of the crude product from Me_2CO–hexane. Recrystallization from EtOAc–hexane gave the analytical specimen: mp 209–212°; $[\alpha]^{25}D$ −78.9°; ir ($CHCl_3$) 3620 and 1720 cm^{-1}. *Anal.* ($C_{20}H_{29}ClO_2$) C, H, Cl.

7-Chloro-5α,6α-epoxy-3β,17β-dihydroxypregn-7-en-20-one 3,17-Diacetate (11a). A solution of **2a** (0.9 g, 2 mmol) and *m*-chloroperbenzoic acid (0.42 g) in CH_2Cl_2 (10 ml) was stirred at room temperature for 30 min, diluted with CH_2Cl_2, and washed in turn with 5% $NaHSO_3$ solution, 5% $NaHCO_3$ solution, and H_2O. The dried (Na_2SO_4) organic layer was evaporated *in vacuo* and crystallization of the resulting solid from CH_2Cl_2–Et_2O gave 0.68 g (72%) of **11a**, mp 224–225°. Two additional crystallizations from the same solvent system afforded the analytical sample: mp 226–227°; $[\alpha]D$ −169.2°; nmr ($CDCl_3$) δ 3.20 (s, 1 H, C_6H). *Anal.* ($C_{25}H_{33}ClO_6$) C, H, Cl.

6β,7-Dichloro-3β,5α,17α-trihydroxypregn-7-en-20-one 3,17-Diacetate (12). A suspension of 11a (0.9 g, 1.93 mmol) in CCl_4 (20 ml) was cooled to 0°. HCl (g) was bubbled through the stirred mixture until the solid dissolved (~4 min). The solvent was removed at low temperature (<15°) under reduced pressure and the resulting solid was crystallized from Et_2O–hexane to give 0.629 g (65%) of 12, mp 197–198°. Recrystallization from the same solvent system gave the analytical sample: mp 198–199°; $[\alpha]D$ −124.0°; ir ($CHCl_3$) 3700 (sharp), 3400 (br), and 1735 cm^{-1}; nmr ($CDCl_3$) δ 4.33 (s, 1 H, C_6H) and 1.23 (s, 3 H, $C_{19}H_3$). *Anal.* ($C_{25}H_{34}Cl_2O_6$) C, H, Cl.

6α,7-Dichloro-3β,5α,17α-trihydroxypregn-7-en-20-one 3,17-Diacetate (13). A solution of 11a (1.0 g, 2.15 mmol) in CH_2Cl_2 (20 ml) was cooled to 0°. HCl (g) was bubbled through the solution for 4 min and the solvent was then removed *in vacuo*. The residue was crystallized from CH_2Cl_2–Et_2O to furnish (0.41 g, 37%) of **13**, mp 209–210° (mmp with **12**, 183–185°). A second crop (0.1 g, 9%, mp 210–211°) was obtained from the mother liquors. Recrystallization from the same solvent mixture afforded the analytical specimen: mp 211–212°; $[\alpha]^{25}D$ −104.5°; ir ($CHCl_3$) 3650 and 1735 cm^{-1}; nmr ($CDCl_3$) δ 4.57 (t, 1 H, C_6H) and 1.01 (s, 3 H, $C_{19}H_3$). *Anal.* ($C_{25}H_{34}Cl_2O_6$) C, H, Cl.

7-Chloro-5α,6α-epoxy-3β,17α-dihydroxypregn-7-en-20-one 17-Acetate (11b). To a solution of **2b** (2.9 g, 7.2 mmol) in CH_2Cl_2 (30 ml) was added *m*-chloroperbenzoic acid (1.8 g). The solution was allowed to stand at room temperature for 1 hr and was worked up as before. The crude product was crystallized from CH_2Cl_2–Et_2O to give 1.9 g (63%) of **14**. A second crop (0.4 g, 13%) was recovered from the mother liquors. Recrystallization from the same solvents furnished the analytical sample: mp 213° dec; $[\alpha]^{25}D$ −179.5°; ir ($CHCl_3$) 3700, 1730, and 1710 cm^{-1}; nmr ($CDCl_3$) δ 3.20 (s, 1 H, C_6H). *Anal.* ($C_{23}H_{31}ClO_5$) C, H, Cl.

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Antimalarials. 4. 4-Pyridinemethanols with Styryl and Benzoyl Substituents†

M. P. LaMontagne

Ash Stevens Inc., Detroit, Michigan 48202. *Received July 13, 1972*

A series of seven α-alkylaminomethyl-4-pyridinemethanols containing styryl substituents in the 2 and/or 6 positions of the pyridine ring has been synthesized. One compound was curative against *Plasmodium berghei* in mice at a dosage of 20 mg/kg, three were curative at 40 mg/kg, two were curative at 80 mg/kg, and one was inactive through 160 mg/kg. In addition, one compound bearing a 4-trifluoromethylbenzoyl substituent in the 2 position of the pyridine ring was prepared. It was curative at 80 mg/kg and showed marginal activity at 40 mg/kg.

