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Antimalarials. 3. 2,6-Bis(aryl)-4-pyridinemethanols with Trifluoromethyl Substituents†

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A series of 21 α-alkylaminomethyl-2,6-bis(aryl)-4-pyridinemethanols, where aryl is substituted phenyl bearing a CF_3 substituent on one or both phenyl rings, were synthesized from the corresponding 2,6-bis(aryl)isonicotinic acids. Among the 21 compounds, 19 were curative against *Plasmodium berghei* in mice at a dosage of 160 mg/kg; 11 of these were curative at 40 mg/kg, 3 were curative at 20 mg/kg, and 2 were active at 10 mg/kg.

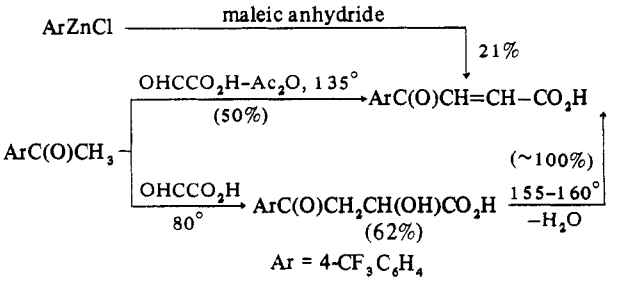
In the preceding paper[1] in this series, we reported the antimalarial activity against *Plasmodium berghei* in mice‡ for 29 α-alkylaminomethyl-2,6-bis(aryl)-4-pyridinemethanols bearing Cl, Br, F, and OCH_3 substituents on the aryl (phenyl) rings. As this earlier work was in progress, other laboratories investigating the related 4-quinolinemethanols[3] and the 9-phenanthrenemethanols[4] observed increased antimalarial efficacy when one or more of the halo substituents were replaced with a CF_3 group. Accordingly, our work was directed to analogs containing a CF_3 group in one or both phenyl rings, the results of which are reported herein.

Chemistry. Candidate antimalarials bearing a CF_3 group on both phenyl rings, or on one ring combined with one or two halo substituents on the other phenyl ring, were prepared by methods described earlier.[1] The six required intermediate isonicotinic acids listed in Table I were prepared by the Zecher–Krohnke ring-closure method.[5] For the important isonicotinic acid Ia, the 4-$CF_3C_6H_4$ group is required in both Zecher–Krohnke intermediates. The pyridinium bromide salt was prepared from 4-$CF_3C_6H_4C(O)CH_3$ in a conventional way and the acrylic acid was prepared in 3 ways as shown by Scheme I.

4-$CF_3C_6H_4C(O)CH{=}CHCO_2H$ was prepared in low (20%) yield by condensing 4-$CF_3C_6H_4ZnCl$ with maleic anhydride.[6] In an improved method, 4-$CF_3C_6H_4C(O)CH_3$ was condensed at 135° with 1 mole of glyoxylic acid in Ac_2O with a little Et_3N as catalyst to yield the acrylic acid in 50% yield. Temperature control, however, was critical to avoid tar formation. In larger scale work, the condensation was performed neat at 80° to form 2-hydroxy-3-(4-trifluoromethylbenzoyl)propionic acid which was isolated and dehydrated neat at 155–160° (1–2 mm).

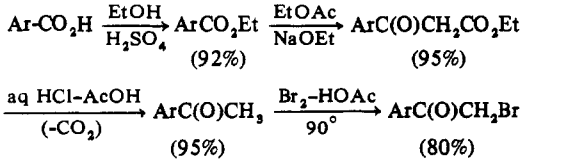
The intermediates for the meta isomer Ib were prepared from the corresponding 3-substituted intermediates. The 4-unsym isonicotinic acids Ic, Id, Ie, and If were prepared from 4-(and 3-)trifluoromethylphenacylpyridinium bromides and the required 4-bromo, 4-chloro-, and 3,4-dichlorobenzoylacrylic acids.[1]

Scheme I



The amino alcohol side chain was introduced by the method of Lutz and coworkers.[7] The sequence was carried through without purification of intermediates, although it is preferable to purify at the bromomethyl ketone stage and 4 examples are listed in Table II. In the case of IIa, the diazo ketone (89% from Ia) was isolated and characterized. For larger scale work, an alternative route to the bromomethyl ketones was sought which did not utilize CH_2N_2. The method selected and developed for IIa used the Claisen condensation[8] as the key step in the sequence.

