the BuOH was azeotroped with cyclohexane. The pure product, **13**, was obtained as a white powder: yield 409 mg (96.5%); mp 191–192°. *Anal.* ($C_{30}H_{35}N_7O_6$) C, H, N.

5'-Deoxypuromycin (1). A solution of 350 mg (0.595 mmol) of **13**, 175 mg 10% Pd/C, and HOAc (30 ml) was shaken under 1 atm of hydrogen until the theoretical amount of hydrogen was absorbed (15 min). Fresh hydrogen was added to the system and the mixture was shaken for an additional 10 min. The catalyst was removed by filtration through Celite and the HOAc was removed *in vacuo* at 30°. The oily residue was dissolved in MeOH and passed through an IRA 400 (OH^-) resin (30 ml) column. The first 50 ml of effluent was evaporated *in vacuo* to an oil which crystallized from 95% EtOH (2.5 ml). Pure **1** was obtained as a white powder: yield 182 mg (67.4%); softens at 104°, melts at 112–120°; $[\alpha]^{22}D$ +17.0° (c 1.01, MeOH); uv_{max} (nm) (pH 1) 267 (ϵ 19,700), (pH 7) 275 (ϵ 19,500), 215 (ϵ 22,700), (pH 13) 275 (ϵ 20,100). *Anal.* ($C_{22}H_{29}N_7O_4$) C, H, N.

Biological Testing. The assay procedures for the antimicrobial testing and the *in vitro* protein synthesis measurements have been described previously.[7,13]

P-388 *in Vitro* Assay. Tenfold dilutions of puromycin aminonucleoside or **12** were tested in duplicate sets of tubes inoculated with 240,000 P-388 cells in 4 ml of Fischer's medium with 10% horse serum. The tubes were plugged with silicone stoppers and incubated for 72 hr at 37° at a 30° angle without agitation. Cell growth was determined by cell count with a hemocytometer, per cent inhibition calculated from the corresponding controls correcting all counts of inoculum.

Acknowledgment. The authors wish to thank Clare Ritter for providing the biological testing data.

References

(1) R. Vince and R. G. Isakson, *J. Med. Chem.*, **16**, 37 (1973) (previous paper).
(2) D. Nathans, *Proc. Nat. Acad. Sci. U. S.*, **51**, 585 (1964).
(3) R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley, New York, N. Y., 1970, pp 43–45.
(4) D. Nathans in "Antibiotics I, Mechanism of Action," D. Gottlieb and P. D. Shaw, Ed., Springer-Verlag, New York, N. Y., 1967, pp 259–277.
(5) R. F. Derr, C. S. Alexander, and H. T. Nagasawa, *Proc. Soc. Exp. Biol. Med.*, **125**, 248 (1967).
(6) E. Kmetec and A. Tirpack, *Biochem. Pharmacol.* **19**, 1493 (1970).
(7) S. Daluge and R. Vince, *J. Med. Chem.*, **15**, 171 (1972).
(8) K. J. Ryan, H. Arzoumanian, E. M. Acton, and L. Goodman, *J. Amer. Chem. Soc.*, **86**, 2497 (1964).
(9) J. M. J. Tronchet and R. Graf, *Helv. Chim. Acta*, **55**, 2286 (1972).
(10) J. A. Montgomery, K. Hewson, A. G. Laster, and M. C. Thorpe, *J. Amer. Chem. Soc.*, **94**, 7176 (1972).
(11) L. B. Townsend in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 2, W. W. Zorbach and R. S. Tipson, Ed., Wiley, New York, N. Y., 1973, pp 330–333.
(12) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(13) R. Vince, S. Daluge, and M. Palm, *Biochem. Biophys. Res. Commun.*, **46**, 866 (1972).
(14) C. Coutsogeorgopoulos, *Biochim. Biophys. Acta*, **129**, 214 (1966).
(15) R. J. Harris, J. E. Hanlon, and R. H. Simons, *ibid.*, **240**, 244 (1971).
(16) N. Yomaoko, K. Aso, and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965).
(17) B. R. Baker, J. P. Joseph, and J. H. Williams, *J. Amer. Chem. Soc.*, **77**, 1 (1955).