In the two preceding papers[1,2] in this series, we reported the preparation and antimalarial activity against *Plasmodium berghei* in mice‡ of a series of α-alkylaminomethyl-2,6-bis(phenyl)-4-pyridinemethanols bearing Cl, Br, F, OCH_3, and CF_3 substituents on the phenyl rings. The very encouraging antimalarial activity demonstrated by several compounds in these series prompted us to investigate the effect of replacing one or both of the phenyl substituents with styryl and benzoyl groups.

Chemistry. The four structural types of compounds described in the present work are shown in Chart I. Compounds of type I were synthesized by the procedure shown in Scheme I.

Ethyl 2,6-dimethylisonicotinate was prepared from 4-cyano-2,6-lutidine[4] *via* hydrolysis and esterification under usual conditions. Condensation of the ester with excess aldehyde afforded the requisite 2,6-bis(styryl)isonicotinic acid esters in approximately 50% yield. Hydrolysis of the esters to the isonicotinic acid, followed by introduction of the amino alcohol side chain by the procedure developed

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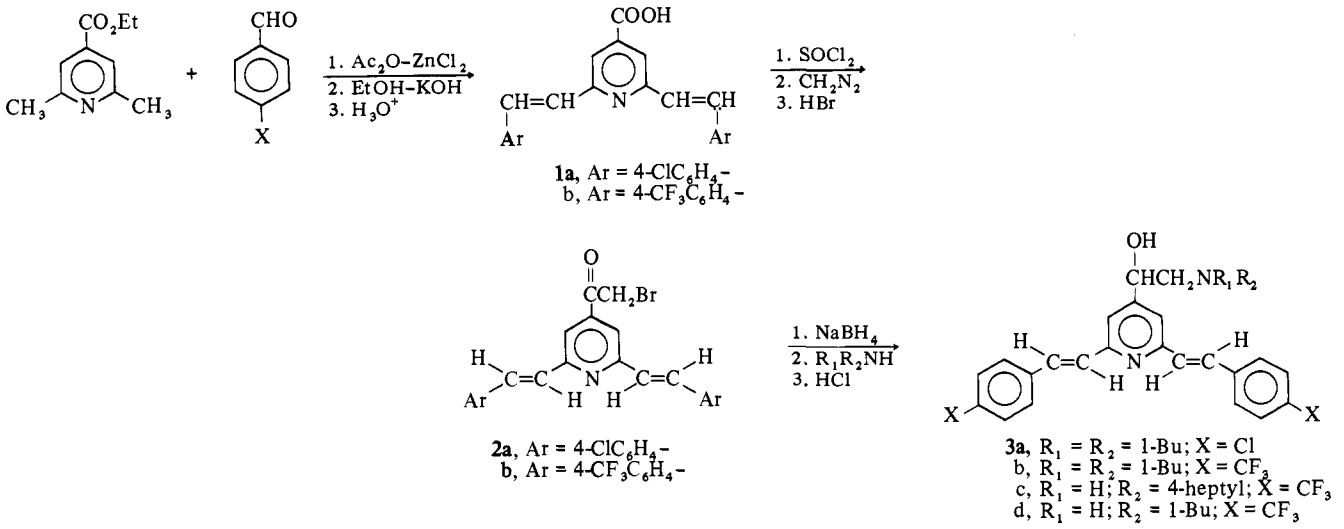
‡The antimalarial tests were performed by Dr. Leo Rane of the University of Miami (see ref 3). See footnote *a*, Table III. Testing results were supplied through the courtesy of Drs. Thomas R. Sweeney and Richard E. Strube of the Walter Reed Army Institute of Research.

Scheme I



1a, Ar = 4-ClC_6H_4-
b, Ar = 4-$CF_3C_6H_4$-

2a, Ar = 4-ClC_6H_4-
b, Ar = 4-$CF_3C_6H_4$-

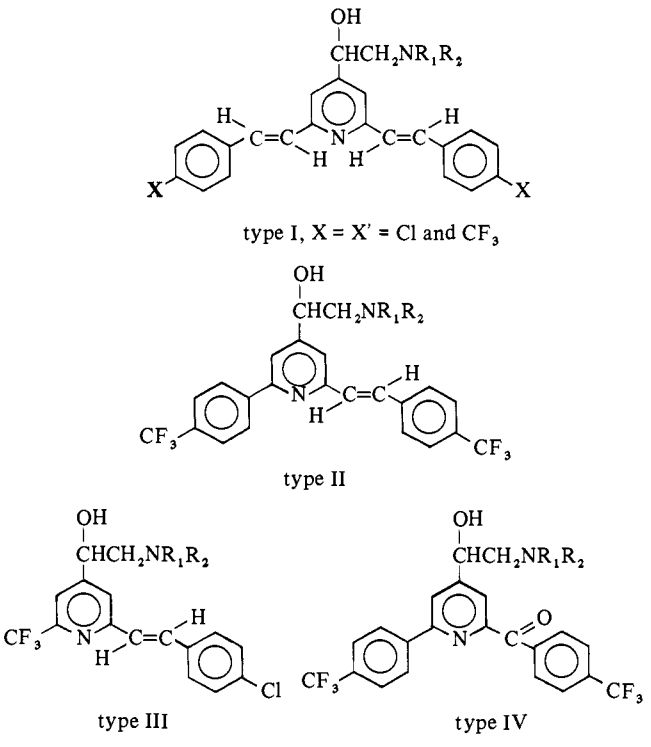
3a, $R_1 = R_2$ = 1-Bu; X = Cl
b, $R_1 = R_2$ = 1-Bu; X = CF_3
c, R_1 = H; R_2 = 4-heptyl; X = CF_3
d, R_1 = H; R_2 = 1-Bu; X = CF_3