Compound Ia was converted to the ethyl ester (92%) which was treated with EtOAc and NaOEt[8] to yield the ethyl 4-pyridinoylacetate (95%). Hydrolysis–decarboxylation using a concd aqueous HCl–AcOH (1 : 1, v/v) system gave the 4-pyridyl methyl ketone in high yield (95–97%). The dropwise addition of Br_2 (1.1 equiv) in AcOH to the methyl ketone in AcOH at 90° gave bromomethyl ketone IIa (80%) with minimum over- or underbromination.



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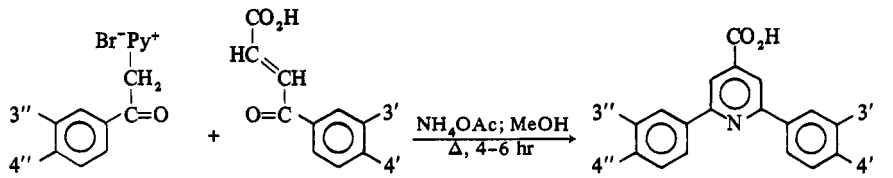
‡The antimalarial tests were performed by Dr. Leo Rane of the University of Miami.[2] See footnote *a*, Table IV. Testing results were supplied through the courtesy of Drs. Thomas R. Sweeney and Richard E. Strube of the Walter Reed Army Institute of Research.

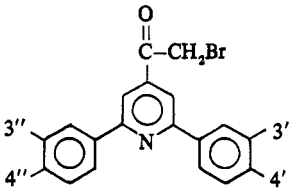
Table I. 2,6-Bis(aryl)isonicotinic Acids



I

No.	Substituents	Mp, °C (solvent)	Yield, %	Formula	Analyses
Ia	4′=4″ = CF_3	287–289 (C_6H_6)	80	$C_{20}H_{11}F_6NO_2$	C, H, N
Ib	3′=3″ = CF_3	219–220 (C_6H_6)	51	$C_{20}H_{11}F_6NO_2$	C, H
Ic	4″-CF_3, 4′-Br	280–283 (AcOH)	60	$C_{19}H_{11}BrF_3NO_2$	C, H, N
Id	4″-CF_3, 4′-Cl	269–271 (*i*-PrOH)	69	$C_{19}H_{11}ClF_3NO_2$	C, H, N, F
Ie	4″-CF_3, 3′=4′=Cl	288–290 (EtOH)	79	$C_{19}H_{10}Cl_2F_3NO_2$	C, H, N
If	3″-CF_3, 3′=4′=Cl	239–240 (aq EtOH)	80	$C_{19}H_{10}Cl_2F_3NO_2$	C, H, N

Table II. Bromomethyl 2,6-Bis(aryl)-4-pyridyl Ketones



II

No.	Substituents	Mp, °C (Solvent)	Yield,[a] %	Formula	Analyses
IIa	4′=4″=CF_3	154–155 ($CHCl_3$-petr ether)	76[b]	$C_{21}H_{12}BrF_6NO$	C, H, N, Br, F
IIb	3′=3″=CF_3	75–77 (EtOH)	48	$C_{21}H_{12}BrF_6NO$	C, H, N
IIc	4″-CF_3, 4′-Br	136–138 (*i*-PrOH)	55	$C_{20}H_{12}Br_2F_3NO$	C, H, N, F
IId	4″-CF_3, 4′-Cl	124–127 (*i*-PrOH)	60	$C_{20}H_{12}BrClF_3NO$	C,[c] H, N
IIe	4″-CF_3, 3′=4′=Cl	Oil	66		
IIf	3″-CF_3, 3′=4′=Cl	Oil	73		

[a] From the corresponding isonicotinic acids, Table I. [b] In 60–70% yield *via* the Claisen condensation route (see text). [c] Calcd C, 52.83; found, 53.41.

