the product from MeOH-Et_2O gave **5** (8.7 g, 96%), mp 156–157°. *Anal.* ($C_9H_{13}ClIN$) C, H.

O-**Iodobenzyltrimethylammonium Iodide (3).** This above HCl salt (3 g, 10 mmol) was converted to the free base in the usual manner. The product without further purification was dissolved in a mixture of absolute MeOH (5 ml) and CH_3I (2 g, 14 mmol). The mixture was allowed to stir at room temperature for 2 hr whereupon most of the solvent was removed under reduced pressure. Trituration of the residue with Me_2CO (10 ml) afforded a crystalline product which was collected by filtration, washed with Et_2O, and allowed to air dry. Recrystallization from MeOH-Et_2O afforded pure **3** (3.9 g, 97%), mp 175–176° dec. *Anal.* ($C_{10}H_{15}I_2N$) C, H.

O-**Iodobenzyldimethylethylammonium Iodide (4).** In a similar manner treatment of the amine with C_2H_5I for 18 hr afforded the ethiodide as an oil (quantitative yield). Trituration of this oil with EtOH afforded a solid which was recrystallized from the same solvent to give **4** as a white solid, mp 187–188°.[§] *Anal.* ($C_{11}H_{17}I_2N$) C, H.

Isotope Exchange and Quaternization. A solution of *O*-iodobenzyldimethylamine hydrochloride (**5**, 75 mg) and $Na^{125}I$ (5 mCi) in reagent grade NH_4OH (4 ml) was refluxed with stirring under an atmosphere of N for 24 hr. The solution was allowed to cool and poured into excess 10% NaOH (20 ml). A $CHCl_3$ extract was washed with H_2O and dried (Na_2SO_4), and the solvent was removed under a slow stream of air. Radioanalysis of the product (62 mg) indicated a specific activity of 76 μCi/mg (94% exchange). Tlc using absolute Et_2O showed a single spot coincident with the radioactive peak displayed on a radiochromatogram (R_f 0.45). The product was dissolved in absolute MeOH (1 ml) and CH_3I (40 mg) added. The solution was stirred at room temperature for 2 hr and the solvent removed under a slow stream of air Precipitation and recrystallization as above afforded radioiodinated **3** (98 mg): mp 177–178° dec; specific activity, 42 μCi/mg. Tlc using MeOH–$CHCl_3$ (1:2) gave a single spot coincident with the radioactive peak displayed on the radiochromatogram. Similarly, quaternization with C_2H_5I afforded **4**, specific activity, 10 μCi/mg.

Tissue Distribution Studies. Radioiodinated compounds were given by subcutaneous injection to immature male Sprague-Dawley albino rats weighing 175–200 g. The dose administered was approximately 50 μCi per rat and the vehicle used as isotonic saline. Groups of three animals were killed by exsanguination through ventricle 2, 6 and 18 hr postinjection. The major organs such as liver, kidney, lung, spleen, auricle, and ventricle were excised, weighed, and homogenized. These organs were washed thoroughly with isotonic saline to remove blood, dried and minced with scissors, and placed in a homogenizer tube containing 20 ml of H_2O in the case of liver and 2 ml of H_2O in the case of other major organs. Homogenates were not prepared for small organs such as adrenal and thyroid. Several samples of homogenates, heparinized blood and plasma specimens, and entire adrenal, thyroid, and other tissue samples such as fat and muscle were placed in scintillation counting vials. To each vial, 0.3 ml of 2.5 *M* NaOH solution was added and left overnight and then heated for at least 10 min at 60° in a water bath to complete the digestion. The vials were allowed to cool and 0.7 ml of 1.1 *M* HOAc, 0.05 ml of 30% H_2O_2, and 10 ml of Aquasol[#] cocktail were added successively to each vial and the contents shaken using a vortex mixer. The vials were kept in a cool dark place for at least 4 hr before counting. Radioactivity was assayed in a Beckman LS-200 liquid scintillation spectrometer. Sufficient counts were accumulated to reduce the probable error of counting to less than 5%. All counts were corrected for quenching by using ^{125}I-quench standards curves.

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§The bromide salt was reported in U. S. Patent 3,037,910 (1962), mp 145–146°.

#Xylene-based liquid scintillation counting solution was obtained from New England Nuclear, Boston, Mass.

Antimalarials. 5. 2-Aryl-6-trifluoromethyl-4-pyridinemethanols

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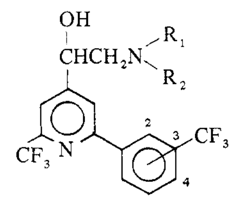
Received April 6, 1973

We have previously reported[1] the synthesis of a series of 2,6-bis(aryl)-4-pyridinemethanols containing Cl, Br, F, OCH_3, and CF_3 substituents on the phenyl rings. These compounds were shown to possess a high degree of activity against *Plasmodium berghei* in mice.[†] Later,[3] a series of styryl- and benzoyl-containing 4-pyridinemethanols were reported which also showed significant antimalarial activity.