by Lutz and coworkers,[5] afforded the desired bis(styryl)-4-pyridinemethanols **3a-d**.

The two examples of type II were prepared as shown in Scheme II. The 2-methyl-6-(4-trifluoromethylphenyl)isonicotinic acid (**1c**) was prepared *via* the modified Zecher-Krohnke ring-closure reaction previously described.[1] The remainder of the sequence was identical with that used to prepare compounds **3a-d**.

The analog of type III was prepared as shown in Scheme III. The starting 2-picoline was also prepared by the modified Zecher-Krohnke cyclization procedure.[1] Conversion to the 2-pyridylcarbinol acetate was by the procedure of Boekelheide and Linn.[6] Hydrolysis with a catalytic amount of sodium ethoxide, followed by oxidation with selenium dioxide, afforded the required aldehyde. The styryl function was introduced in good yield by the reaction of the 2-pyridinecarboxaldehyde with 4-chlorophenyltriphenylphosphonium methylide. Hydrolysis to the isonicotinic acid, followed by the introduction of the side chain by the usual sequence, afforded the target compound. The benzoyl analog synthesized (**3h**) was prepared as shown in Scheme IV (see Tables I and II)

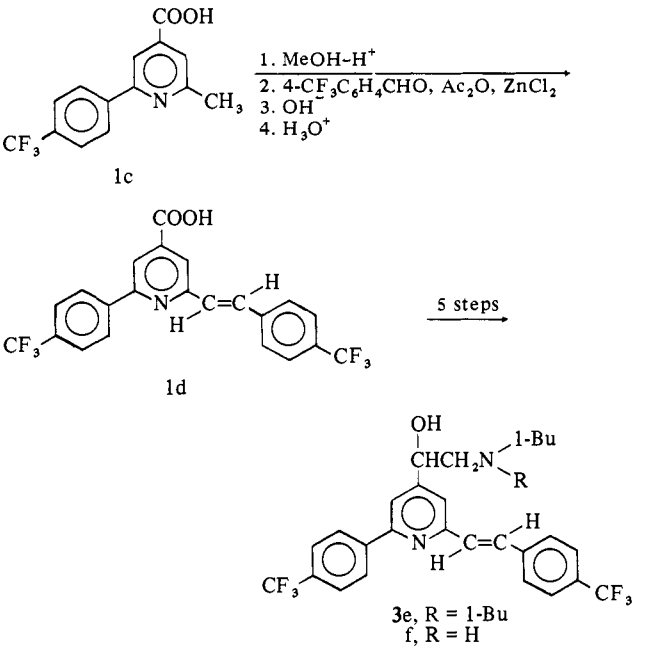
Chart I



Biological Activity. Antimalarial activity data against *P. berghei* in mice, as measured by the Rane test,[‡,3] are presented in Table III. All compounds prepared were curative at a dosage of 80 mg/kg or less, except **3d** which was inactive through 160 mg/kg (the highest dose level tested); three compounds were curative at 40 mg/kg and one was active at 20 mg/kg.

In preceding papers, we have reported results for the substituted 2,6-bis(phenyl)-4-pyridinemethanols.[1,2] If we compare the 2,6-bis(trifluoromethylphenyl) analogs[2] with the present styryl and benzoyl counterparts, we observe a decrease in activity; on the other hand, α-(di-*n*-butylaminomethyl)-2,6-bis(4-chlorostyryl)-4-pyridinemethanol is one dosage level more active than the corresponding 2,6-bis(4-chlorophenyl) compound,[1] but the data are too limited to generalize that Cl substituents are more effective than CF_3 substituents in the styryl series. Again, while examples are