The bromomethyl ketones were reduced with $NaBH_4$ in the usual manner[1] to yield crude epoxides containing one or more by-products. The crude epoxides were converted successfully,[1] however, to the candidate antimalarials listed in Table III. Studies of the reduction of bromo ketone IIa to epoxide with $NaBH_4$ were successful in reducing by-products to trace quantities with a significant improvement in the yields. The key factors were (1) minimum $NaBH_4$ and (2) a low initial reaction temperature.

Biological Activity. Antimalarial activity data against *P. berghei* in mice, as measured by the Rane test,‡ are presented in Table IV. The compounds are listed according to the phenyl groups in the 2 and 6 positions of the pyridine ring, reflecting the isonicotinic acids of Table I from which they were synthesized. Among the 21 compounds, 19 were curative in the Rane test at a dosage of 160 mg/kg; 11 of these were curative at 40 mg/kg, 3 were curative at 20 mg/kg, and 2 were active at 10 mg/kg (**1** and **5**). These results show that the CF_3 group increased the antimalarial activity of the 2,6-bis(aryl)-4-pyridinemethanols relative to Cl, Br, F, H, or OCH_3 substituents, the results for which were reported earlier.[1]

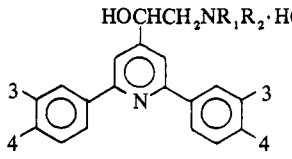
None of the compounds was toxic to the host through 640 mg/kg. Further, they are significantly less phototoxic than the 2-phenyl-4-quinolinemethanols.[9§] Compound **1** has been prepared on a large scale in these laboratories as a potential clinical drug. The *O*-succinoyl derivative of **1** was prepared (**1a**, Table III), but the antimalarial activity was unchanged, indicating *in vivo* removal of the succinoyl group.

Certain structure–activity relationships may be noted based on the Rane data of Table IV. In terms of substituents on phenyl, a CF_3 in the 4 position of each ring is superior to all other combinations tested. The 2,6-bis(3-trifluoromethylphenyl) analog **16** is less effective than its 2,6-bis(4-trifluoromethylphenyl) counterpart **6**. The substitution of one CF_3 group with Br results in only slight loss of activity (compare **17** with **6** and **18** with **1**), but a greater loss of activity results if one CF_3 group is replaced with Cl (**19**) and two chloro groups on one ring results in a marked loss of activity (**20** and **21**).

Turning to the impact of the amino alcohol side chain, compounds **4**, **5**, and **6**, which possess the secondary amine configuration (R_1 = H) are the most active compounds reported herein, based on curative activity at 20 mg/kg. A similar result was observed in the 2,6-bis(chlorophenyl)

§ W. E. Rothe, Walter Reed Army Institute of Research, personal communication.