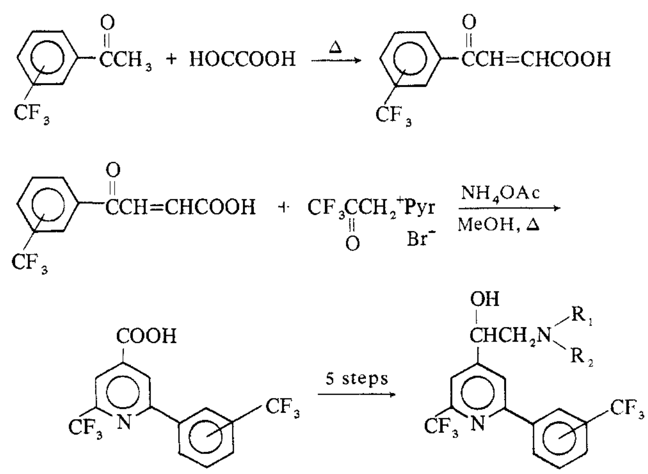
In a continuing effort to maximize the activity of the 4-pyridinemethanols, a series of 2-aryl-6-trifluoromethyl-4-pyridinemethanols (represented by structure I) was synthesized.



I

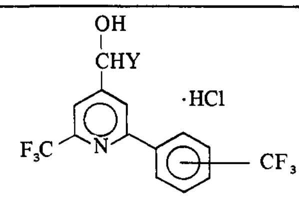
Chemistry. The requisite 2,6-disubstituted isonicotinic acids were prepared *via* the modified Zecher-Krohnke ring-closure method previously described.[1,4] The intermediate trifluoromethyl-substituted benzoylacrylic acids were prepared by reacting the appropriate acetophenone with glyoxylic acid.[1b] Conversion to the 4-pyridylethylene oxide was by the procedure developed by Lutz and coworkers.[5] Ring opening with the appropriate mono- or dialkylamine afforded the eight α-*N*-alkylaminomethyl-2-aryl-6-trifluoromethyl-4-pyridinemethanols shown in Table I. The sequence is shown in Scheme I.

Scheme I



†The antimalarial tests were performed by Dr. Leo Rane of the University of Miami.[2] See footnote *a*, Table II. Testing results were supplied through the courtesy of Drs. Thomas R. Sweeney and Bing T. Poon of the Walter Reed Army Institute of Research.

Table I. 2-Aryl-6-trifluoromethyl-4-pyridinemethanols



No.	Position of CF_3 on phenyl	Y	Mp, °C	Solvent	Yield,[a] %	Formula	Analyses[b]
1	4	$CH_2NH(1\text{-}Bu)$	184–186	CH_3CN	32	$C_{19}H_{21}ClF_6N_2O$	
2	4	$CH_2N(1\text{-}Bu)_2$	128–129.5	Et_2O–petroleum ether	18	$C_{23}H_{29}ClF_6N_2O$	Cl
3	4	$CH_2NH(4\text{-heptyl})$	183–184	CH_3CN	53	$C_{22}H_{27}ClF_6N_2O$	Cl
4	4	$CH_2N(\text{isopentyl})_2$	138–140	Et_2O–petroleum ether	40	$C_{25}H_{33}ClF_6N_2O$	F
5	4	$CH_2NH(3\text{-pentyl})$	196–198	CH_3CN	43	$C_{20}H_{23}ClF_6N_2O$	F
6	2	$CH_2N(1\text{-}Bu)_2$	120–122	Et_2O–petroleum ether	40	$C_{23}H_{29}ClF_6N_2O$	Cl
7	2	$CH_2NH(1\text{-}Bu)$	184–186	CH_3CN	65	$C_{19}H_{21}ClF_6N_2O$	Cl
8	3	$CH_2NH(1\text{-}Bu)$	215–216	CH_3CN	60	$C_{19}H_{21}ClF_6N_2O$	Cl

[a]From ethylene oxide. [b]In addition to C, H, and N.

Biological Activity. Antimalarial activity data against *P. berghei* in mice, as measured by the Rane test,[2] are presented in Table II. Five of the compounds prepared were curative at a dosage of 80 mg/kg or less and one was inactive through 160 mg/kg (the highest dose level tested). One compound, **3**, was curative at 20 mg/kg and two, **1** and **3**, were active at 10 mg/kg.