Scheme II

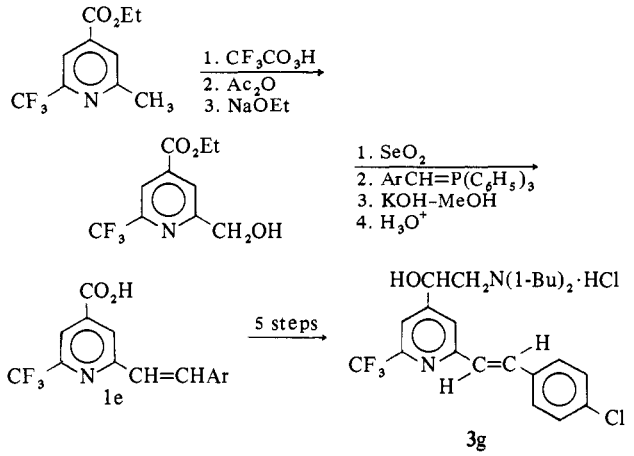


limited, the effects of the amino alcohol side-chain configuration upon activity differ with styryl *vs.* phenyl substituents. Particularly striking is that α-(*n*-butylaminomethyl)-2,6-bis(4-trifluoromethylstyryl)-4-pyridinemethanol (**3d**) is inactive through 160 mg/kg, whereas the di-*n*-butyl analog **3b** is curative at 80 mg/kg. Compare also **3e** and **3f**. None of the compounds were toxic to the host at the dosages tested.

Experimental Section

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%.

Scheme III



Preparation of Styryl-Containing Isonicotinic Acids. Ethyl 2,6-Dimethylisonicotinate. A solution of 4-cyano-2,6-lutidine[4] (15 g, 0.115 mol) in H_2O (300 ml) containing NaOH (50 g) was heated at reflux until NH_3 evolution ceased. The solution was acidified with HCl and concentrated to dryness at reduced pressure. The residue was dissolved in EtOH (500 ml) containing H_2SO_4 (20 g) and the solution was heated at reflux 6 hr. The reaction mixture was carefully poured into H_2O containing $NaHCO_3$ (80 g) and the product was extracted with Et_2O. The Et_2O was dried ($MgSO_4$) and concentrated and the residue distilled to yield the ester (13.5 g, 75%), bp 95–97° (2 mm) [lit.[7] bp 115–118° (5 mm)].

Ethyl 2,6-Di-*p*-chlorostyrylisonicotinate. A solution of ethyl 2,6-dimethylisonicotinate (5.4 g, 0.03 mol) and *p*-chlorobenzaldehyde (15.1 g, 0.12 mol) in Ac_2O (25 g) containing $ZnCl_2$ (0.2 g) was heated to reflux for 19 hr. The HOAc and Ac_2O were distilled until the pot temperature reached 215°. The viscous oil crystallized upon cooling. The solid was triturated with petroleum ether (two times) and with dilute K_2CO_3. The solid was crystallized from C_6H_6 to afford the product (7.0 g, 55%), mp 158–160°

Anal. ($C_{24}H_{19}Cl_2NO_2$) C, H, Cl, N.

2,6-Di-*p*-chlorostyrylisonicotinic Acid (1a). The above ester (6.5 g, 15 mmol) was heated at reflux in 5% ethanolic KOH (150 ml) for 2 hr. Water was added and the precipitate dissolved. The solution was acidified to pH 2 with dilute HCl. The solid was filtered and recrystallized from HOAc to yield the acid (5.5 g, 92%), mp 283–286°

Anal. ($C_{22}H_{15}Cl_2NO_2$) C, H, Cl.

The same procedure was used to prepare 1b.

2-Methyl-6-(4-trifluoromethylphenyl)isonicotinic Acid (1c). A solution of 3-(4-trifluoromethylbenzoyl)acrylic acid[2] (50 g, 0.2 mol), acetylmethylpyridinium bromide (44 g, 0.2 mol), and NH_4OAc (165 g) in MeOH was heated at reflux 6 hr. MeOH was removed and the solid was slurried in dilute AcOH. The mixture was extracted with $CHCl_3$ (two times), dried ($MgSO_4$), and concentrated. The crude

Scheme IV

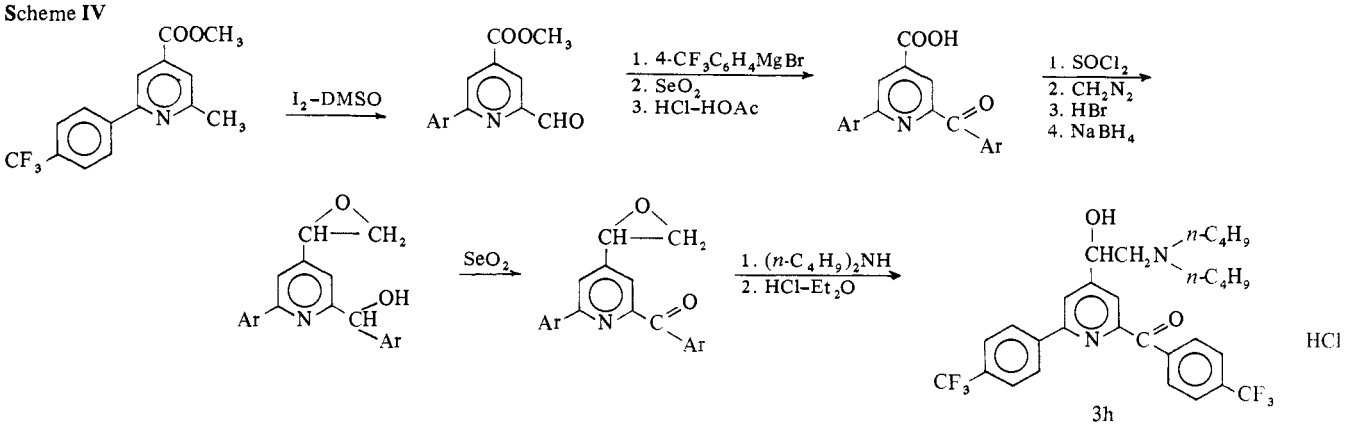
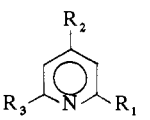