Table III. 2,6-Bis(aryl)-4-pyridinemethanols



No.	R_1	R_2	Mp, °C (solvent)	Yield,[a] %	Formula	Analyses[b]
			2,6-Bis(4-trifluoromethylphenyl)-			
1	1-Bu	1-Bu	233–235 (EtOH–H_2O)	71	$C_{29}H_{33}ClF_6N_2O$	Cl
1a[c]	1-Bu	1-Bu	176–178 (*i*-PrOH)	85[c]	$C_{33}H_{37}ClF_6N_2O_4$	
2	4-Hept	4-Hept	211–213 (CH_3CN)	25	$C_{35}H_{45}ClF_6N_2O$	
3	1-Pent	1-Pent	225–228 (EtOH–H_2O)	48	$C_{31}H_{37}ClF_6N_2O$	
4[d]	H	2-Pent	128–129.5 (CH_3CN)	41	$C_{26}H_{26}F_6N_2O$	
5	H	4-Hept	202–204 (CH_3CN)	64	$C_{28}H_{31}ClF_6N_2O$	
6	H	1-Bu	253–255 (EtOH–Et_2O)	42	$C_{25}H_{25}ClF_6N_2O$	F, Cl
7	H	1-Pent	255–257 (CH_3CN)	63	$C_{26}H_{27}ClF_6N_2O$	Cl
8	H	Cyclohex	266–268 (EtOH)	57	$C_{27}H_{27}ClF_6N_2O$	
9	H	2-Bu	242–245 (EtOH–Et_2O)	73	$C_{25}H_{25}ClF_6N_2O$	
10	H	1-Pr	267–269 (EtOH–CH_3CN)	77	$C_{24}H_{23}ClF_6N_2O$	
11	H	Et	275–276 (EtOH)	77	$C_{23}H_{21}ClF_6N_2O$	
12	H	1-Hex	208–209 (CH_3CN)	68	$C_{27}H_{29}ClF_6N_2O$	Cl
13	H	Cyclobu	265–267 (CH_3CN)	63	$C_{25}H_{23}ClF_6N_2O$	
14	H	1-Oct	184–186 (CH_3CN)	68	$C_{29}H_{33}ClF_6N_2O$	Cl
15	H	1-Hept	198–199 (CH_3CN)	65	$C_{28}H_{31}ClF_6N_2O$	Cl
			2,6-Bis(3-trifluoromethylphenyl)-			
16	1-Bu	1-Bu	256–258 (EtOH–Et_2O)	32	$C_{25}H_{25}ClF_6N_2O$	
			2-(4-Trifluoromethylphenyl)-6-(4-bromophenyl)-			
17[d]	H	1-Bu	233–235 (*i*-PrOH)	44	$C_{29}H_{24}BrF_3N_2O$	F
18	1-Bu	1-Bu	229–231 (*i*-PrOH)	39	$C_{28}H_{33}BrClF_3N_2O$	F
			2-(4-Trifluoromethylphenyl)-6-(4-chlorophenyl)-			
19	1-Bu	1-Bu	229–231 (*i*-PrOH)	34	$C_{28}H_{33}Cl_2F_3N_2O$	Cl, F
			2-(4-Trifluoromethylphenyl)-6-(3,4-dichlorophenyl)-			
20	1-Bu	1-Bu	208–210 (CH_3CN–H_2O)	35	$C_{28}H_{32}Cl_2F_3N_2O$	
			2-(3-Trifluoromethylphenyl)-6-(3,4-dichlorophenyl)-			
21	1-Bu	1-Bu	178–179 (*i*-PrOH)	35	$C_{28}H_{32}Cl_2F_3N_2O$	

[a] From bromomethyl ketone, Table II. [b] In addition to C, H, N. [c] *O*-Succinoyl derivative, yield from 1. [d] Free base.

series.[1] For this reason, compounds **4–15** inclusive were prepared to assess the secondary amine configuration more fully. These are listed in the order of descending activity, based on curative activity at a given dosage level. If we direct our attention to the case where R_2 is linear alkyl, the descending order of activity with respect to R_2 is as follows: 1-Bu (**6**) > 1-Pent (**7**) > 1-Pr (**10**) > Et (**11**) > 1-Hex (**12**) > 1-Oct (**14**) > 1-Hept (**15**). The effect of branching on the alkyl group R_2 (R_1 = H) is pronounced, however. Thus, 2-Pent (**4**) imparts about one dose level more activity than 1-Pent (**7**) and 4-Hept (**5**) imparts nearly three dose levels more activity than 1-Hept (**15**). Further, **5** shows the greatest extension of life at 10 mg/kg, 9.1 days. Among the two alicylic amines employed, cyclohexyl (**8**) is somewhat superior to cyclobutyl (**13**) in that it is curative at 40 mg/kg, but **13** is active at 20 mg/kg, whereas 8 is not.

Only three tertiary amine configurations (R_1 = R_2) were tested: 1-Bu (**1**), 4-Hept (**2**), and 1-Pent (**3**). The differences are not great, but **3** is the least active. Two of these compounds give 3 or more days extension of life at 10 mg/kg, even though they are noncurative at 20 mg/kg.

Finally, we note that the parent compound, α-(di-1-butyl)aminomethyl-2,6-bis(phenyl)-4-pyridinemethanol, was active but noncurative through 640 mg/kg in the Rane test.[1,2] Accordingly, the results reported herein and in a preceding paper[1] demonstrate the considerable increase in antimalarial efficacy that was achieved by variations in substituents on the phenyl rings and in the alkyl groups attached to nitrogen to yield a new class of compounds of potential clinical utility in the treatment of malaria.