It can be seen by examination of the data that optimum antimalarial activity is obtained when the trifluoromethyl group is in the 4 position of the phenyl ring. In the case of the mono-1-butylaminomethyl compounds, the 4-trifluoromethylphenyl compound **1** is more active than either the meta isomer **8** or the ortho isomer **7**, the last two compounds being of comparable activity. It is interesting to note that the 2-trifluoromethylphenyl isomer having a di-1-butylaminomethyl side chain is inactive through 160 mg/kg.

It is interesting to note that replacement of a 4-trifluoromethylphenyl substituent by a simple trifluoromethyl group in the 4-pyridinemethanols does not greatly affect the antimalarial activity against *P. berghei* as measured by the Rane test.[2] In some cases, the activity is enhanced. It is possible that the present series of compounds would behave differently than the bisaryl analogs against other strains of malaria.

Table II. Antimalarial Activity against *Plasmodium berghei*

Compd	Rane data,[a] ΔMST, days at mg/kg (C = cure) 5	10	20	40	80
1	4.7	8.7	14.1	3C	4C
2		3.8	11.5	3C	5C
3	3.3	7.9	3C	5C	5C
4			3.7	10.5	13.1[b]
5				14.3[c]	*d*
6				*e*	
7		1.0	6.8	13.3	3C
8		2.9	7.7	14.1	2C

[a]Test method described by T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967). This test has been made as a highly standardized procedure in which the *P. berghei* causes death of control mice at essentially 6 days. An increase in survival of mice by more than 2.5 days beyond this time has been found to be statistically significant. Mice which live more than 60 days are regarded as cured (C). Drugs which prolong the life of the mice beyond 14 days are considered active (A). Groups of five mice have been used as each dose level of the drugs. [b]2C at 320 mg/kg; 3C at 640 mg/kg. [c]2C at 160 mg/kg; 5C at 640 mg/kg. [d]Not available. [e]Inactive through 160 mg/kg.

Experimental Section‡

3-(3-Trifluoromethylbenzoyl)acrylic Acid. The title compound was prepared according to the procedure used for the 4-trifluoromethyl isomer.[1b] From 3-trifluoromethylacetophenone (20 g, 0.106 mol) and glyoxylic acid hydrate (20 g) was obtained the acrylic acid (21.9 g) as an oil of *ca.* 90% purity by tlc. This material could be used for the preparation of the isonicotinic acid. An analytical sample was obtained *via* crystallization from C_6H_6 (twice) to give mp 114–115°. *Anal.* ($C_{11}H_7F_3O_3$) C, H.

3-(2-Trifluoromethylbenzoyl)acrylic Acid. The title acid was prepared as described above. From 2-trifluoromethylacetophenone (50 g, 0.266 mol) and glyoxylic acid acid hydrate (50 g) was obtained the title acid (37 g) as an oil which was suitable for conversion to the isonicotinic acid.

Trifluoromethylacylpyridinium Bromide. 1,1,1-Trifluoro-3-bromoacetone was converted to the pyridinium salt *via* the usual procedure.[1] The yield was 70%, mp 189–191° (CH_3CN).

2-(2-Trifluoromethylphenyl)-6-trifluoromethylisonicotinic acid was prepared *via* the condensation of trifluoromethylacylpyridinium bromide with β-(2-trifluoromethylbenzoyl)acrylic acid by the procedure previously described.[1] The yield was 44%, mp 155–157° (toluene). *Anal.* ($C_{14}H_7F_6NO_2$) C, H, N.

2-(3-Trifluoromethylphenyl)-6-trifluoromethylisonicotinic acid was prepared by the above procedure in 16% yield, mp 185–186° ($CHCl_3$). *Anal.* ($C_{14}H_7F_6NO_2$) C, H, N.

2-(4-Trifluoromethylphenyl)-6-trifluoromethylisonicotinic acid was prepared from 3-(4-trifluoromethylbenzoyl)acrylic acid[1b] and trifluoromethylacylpyridinium bromide in 56% yield, mp 204–205° (C_6H_6). *Anal.* ($C_{14}H_7F_6NO_2$) C, H, N.

***α-N*-Alkyl-2-aryl-6-trifluoromethyl-4-pyridinemethanols.** The above isonicotinic acids were converted to the amino alcohols *via* the standard diazomethyl ketone sequence reported earlier.[1] The physical data are tabulated in Table I.

‡Melting points were taken in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. Analyses indicated by element symbols agree with calculated values within ±0.4%.

Acknowledgment. This work was supported by the U. S. Army Medical Research and Development Command under Contract No. DADA17-69-C-9065. This is Contribution No. 1158 from the Army Research Program on Malaria. The advice and timely suggestions of Drs. T. R. Sweeney, R. E. Strube, and B. T. Poon of the Walter Reed Army Institute of Research are gratefully acknowledged.

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