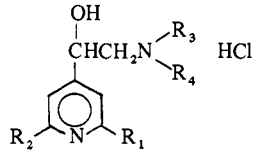
Table I. Isonicotinic Acids and Bromo Ketone Intermediates



Compd	R_1	R_2	R_3	Mp, °C (solvent)	Yield, %	Formula	Analyses
1a	4-ClC$_6$H$_4$CH=CH-	COOH	4-ClC$_6$H$_4$CH=CH-	283–286 (HOAc)	50[a]	$C_{22}H_{15}Cl_2NO_2$	C, H, Cl
1b	4-CF$_3$C$_6$H$_4$CH=CH-	COOH	4-CF$_3$C$_6$H$_4$CH=CH-	282–285 (HOAc)	47[a]	$C_{24}H_{15}F_6NO_2$	C, H, F
1c	CH_3	COOH	4-CF$_3$C$_6$H$_4$-	162–164 (C_6H_6)	74[b]	$C_{14}H_{10}F_3NO_2$	C, H, N, F
1d	4-CF$_3$C$_6$H$_4$CH=CH-	COOH	4-CF$_3$C$_6$H$_4$-	234–237 ($C_6H_5CH_3$)	38[c]	$C_{22}H_{13}F_6NO_2$	C, H, F, N
1e	4-ClC$_6$H$_4$CH=CH-	COOH	CF_3	268–270 (HOAc)	84[d]	$C_{15}H_9ClF_3NO_2$	C, H, Cl
1f	4-CF$_3$C$_6$H$_4$C(O)-	COOH	4-CF$_3$C$_6$H$_4$-	215–217 ($C_6H_5CH_3$)	64[d]	$C_{21}H_{11}F_6NO_3$	C, H, F, N
2a	4-ClC$_6$H$_4$CH=CH-	C(O)CH$_2$Br	4-ClC$_6$H$_4$CH=CH-	183–185 ($CHCl_3$-*i*-PrOH)	62[e]	$C_{23}H_{16}BrCl_2NO$	N
2b	4-CF$_3$C$_6$H$_4$CH=CH-	C(O)CH$_2$Br	4-CF$_3$C$_6$H$_4$CH=CH-	*f*			
2c	4-CF$_3$C$_6$H$_4$CH=CH-	C(O)CH$_2$Br	4-CF$_3$C$_6$H$_4$-	132–134 (*i*-PrOH)	90[e]	$C_{23}H_{14}BrF_6NO$	C, H, F, N
2d	4-ClC$_6$H$_4$CH=CH-	C(O)CH$_2$Br	CF_3	115–117 (*i*-PrOH-H_2O)	64[e]	$C_{16}H_{10}BrClF_3NO$	C, H, N
2e	4-CF$_3$C$_6$H$_4$-	C(O)CH$_2$Br	4-CF$_3$C$_6$H$_4$C(O)-	140–142 (*i*-PrOH)	79[e]	$C_{22}H_{12}BrF_6NO_2$	C, H, Br

[a] From ethyl 2,6-dimethylisonicotinate. [b] From cyclization reaction. [c] From **1c**. [d] From pyridinecarboxaldehyde. [e] From isonicotinic acid. [f] Isolated as a mixture of base and HBr salt.