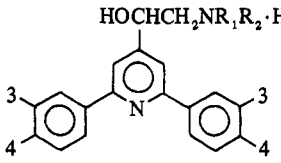
Experimental Section#

2,6-Bis(4-trifluoromethylphenyl)isonicotinic Acid (Ia). 4-Trifluoromethylphenacylpyridinium Bromide. To a soln of 4-trifluoromethylacetophenone (25 g, 0.13 mole) in $CHCl_3$ (100 ml) was added a soln of Br_2 (10.5 g, 0.13 mole) in $CHCl_3$ (40 ml). The mixt was stirred at room temp for 15 min. The soln was washed with H_2O (×4), dried (Na_2SO_4), and concd. The crude product was recrystd from petr ether (bp 30–60°) to yield 4-trifluoromethylphenacyl bromide (29.3 g, 83%), mp 54–56°. *Anal.* ($C_9H_6BrF_3O$) C, H, F. A soln of the bromo ketone (80.8 g, 0.3 mole) in EtOH (200 ml) contg pyridine (30 ml) was refluxed for 15 min. Et_2O was added to the cooled soln until turbid, and the soln was allowed to stand overnight. Filtration afforded 97 g (95%), mp 219–221° dec. *Anal.* ($C_{14}H_{11}BrF_3NO$) C, H, N. F.

3-(4-Trifluoromethylbenzoyl)acrylic Acid. Freshly fused $ZnCl_2$ (82 g, 0.6 mole) was dissolved in dry Et_2O (400 ml) and added dropwise to the Grignard reagent prepd from 4-bromobenzotrifluoride (112.5 g, 0.5 mole) and Mg (12.2 g, 0.5 g-atom) in Et_2O (600 ml). Maleic anhydride (44 g, 0.45 mole) in Et_2O (400 ml) was added over 30 min

#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%.

Table IV. 2,6-Bis(aryl)-4-pyridinemethanols. Antimalarial Activity against *Plasmodium berghei*



No.	R_1	R_2	ΔMST or C[a,b] Dosage, mg/kg 10	20	40	80	160
			2,6-Bis(4-trifluoromethylphenyl)-				
1	1-Bu	1-Bu	5.5 (A)	8.6	2C	5C	5C
2	4-Hept	4-Hept	4.1	12.2 (A)	2C	5C	5C
3	1-Pent	1-Pent		4.8	9.0 (A)	4C	5C
4[c]	H	2-Pent	3.8	3C	5C	5C	5C
5	H	4-Hept	9.1 (A)	2C	4C	5C	5C
6	H	1-Bu	5.0	1C	3C	5C	5C
7	H	1-Pent	0.3	8.0 (A)	3C	5C	5C
8	H	Cyclohex	0.3	1.4	3C	5C	5C
9	H	2-Bu	0.7	1.3	3C	5C	5C
10	H	1-Pr	0.7	4.9	2C	5C	5C
11	H	Et	1.1	1.3	1C	2C	5C
12	H	1-Hex		1.6	11.9 (A)	5C	5C
13	H	Cyclobu	1.5	7.9 (A)	12.9	3C	5C
14	H	1-Oct		0.9	7.8	2C	4C
15	H	1-Hept	0.3	1.1	7.3	13.7	5C
			2,6-Bis(3-trifluoromethylphenyl)-				
16	H	1-Bu	0.7	4.6	13.3 (A)	5C	5C
			2-(4-Trifluoromethylphenyl)-6-(4-bromophenyl)-				
17[c]	H	1-Bu	3.0	11.8 (A)	2C	5C	5C
18	1-Bu	1-Bu	0.8	7.8 (A)	10.8	1C	3C
			2-(4-Trifluoromethylphenyl)-6-(4-chlorophenyl)-				
19	1-Bu	1-Bu	2.2	4.4	9.6 (A)	1C	2C
			2-(4-Trifluoromethylphenyl)-6-(3,4-dichlorophenyl)-				
20	1-Bu	1-Bu	0.3	0.5	8.1 (A)	12.1	18.1
			2-(3-Trifluoromethylphenyl)-6-(3,4-dichlorophenyl)-				
21	1-Bu	1-Bu		1.6	3.8	5.6	7.2

[a]The test method described in ref 2 is a highly standardized procedure in which the *P. berghei* causes death of control mice at essentially 6.2 days. An increase in the mean survival time of five mice by more than 2.5 days beyond this time is statistically significant. Mice surviving more than 60 days are regarded as cured (C). A candidate drug is considered active (A) at a given dosage if one or more mice are alive on day 14. [b]All compounds listed are nontoxic and curative (5C) through 640 mg/kg, except **21** which is curative (2C) at 640 mg/kg only. [c]Free base.