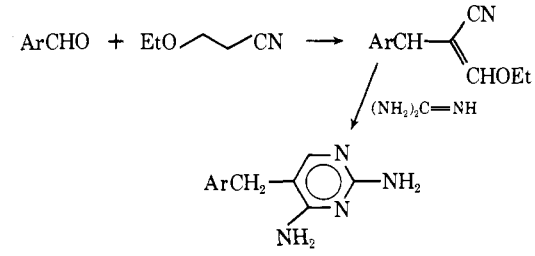
Effect of Trifluoromethoxy, Chlorodifluoromethoxy, and Trifluoromethyl on the Antimalarial Activity of 5-Benzyl- and 5-Phenyl-2,4-diaminopyrimidines

Eugene L. Stogryn

Government Research Laboratory, Esso Research and Engineering Company, Linden, New Jersey 07036.
Received June 13, 1973

Halogens are prominent for their pharmacophoric behavior[1] in many classes of antimalarial agents. Recent drug syntheses have noted that dramatic improvements in drug efficacy may occur when these simple halogens are replaced by CF_3[2] groups. The significance of this functionality to the antimalarial activity of benzyl- and phenyl-2,4-diaminopyrimidines appears to have escaped synthetic and biological attention. Considering the relevance of this class of drugs, as exemplified by pyrimethamine [5-(*p*-chlorophenyl)-2,4-diamino-6-ethylpyrimidine], to the treatment of various malarial infections, synthesis of benzyl- and phenyl-2,4-diaminopyrimidines substituted with CF_3 groups warranted study. In addition, this paper details the introduction of two related perhalomethyl functions into this class of diaminopyrimidines, namely, the CF_3O- and the CF_2ClO- groups. The rationale for their inclusion in this study is based on the fact that the magnitude and the direction of their group electronic character is diametrically opposed to CF_3, being more akin to the simple halogens.

Chemistry. The synthetic strategy employed to obtain trifluoromethyl- and perhalomethoxybenzyldiaminopyrimidines used for our study was detailed by Stenbuck and Baltzly.[3] Although the yields were low, the sequential base condensation of aromatic aldehyde with ethoxypropionitrile and guanidine occurred without undue complication.



One exception to this preparative method was encountered with 4-(α,α,α-trifluoro)tolualdehyde. Since the trifluoromethylbenzaldehydes **1**, **3**, and **4** are amenable to these series of reactions, it would appear that the normal condensations are only impeded by para-positioned electron-withdrawing groups.

The perhalomethylarylaldehydes required for the synthesis of the target compounds *via* the indicated scheme are listed in Table I.

A halogen–metal interchange between commercially available trifluoromethyl- and trifluoromethoxybromobenzenes and BuLi followed by reaction with DMF was used to prepare the trifluoromethyl- and trifluoromethoxybenzaldehydes **1–5**. Several of these aldehydes have previously been reported; however, the reaction sequence detailed in the Experimental Section appears to offer procedural advantages.

The unavailability of the appropriate trifluoromethoxybromobenzene precluded synthesis of **9** *via* method A. The reaction sequence shown in Scheme I was employed for the synthesis of the benzaldehyde **9**. Conversion of *m*-anisic acid to *m*-(α,α,α-trichloro)anisoyl chloride was realized after the method Yagupol'skii[4] detailed for preparation of the para isomer.