Table II. 4-Pyridinemethanols



Compd	R_1	R_2	R_3	R_4	Mp, °C (solvent)	Yield,[a] %	Formula	Analyses
3a	4-ClC_6H_4CH=CH-	4-ClC_6H_4CH=CH-	1-Bu	1-Bu	195-197 (*i*-PrOH)	28	$C_{31}H_{37}Cl_3N_2O$	C, H, Cl, N
3b	4-$CF_3C_6H_4CH$=CH-	4-$CF_3C_6H_4CH$=CH-	1-Bu	1-Bu	188-189 (CH_3CN)	45	$C_{33}H_{37}ClF_6N_2O$	C, H, Cl, F, N
3c	4-$CF_3C_6H_4CH$=CH-	4-$CF_3C_6H_4CH$=CH-	H	4-Heptyl	110-112[b] (*i*-PrOH)	34	$C_{32}H_{34}F_6N_2O$	C, H, F, N
3d	4-$CF_3C_6H_4CH$=CH-	4-$CF_3C_6H_4CH$=CH-	H	1-Bu	137-139[b] (*i*-PrOH)	51	$C_{29}H_{28}F_6N_2O$	C, H, F, N
3e	4-$CF_3C_6H_4CH$=CH-	4-$CF_3C_6H_4$-	1-Bu	1-Bu	194-196 (CH_3CN)	42	$C_{31}H_{35}ClF_6N_2O$	C, H, F, N
3f	4-$CF_3C_6H_4CH$=CH-	4-$CF_3C_6H_4$-	H	1-Bu	111-113[b] (CH_3CN)	56	$C_{27}H_{26}F_6N_2O$	C, H, F, N
3g	4-ClC_6H_4CH=CH-	CF_3	1-Bu	1-Bu	162-163.5 (C_6H_6)	44	$C_{24}H_{31}Cl_3F_3N_2O$	C, H, N
3h	4-$CF_3C_6H_4C$(O)-	4-$CF_3C_6H_4$-	1-Bu	1-Bu	90.5-92 ($C_6H_5CH_3$)	43	$C_{30}H_{33}F_6ClN_2O_2$	C, H, Cl, N

[a] From bromo ketone precursor. [b] Free base.

Table III. Antimalarial Activity against *P. berghei*

Compd	ΔMST or C[a,b] Dosage, mg/kg				
	10	20	40	80	160
3a	1.1	4.9	3C	5C	5C
3b		0.2	2.9	2C	5C
3c	1.1	3.1	4C	5C	5C
3d			Inactive		
3e	3.7	13.5	4C	5C	5C
3f		0.5	13.6	4C	5C
3g	4.5	2C	4C	5C	5C
3h		1.3	6.7	3C	5C

[a] The test method, described in ref 3, is a highly standardized procedure in which the *P. berghei* causes death of control mice at essentially 6 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, with the exception of **3d**, were nontoxic and curative (5C) through 640 mg/kg. Data for dosages above 160 mg/kg for compound **3d** are not available.

product was crystallized from C_6H_6 (500 ml) to yield the acid (42 g, 74%), mp 162-164°.

Anal. ($C_{14}H_{10}F_3NO_2$) C, H, F, N.

Methyl 2-Methyl-6-(4-trifluoromethylphenyl)isonicotinate. A solution of the isonicotinic acid (42 g, 0.15 mol) in dry MeOH (600 ml) containing concentrated H_2SO_4 (35 ml) was heated at reflux 17 hr. The solution was concentrated to one-third volume under reduced pressure. H_2O was added and the slurry was extracted with $CHCl_3$ (two times). The $CHCl_3$ was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was crystallized from EtOH-H_2O to yield the title ester (33 g, 75%), mp 164-166°.

Anal. ($C_{15}H_{12}NF_3O_2$) C, H, N.

2-(4-Trifluoromethylstyryl)-6-(4-trifluoromethylphenyl)isonicotinic Acid (1d). A solution of the above ester (8.85 g, 0.03 mol), 4-trifluoromethylbenzaldehyde (11 g, 0.06 mol), and $ZnCl_2$ (0.2 g) in Ac_2O (35 ml) was heated at reflux 18 hr. The solvents were distilled to an internal temperature of 220°. The oily residue was placed onto a silica gel column and eluted with C_6H_6-petroleum ether (1:1). The fast-moving material was collected and the solvent was removed under reduced pressure. The material crystallized on standing. Recrystallization from C_6H_6-petroleum ether gave the ester (5.5 g, 41%). The ester was hydrolyzed as described for **1a**. Crystallization from toluene gave the acid (5.0 g, 92%), mp 234-237°.

Anal. ($C_{22}H_{13}F_6NO_2$) C, H, F, N.

Ethyl 2-Methyl-6-trifluoromethylisonicotinate. A solution of trifluoromethylacylpyridinium bromide (25.5 g, 0.1 mol), ethyl β-acetylacrylate (14.2 g, 0.1 mol), and NH_4OAc (85 g) in EtOH (150 ml) containing HOAc (50 ml) was heated at reflux for 6 hr. The solvent was removed under reduced pressure. H_2O was added and the mixture was extracted with $CHCl_3$ (three times). The $CHCl_3$ was washed with H_2O, dried ($MgSO_4$), and concentrated. The dark residual liquid was distilled *in vacuo* to afford the title ester (6 g, 32%), bp 65-70° (0.5 mm).

Anal. ($C_{10}H_{10}F_3NO_2$) C, H.

Ethyl 2-Methyl-6-trifluoromethylisonicotinate *N*-Oxide. A solution of the ester (19 g, 0.08 mol) in CF_3COOH (150 ml) containing 35% H_2O_2 (36 cc) was refluxed 2.25 hr. The solution was diluted with H_2O and extracted with $CHCl_3$ (three times). The $CHCl_3$ was washed with H_2O and aqueous K_2CO_4, dried ($MgSO_4$), and concentrated. The residual solid was crystallized (petroleum ether) to yield the product (11 g, 57%), mp 71-73°.