with stirring at reflux. After 2 hr, the mixt was cooled and acidified to pH 2 with 10% HCl. The Et_2O layer was sepd and dried ($MgSO_4$), and the Et_2O evapd. The residue was recrystd from C_6H_6 (×3) to yield the title compd, 24.5 g (21%), mp 149–151°. *Anal.* ($C_{11}H_7F_3O_3$) C, H, F. An alternative procedure is as follows. A mixt of 4-trifluoromethylacetophenone (18.8 g), glyoxylic acid monohydrate (18.8 g), Ac_2O (20 ml), and a drop of Et_3N was heated to 135°, internal temp. More Et_3N (2 ml) was added, and the mixt was held at 135° for 20 min. The mixt was cooled and evapd to dryness *in vacuo*. The solid residue was digested with H_2O, filtered, dried, and recrystd from C_6H_6 to give the title compd, 12.2 g (50%), mp 149–151°.

This procedure required close temp control to avoid tar formation. To avoid this, the method was modified to a two-step process wherein the intermediate α-hydroxy acid was isolated and pyrolyzed separately. 4-Trifluoromethylacetophenone (75.2 g, 0.4 mole) and $OHCCO_2H \cdot H_2O$ (75.2 g) were heated neat at 79–80° for 8 hr. The hot mixt was poured into dil aqueous HCl (7.5 ml of concd HCl and 800 ml of H_2O) with stirring. The aqueous mixt was extd with Et_2O (2 × 250 ml), and the aqueous phase was discarded. The ext was washed with H_2O (2 × 100 ml), and dried (Na_2SO_4), and Et_2O was removed (aspirator). The resulting residue was digested with hot $CHCl_3$ (100 ml), and the mixt was concd to a vol of 80–85 ml. Petr ether (30–60°, 250 ml) was added with stirring. The resulting precipitate was collected and washed with petr ether (100 ml). (Removal of petr ether from the combined washes and filtrate yielded unreacted acetophenone, 39.3 g, 52.3%, suitable for recycling.) The solid was digested again with $CHCl_3$ (150 ml), filtered, and air-dried to yield **2-hydroxy-3-(4-trifluoromethylbenzoyl)propionic acid** (31.2 g, 62%), mp 118–120°. *Anal.* ($C_{11}H_9F_3O_4$) C, H. The α-hydroxy acid was heated neat under vacuum (1–2 mm) in an oil bath until the internal temp reached 155°. The temp was increased to 160° over 40 min to complete the elimination of H_2O. The flask was allowed to cool and crystn of the title acrylic acid usually began at around 138°. The product was sufficiently pure for conversion to isonicotinic acid.

2,6-Bis(4-trifluoromethylphenyl)isonicotinic Acid (Ia). To 3-(4-trifluoromethylbenzoyl)acrylic acid (24 g, 0.08 mole) in MeOH–AcOH (3:1 v/v, 300 ml) was added 4-trifluoromethylphenacylpyridinium bromide (28 g, 0.08 mole) and NH_4OAc (66 g). The soln was refluxed (6 hr) and evapd. The residue was dissolved in hot 50% AcOH (80 ml) and cooled. The solid was collected, washed with H_2O, dried, and recrystd (dioxane–toluene, 1:4) to yield the title acid, 33 g (80%), mp 285–286°. *Anal.* (Table I).

2-(4-Bromophenyl)-6-(4-trifluoromethylphenyl)isonicotinic Acid (Ic). To 3-(4-bromobenzoyl)acrylic acid[1] (10.2 g, 0.04 mole) in MeOH (65 ml) was added 4-trifluoromethylphenacylpyridinium bromide (14.0 g, 0.04 mole) and ammonium acetate (32 g). The soln was refluxed for 5 hr. The NH_4 salt did not ppt. AcOH (50 ml) and H_2O (10 ml) were added, and the soln was filtered hot and allowed to cool. The resulting solid was crystd from AcOH to yield compd Ic (10.0 g, 60%), mp 280–283°. *Anal.* (Table I).

