanol (200 ml) were refluxed 5 hr. Work-up, as described for compound **3**, gave the free base (47 g), mp 74–78°. Conversion to the HCl salt and recrystallization from isopropyl alcohol yielded 42.5 g (84%) of pure title compound **7**, mp 225–227° dec.

α-*n*-Butylaminomethyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol Hydrochloride (8). Crude bromomethyl 2,8-bis(trifluoromethyl)-4-quinolyl ketone (6.6 g) in EtOH (100 ml) at 0–5° was treated with a solution of $NaBH_4$ (0.8 g) in H_2O (6 ml). The solution was stirred at room temperature for 1 hr and water (200 ml) was added. The solution was extracted with $CHCl_3$ (200 ml, twice), dried ($MgSO_4$), and concentrated under reduced pressure to yield the intermediate crude epoxide (6.4 g). (For preparation of pure oxirane, see above.) A solution of the crude oxirane (6.4 g, 0.02 mol) in EtOH (100 ml) containing *n*-butylamine (8 ml) was refluxed 17 hr. The solution was taken to dryness; the residue was slurried in petroleum ether and filtered. The crude free base was dissolved in CH_3CN (40 ml) and concentrated HCl (1.4 ml) was added. The resulting crystalline title HCl salt (3.6 g) was recrystallized from CH_3CN (45 ml) to yield the pure compound **8** (2.55 g, 31%), mp 232–233°.

α-Di-*n*-butylaminomethyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol Hydrochloride (9). A solution of the oxirane (10 g, 0.03 mol) in EtOH (150 ml) containing di-*n*-butylamine (12 ml) was refluxed 17 hr. The solution was concentrated to dryness. The residual oil was dissolved in ether and treated with ethereal HCl to pH 2. The solid was filtered, stirred in warm water (150 ml) to remove dibutylamine hydrochloride, and filtered. The crude product (8.3 g) was crystallized from ethyl acetate–petroleum ether to afford the target compound (5.9 g, 39%), mp 167–169°.

1-[2,8-Bis(trifluoromethyl)-4-quinolyl]-2-methyl-1-propanol. 2,8-Bis(trifluoromethyl)-4-bromoquinoline (20.6 g, 0.06 mol) in dry ether (180 ml) was added over a 90-min period to a cold (−75°) solution of methyllithium (64.4 ml, 0.195 mol) in dry ether (250 ml) under a dry nitrogen atmosphere. The solution was stirred at −75° for 30 min and treated dropwise with a solution of isobutyraldehyde (14.2 g, 0.2 mol) in dry ether (100 ml). The mixture was stirred (ca. 30 min at −75°), allowed to warm gradually to room temperature, and stirred an additional 30 min. The mixture

was cooled to 0–5° and 1 *N* HCl (100 ml) was added. The organic layer was separated, washed well with water, and dried ($MgSO_4$). The solvent was evaporated (aspirator) and the unreacted isobutyraldehyde and low-boiling by-products were removed in vacuo [bp 100° (0.3 mm)]. The oil residue crystallized slowly on standing. Recrystallization from petroleum ether (bp 30–60°) afforded 11.5 g (56%) of beige crystals, mp 50–53°. Anal. ($C_{15}H_{13}F_6NO$) C, H, N.

2,8-Bis(trifluoromethyl)-4-quinolyl Isopropyl Ketone. A mixture of the above alcohol (6.8 g, 0.02 mol), potassium dichromate (6.8 g, 0.023 mol), and glacial acetic acid (100 ml) was heated on a steam bath for 15 min. The mixture was cooled, diluted with water, and extracted with ether. The ether layer was washed consecutively with water, 10% aqueous $NaHCO_3$, and water and dried ($MgSO_4$). After the removal of the solvent, the oily ketone (6.1 g, 90%) was obtained which was suitable for the next step.

2,6-Bis(trifluoromethyl)-4-quinolyl α-Bromoisopropyl Ketone. The preceding ketone (6.1 g, 0.018 mol) was converted to the title compound (4.8 g, 66%), mp 108–110°, after recrystallization from petroleum ether (bp 30–60°) in the same manner as described above as part of the sequence to **3**. Anal. ($C_{15}H_{10}BrF_6NO$) C, H, Br.

1-[2,8-Bis(trifluoromethyl)-4-quinolyl]-1-methoxy-2,2-dimethyloxirane. To a suspension of sodium methoxide (5.4 g, 0.1 mol) in dry ether (100 ml), a solution of the above α-bromo ketone (4.1 g, 0.01 mol) in ether (50 ml) was added at 0–5°. The suspension was stirred at room temperature for 48 hr, water was added, and the layers were separated. The ether layer was dried (K_2CO_3) and concentrated. The residue was crystallized from MeOH to give 2.9 g (80%) of the title compound, mp 98–100°. Anal. ($C_{16}H_{13}F_6NO_2$) C, H, N.

α-(2-Ethylamino-2-propyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol Hydrochloride (10). A solution of the above epoxy ether (3.65 g, 0.01 mol) in EtOH (80 ml) containing ethylamine (20 ml) was refluxed 72 hr. The solvent and excess amine were removed under reduced pressure. The residue was dissolved in EtOH (50 ml) containing concentrated HCl (10 ml) and heated for 5 hr on a steam bath to hydrolyze any imine. The solution was concentrated and the residue was diluted with water. The crystalline product was filtered and recrystallized from 2-propanol to yield 3.1 g (70%), mp 237–239°, of α-2-ethylamino-2-propyl-2,8-bis(trifluoromethyl)-4-quinolyl ketone. Anal. ($C_{17}H_{17}ClF_6N_2O$) C, H, N. To a slurry of the ethylamino ketone (2.2 g, 5 mmol) in EtOH (100 ml) was added a solution of $NaBH_4$ (0.6 g in 5 ml of H_2O). The mixture was stirred at room temperature for 3 hr. The solution was concentrated and made acidic with 10% HCl. The product was filtered, washed with cold water, and recrystallized from 2-propanol. The yield of the title carbinolamine **10** was 65%, mp 239–241°.

α-[2-(1-Butylamino)-2-propyl]-2,8-bis(trifluoromethyl)-4-quinolinemethanol Hydrochloride (11). The required precursor butylamino ketone (65%, mp 240–243°) was prepared from the epoxy ether and butylamine using the procedure described above for the ethyl analog. Anal. ($C_{19}H_{21}ClF_6N_2O$) C, H, N. The butylamino ketone was converted to the title carbinolamine **11** (81%, mp 238–240°) by the procedure described above for the ethyl analog.

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3-Arylquinolizidines, Potential Antidepressant Agents†

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The synthesis, structure elucidation, and pharmacological evaluation of some 3-arylquinolizidines as semirigid phenethylamines are described. Many of the derivatives possess antidepressant activity. Some anticonvulsant effects are noted.

In a continuation of our investigation of 3-substituted quinolizidines as semirigid phenethylamines, a series of 3-arylquinolizidines (**2**, Table I) was prepared from the appropriate 3-aryl-3-hydroxyquinolizidines[1] either by hydrogenolysis of **1** or by the dehydration of **1** followed by hydrogenation of the unsaturated intermediate **3** (Scheme I).

It was anticipated that the hydrogenolysis of **4** and **5** over Pd/C would proceed stereospecifically to give prod-

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