Anal. ($C_{10}H_{10}F_3NO_3$) C, H, F, N.

4-Carbethoxy-6-trifluoromethyl-2-pyridylcarbinol Acetate. A solution of the above *N*-oxide (11.8 g, 0.05 mol) in Ac_2O (120 ml) was heated at reflux 65 hr. The Ac_2O was removed under reduced pressure and the residue was distilled *in vacuo* to yield the product (7.5 g, 55%), bp 95-100° (0.25 mm).

Anal. ($C_{12}H_{12}F_3NO_4$) C, H, N.

4-Carbethoxy-6-trifluoromethyl-2-pyridylcarbinol. To a solution of the above ester (5.0 g, 0.018 mol) in anhydrous EtOH was added a catalytic amount of NaOEt in EtOH. The solution was stirred 15 min and neutralized with HOAc. The solvent was removed at reduced pressure. The residue was dissolved in Et_2O and washed with H_2O (two times). The Et_2O was dried ($MgSO_4$) and concentrated to give the product (4.0 g), an oil.

Anal. ($C_{10}H_{10}F_3NO_3$) C, H, N.

4-Carbethoxy-6-trifluoromethyl-2-pyridinecarboxaldehyde. A solution of the carbinol (3.6 g, 0.015 mol) and SeO_2 (1.8 g) in dioxane (70 ml) was heated for 17 hr. The selenium was removed *via* filtration (Celite) and the solvent was removed *in vacuo*. The residue was chromatographed over a silica gel column and eluted with C_6H_6. The product was collected (2.9 g, 81%), an oil.

Anal. ($C_{10}H_8F_3NO_3$) C, H.

4-Chlorobenzyltriphenylphosphonium Chloride. A solution of triphenylphosphine (5 g) and α,*p*-dichlorotoluene (3 g) in *p*-xylene (50 ml) was heated at reflux 5 hr. The solution was cooled and filtered to afford the phosphonium salt (3.9 g), mp 285-287°.

2-(4-Chlorostyryl)-4-carbethoxy-6-trifluoromethylpyridine. To a slurry of the above phosphonium salt (4.8 g, 0.01 mol) in anhydrous Et_2O (20 ml) was added *n*-BuLi in hexane (2.56 *M*, 4.6 cc). The orange slurry was stirred 0.5 hr. To this slurry was added 4-carbethoxy-6-trifluoromethyl-2-pyridinecarboxaldehyde (2.85 g, 0.011 mol). The resulting slurry was stirred an additional hour. The triphenylphosphine oxide and LiCl were filtered and the filtrate was dried ($MgSO_4$) and concentrated to afford the product (4.0 g, 99%), an oil. A sample was purified by chromatography over a silica gel column and elution with C_6H_6.

Anal. ($C_{17}H_{13}ClF_3NO_2$) C, H, N.

2-(4-Chlorostyryl)-6-trifluoromethylisonicotinic Acid (1e). A solution of the above ester (4 g, 0.011 mol) in 5% KOH-EtOH (60 ml) was stirred at room temperature for 0.5 hr. H_2O was added until all the salt dissolved. Most of the EtOH was removed under reduced pressure. Dilute aqueous K_2CO_3 (100 ml) was added and the mixture was extracted with Et_2O (two times). The aqueous layer was acidified to pH 2 and extracted with Et_2O (three times) to afford the crude acid which was crystallized from HOAc to yield pure product (3.1 g, 84%), mp 268-270°.

Anal. ($C_{15}H_9ClF_3NO_2$) C, H, Cl.

Styryl-Containing 4-Pyridinemethanols. The above isonicotinic acids were converted to the amino alcohols *via* the procedure described previously.[1] The analytical data are shown in Table II.

4-Carboxymethyl-6-(4-trifluoromethylphenyl)-2-pyridinecarboxaldehyde. A mixture of methyl 2-methyl-6-(4-trifluoromethylphenyl)isonicotinate (15 g, 0.05 mol) and I_2 (12.58 g) was heated at

125° for 20 min. The solution was diluted with DMSO (30 ml) and added to DMSO (60 ml) preheated to 130°. This solution was heated at 165° (bath) under N_2 for 4 hr and cooled and $CHCl_3$ was added. The solution was washed successively with H_2O, dilute sodium thiosulfate, and dilute KOH. The organic layer was dried ($MgSO_4$) and concentrated at reduced pressure. The crude aldehyde was dissolved in C_6H_6 (25 ml) and added to sodium bisulfite solution (75 ml). The addition compound was filtered and stirred with saturated aqueous $NaHCO_3$ (650 ml) and Et_2O (850 ml). The Et_2O layer was dried and concentrated under reduced pressure to yield the title aldehyde (7.2 g, 48%), mp 118–120°. Crystallization from acetonitrile gave mp 118–120°

Anal. ($C_{15}H_{10}F_3NO_3$) C, H, N.