The above two syntheses are typical of the syntheses of 2,6-bis(phenyl)isonicotinic acids (see also ref 1).

Bromomethyl 2,6-Bis(4-trifluoromethylphenyl)-4-pyridyl Ketone (IIa). A. Diazo Ketone Sequence. 2,6-Bis(4-trifluoromethylphenyl)isonicotinic acid (17 g) was dissolved in $SOCl_2$ (150 ml), refluxed 3 hr, concd, and azeotroped with C_6H_6. The crude acid chloride in CH_2Cl_2 (200 ml) was added to a soln of CH_2N_2 (*ca.* 15 g) in

Et_2O at 0° and held at 5° overnight. The soln was evapd (aspirator) to yield crude cryst **diazomethyl 2,6-bis(4-trifluoromethyl)-4-pyridyl ketone** which, after washing with Et_2O–petr ether (30–60°), weighed 15.5 g (89%), mp 152–165° dec. This was used directly in the next step. Recrystn of a sample from ether–petr ether (30–60°) gave pure diazo ketone, mp 165–166° dec. *Anal.* ($C_{21}H_{11}F_6N_3O$) C, H, N. The diazo ketone (15.5 g) was added portionwise to 48% HBr (40 ml) in AcOH (400 ml). The soln was stirred at room temp for 1 hr and dild with cold H_2O. The resulting ppt was suspended in dil Na_2CO_3, filtered, washed with H_2O, and dried. Recrystn from EtOH gave the title bromomethyl ketone, 14.8 g (86%), mp 153–154°. *Anal.* (Table II). A repeat run, larger scale, gave 92% yield.

B. Claisen Condensation Sequence. A mixt of 2,6-bis(4-trifluoromethylphenyl)isonicotinic acid (100 g, 0.245 mole) and H_2SO_4 (25 ml) in dry EtOH (2.5 l.) was refluxed overnight. The soln was cooled to 5° and filtered, and the solid was washed with cold EtOH and H_2O. The solid was slurried in 5% $NaHCO_3$, filtered, and washed thoroughly with H_2O. After recrystn from EtOH (2.5 l.), there was obtained 93 g (87%) of **ethyl 2,6-bis(4-trifluoromethylphenyl)isonicotinate,** mp 125–126°. *Anal.* ($C_{22}H_{15}F_6NO_2$) C, H, N.

Ethyl 2,6-Bis(4-trifluoromethylphenyl)-4-pyridinoylacetate. A soln of the ethyl isonicotinate (93 g, 0.21 mole) in EtOAc (600 ml) was added to NaOEt [prepd by heating Na (8 g, 0.35 g-atom) in dry EtOH (100 ml) and evapg to dryness]. The mixt was refluxed 1.5 hr and poured into H_2O (2 l.). The soln was acidified to pH 5 with concd HCl. EtOAc was removed (aspirator), and the resulting ppt was filtered and washed with H_2O. Recrystn from EtOH (4.5 l.) gave 89 g (87%) of the title keto ester, mp 137–139°, homogeneous by tlc (EtOH–petr ether, 30–60°, 1:9). *Anal.* ($C_{24}H_{17}F_6NO_3$) C, H, N. A repeat run gave 95% yield.

Methyl 2,6-Bis(4-trifluoromethylphenyl)-4-pyridyl Ketone. A soln of the keto ester (88 g) in concd HCl (600 ml) and AcOH (600 ml) was refluxed for 1.5 hr. The soln was poured into cold H_2O (4.5 l.) with stirring. The ppt was filtered, washed with H_2O, and dried at room temp to yield the title ketone, 71 g (95%), mp 136.5–138°. Recrystn gave mp 140.5–141.5°. *Anal.* ($C_{21}H_{13}F_6NO$) C, H, N. A repeat run gave 97% yield.