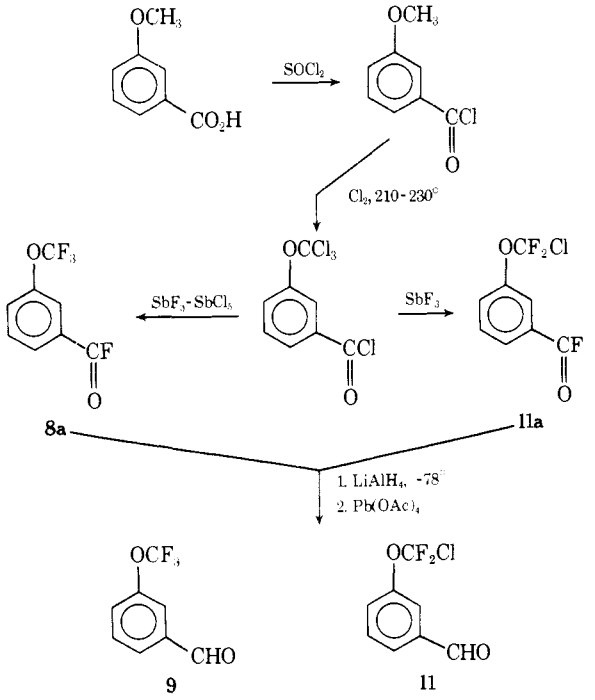
Initial attempts to effect the fluorine–chlorine metathesis with SbF_3 yielded a mixture containing predominately two fairly close boiling components. One of these was identified as **8a** by hydrolysis to the known 3-(α,α,α-trifluoro)anisic acid.[5] The proportion of **8a** in the mixture could be increased by employing higher exchange reaction temperatures or preferably by using SbF_3–$SbCl_5$ for the metathesis. The proton spectrum of the other component was almost superimposable with that of **8a**. This, in con-

Table I

No.	R	Y	Method[a]	Yield, %	Bp (mm), °C	Formula	Analyses[b]
1	3-CF_3	CHO	A	75	72–75 (12)[c]		
2	4-CF_3	CHO	A	47	80–81 (12)[d]		
3	3,5-$(CF_3)_2$	CHO	A	68	70–71 (10)	$C_9H_4F_6O$	C, H, F
4	3-CF_3, 4-OCH_3	CHO	A	76	120 (6)	$C_9H_7F_3O_2$	C, F; H[e]
5	4-CF_3O	CHO	A	76	95–97 (27)[f]		
6	4-CF_2ClO	CH_2OH	C		122–125 (10)	$C_8H_7F_2ClO_2$	C, H; F[g]
7	4-CF_2ClO	CHO	C	52	118–121 (28)	$C_8H_5F_2ClO_2$	C, H
8	3-CF_3O	CH_2OH	B		97–98 (11)	$C_8H_7F_3O_2$	
9	3-CF_3O	CHO	B	65	83–86 (24)	$C_8H_5F_3O_2$	H, F; C[h]
10	3-CF_2ClO	CH_2OH	C		114–117 (10)	$C_8H_7F_2ClO_2$	C, H, F, Cl
11	3-CF_2ClO	CHO	C	33	93–96 (10)	$C_8H_5F_2ClO_2$	C, H, Cl; F[i]

[a]Synthetic methods are detailed in the Experimental Section. [b]Where analyses are indicated by symbols of elements, analytical results were obtained for those elements within ±0.4% of the theoretical value. [c]Reported bp 59–62° (10 mm): M. Hudlicky, *Chem. Abstr.*, **55**, 1503c (1961). [d]Reported bp 84° (13 mm): R. Filler and H. Novar, *J. Org. Chem.*, **25**, 733 (1960). [e]H: calcd, 3.43; found, 2.72. [f]Reported bp 93° (27 mm): L. M. Yagupol'skii and V. I. Troitskaya, *Chem. Abstr.*, **55**, 17564*a* (1961). [g]F: calcd, 18.27; found, 18.68. [h]C: calcd, 50.54; found, 51.28. [i]F: calcd, 18.45; found, 17.99.