4-(Carboxymethyl)-6-(4-trifluoromethylphenyl)-2-pyridyl-(4-trifluoromethylphenyl)carbinol. A slurry of the above aldehyde (6.6 g) in anhydrous Et_2O (150 ml) was treated with a solution of 4-trifluoromethylphenylmagnesium bromide (from 5.4 g of 4-bromobenzotrifluoride and 0.58 g of Mg) in Et_2O. The solution was stirred at room temperature for 1 hr. The mixture was poured into dilute aqueous NH_4OAc (150 ml). The Et_2O layer was dried ($MgSO_4$) and concentrated. The crude carbinol was crystallized from C_6H_6–petroleum ether to yield the title compound (6.9 g, 73%), mp 132–134°.

Anal. ($C_{22}H_{15}F_6NO_3$) C, H, F, N.

Methyl 2-(4-Trifluoromethylbenzoyl)-6-(4-trifluoromethylphenyl)isonicotinate. The title compound was prepared according to the procedure described for 4-carbethoxy-6-trifluoromethyl-2-pyridinecarboxaldehyde. A sample, crystallized from *i*-PrOH, had mp 167–169°.

Anal. ($C_{22}H_{23}F_6NO_3$) C, H, F, N.

2-(4-Trifluoromethylbenzoyl)-6-(4-trifluoromethylphenyl)isonicotinic Acid (1f). A solution of the above ester (5.0 g, 11 mmol) in AcOH (140 ml) and concentrated HCl (27 ml) was refluxed 3.5 hr. Additional HCl (30 ml) was added and the solution was heated an additional 90 min. Filtration gave the title acid (4.4 g, 90%), mp 215–217°. A sample, recrystallized from toluene, had mp 215–217°

Anal. ($C_{21}H_{11}F_6NO_3$) C, H, F, N.

This acid was converted to the bromomethyl ketone **2e** as previously described.

2-(4-Trifluoromethylbenzoyl)-6-(4-trifluoromethylphenyl)-4-pyridylethylene Oxide. The bromo ketone was reduced with $NaBH_4$ as previously described.[1] The resulting epoxycarbinol was oxidized with SeO_2 as described for 4-carbethoxy-6-trifluoromethyl-2-pyridinecarboxaldehyde. Crystallization from *i*-PrOH (10 ml) gave the title compound (2.2 g, 67%), mp 104–106°. A sample, recrystallized from *i*-PrOH, had mp 110–112°.

Anal. ($C_{22}H_{13}F_6NO$) N.

The ethylene oxide was converted to the amino alcohol **3h** by the procedure previously described.[1]

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Structure and Antischistosomal Activity in the Nitrofuran Series. Requirement for a 5-Nitro-2-furyl–Vinyl Moiety Based on Comparison of 3-(5-Nitro-2-furyl)-Substituted Propionic, Acrylic, and Propiolic Acid Derivatives†

P. B. Hulbert, E. Bueding, and C. H. Robinson*

Department of Pharmacology and Experimental Therapeutics, School of Medicine, and Department of Pathobiology, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, Maryland 21205. *Received May 24, 1972*

The structural features required for antischistosomal activity in the nitrofuran series have been postulated to include linkage of the nitrofuran *via* a vinyl group to a nitrogen atom of low basicity. This proposal has been examined by the synthesis and testing against *Schistosoma mansoni* of a series of amides of 3-(5-nitro-2-furyl)propionic acid (Ia) and 3-(5-nitro-2-furyl)propiolic acid (IIIa) for comparison with a corresponding series of amides derived from 3-(5-nitro-2-furyl)acrylic acid (IIa). A direct comparison of active amides derived from IIa with exact analogs differing only in the substitution of a C≡C or CH_2CH_2 grouping for a *trans*-CH=CH group has been made. The results show that the vinyl bridge is required for manifestation of antischistosomal activity by such nitrofuran derivatives. Differences in activity among the various amides of IIa are attributed to differences in lipophilicity. Additional studies using *Schistosoma japonicum* revealed that whereas two of the most active amides, IId and IIg, effected few parasitological cures at tolerated doses, the nitrofuran derivative VII was highly effective using large but tolerated doses.

Schistosomiasis, a parasitic disease afflicting approximately 200 million of the world's population, remains a great challenge to the medicinal chemist. (For a recent review, see ref 2.) It has been estimated that over a quarter of a million compounds have been tested for antischistosomal activity;[3] yet no drug has yet emerged which has gained general acceptance and widespread use.

We have already described[4] the general structural and conformational features present in those few nitrofurans and nitrothiazoles which demonstrate good antischistosomal activity and indicated that these features are rather specific. While it is well recognized that nitrofurans may be chemotherapeutically useful against a wide spectrum of organisms,[5] very few of these compounds exhibit antischistosomal activity, suggesting that the structural features necessary for nitrofurans to show this anthelmintic activity are far more precise.

We have reported that *trans*-5-amino-3-[(5-nitro-2-furyl)-vinyl]-1,2,4-oxadiazole (VII)[4] and some close analogs[6]

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