Bromomethyl 2,6-Bis(4-trifluoromethylphenyl)-4-pyridyl Ketone (IIa). The bromination of the above methyl ketone was studied to obtain optimum conditions. A soln of the methyl ketone (4.09 g, 10 mmoles) in glacial AcOH (25 ml) was heated to 90°. Br_2 (1.7 g, 11 mmoles) in glacial AcOH (7 ml) was added dropwise to observe the color change. After the addn, the mixt was cooled to 30°, poured into H_2O (150 ml), and extd with $CHCl_3$. The ext was washed successively with H_2O, 5% $NaHCO_3$, and H_2O and dried ($MgSO_4$). The vol was reduced to 15 ml, and petr ether (30–60°) was added to ppt the product. Filtration yielded the title bromo ketone, 3.5 g (71%), mp 148–150°. Tlc examn indicated three minor impurities. Recrystn from $CHCl_3$–petr ether gave mp 154–155°, one spot by tlc. *Anal.* (Table II). Larger-scale runs gave 79–84% yields.

2,6-Bis(4-trifluoromethylphenyl)-4-pyridinemethanols. In general the bromomethyl ketones listed in Table II were reduced with $NaBH_4$ to yield crude epoxide which was treated directly with mono- and dialkylamines as described previously.[1] The yields listed in Table III reflect this approach. Later, the $NaBH_4$ reduction step was studied, and a procedure to yield pure epoxide was developed, as follows.

4-(Epoxyethyl)-2,6-bis(4-trifluoromethylphenyl)pyridine. The bromomethyl ketone IIa (9.8 g, 20 mmoles) was suspended in a solvent system comprising EtOH (40 ml)–H_2O (20 ml)–$EtOC_2H_4OH$ (20 ml). After cooling to −20°, a soln of $NaBH_4$ (0.92 g, 24 mmoles) in H_2O (20 ml) was added, followed by more $EtOC_2H_4OH$ (140 ml). The mixt was allowed to warm to 10° over 30–40 min, then warmed to 30° and stirred for 30 min. Aqueous NaOH (0.8 g in 2 ml of H_2O) was added and the mixt was stirred at 30° for 20 min and acidified to pH 6. Water (240 ml) was added and the mixt was cooled to 0°. The solid was filtered, washed with H_2O, dissolved in $CHCl_3$, washed again with H_2O, and dried ($MgSO_4$). The soln was evapd, and the residue was crystd from EtOH to give the title epoxide, 6.35 g (77%), mp 121–123°; this material was used directly in the amination step. Recrystn from EtOH gave mp 122–123.5°. *Anal.* ($C_{21}H_{13}F_6NO$) C, H, N, F. The by-product was identified as the methyl carbinol (isolated and identified by elemental analysis and nmr).

α-Di-*n*-butylaminomethyl-2,6-bis(4-trifluoromethylphenyl)-4-pyridinemethanol Hydrochloride (1). The precursor epoxide (11 g) and $HN(n\text{-}Bu)_2$ (20 ml) in EtOH (20 ml) were refluxed 15 hr. The mixt was evapd to dryness. The residue was dissolved in min EtOH, and the soln was acidified with 10% HCl. Cryst compd sepd after standing at room temp for several hours. The product was sepd, washed with H_2O, suspended in Et_2O, sepd again, and dried. Recrystn from EtOH–H_2O gave the title compd, 11.5 g (79%), mp 233–235°. *Anal.* (Table III). The free base (1 g) and succinic anhydride (210 mg) were dissolved in dry acetone and refluxed 1 hr. After solvent removal, the residue was suspended in H_2O and acidified with HCl to pH 4. After cooling, the solid was filtered and crystd from *i*-PrOH to yield the *O*-succinoyl derivative **1a**, 990 mg (85%), mp 176–178°. *Anal.* (Table III).

α-*n*-Butylaminomethyl-2,6-bis(4-trifluoromethylphenyl)-4-pyridinemethanol Hydrochloride (5). A soln of the above epoxide (42 g, 0.103 mole) and $n\text{-}BuNH_2$ (210 ml) in EtOH (630 ml) was refluxed for 16 hr. The solvent and volatiles were removed under reduced pressure. The residue was slurried in EtOH (150 ml) and acidified to pH 2 with 20% HCl in EtOH. The soln was concd until pptn occurred. The mixt was dild to 1500 ml with H_2O, stirred for 2 hr, and filtered. The solid was washed liberally with H_2O and recrystd from *i*-PrOH–Et_2O (200:800 ml) to yield 30 g of the title compd. Recrystn from *i*-PrOH gave 29 g (54%), mp 250–251° partial dec. *Anal.* (Table III).

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