Scheme I



junction with the elemental analysis, suggested **11a** as opposed to a rearranged or ring-halogenated product. The formation of **8a** from **11a** *via* its reaction with SbF_3–$SbCl_5$ confirmed the structural assignment of **11a**. Yarovenko and Vasil'eva[6] observed a similar incomplete metathesis for the reaction of α,α,α-trichloroanisole with SbF_3 at about 75°.

Subjecting *p*-anisic acid to the sequence of reactions depicted in Scheme I similarly yielded 4-(α-chloro-α,α-difluoro)anisaldehyde.

It is worth noting that integrity of the CF_2ClO functionality was maintained throughout the various chemical transformations to which it was subjected (oxidants, reductants, and strong bases). This unusual stability of an α-chloromethyl ether apparently is a manifestation of the two fluorine atoms on the same carbon as chlorine.

The benzyldiaminopyrimidines prepared for this structure–activity study are listed in Table II. Also included is the CF_3O analog of pyrimethamine synthesized for this study. The preparation of this variation follows the well-known pyrimethamine synthesis.[7] The requisite 4-trifluoromethoxybenzyl cyanide was realized *via* standard techniques which are detailed in the Experimental Section.

Biological Evaluation.† The diaminopyrimidines listed in Table II were examined for activity against *Plasmodium berghei*[8] infected mice. Target compounds **15** and **22** sufficiently increased survival time of the parasitized mice to be classified as active. At the 640 mg/kg dose level, **22** was acutely toxic, causing five deaths per five test animals. Compounds **13**, **17**, and **23** were not examined in this screen. In the bird activity screen against *Plasmodium gallinaceum* **22** gave one cure per five test animals at a dosage of 40 mg/kg. However, the next higher dose level, 80 mg/kg, produced death to all the test animals. Compounds **12–14** and **18–20** were inactive against *P. gallinaceum*.

A comparison of the behavior of pyrimethamine in the Rane screen[8] (see Table II) with the diaminopyrimidines prepared for this study reveals an adverse effect of the perhalomethyl function on the antimalarial properties of this class of materials. It is significant that this influence is manifest with the electron-withdrawing CF_3 group or with the "pseudohalogens," CF_3O and CF_2ClO.

Experimental Section

2,4-Diamino-5-(3-trifluoromethoxybenzyl)pyrimidine (18). The preparation of compound **18** illustrates the procedure used to obtain the benzyldiaminopyrimidines listed in Table II.

A solution of 15.9 g of 3-(α,α,α-trifluoro)anisaldehyde and 10.4 g of ethoxypropionitrile in 250 ml of 0.1 *M* NaOEt in EtOH was refluxed for 8 hr. Guanidine (0.24 mol) in 90 ml of EtOH was added and refluxing continued for an additional 5 hr. The solution was evaporated and the residue extracted with hot PhH. Evaporation of the PhH and recrystallization yielded 3 g of the titled compound.

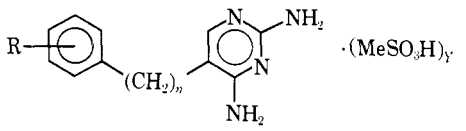
Trifluoromethyl- and Perhalomethoxybenzaldehydes. Typical examples of the synthetic procedures used to prepare the substituted benzaldehydes listed in Table I are given.

Method A. BuLi (1 equiv) in hexane was added to a 10% solution of 4-bromo-α,α,α-trifluoroanisole in Et_2O at −40°. After an additional 1–2 hr at this temperature, 3 equiv of DMF was added and the reaction mixture allowed to come to room temperature. Standard isolation procedures gave a 76% yield of 4-(α,α,α-trifluoro)anisaldehyde.

Method B. 3-(α,α,α-Trichloro)anisoyl chloride (106 g), 105 g of

†The rodent and avian activity screens were performed by Dr. L. Rane.

Table II



No.	R	n	Y	Mp, °C	Recrystn solvent[a]	Analyses[b]	Antimalarial act.,[c,d] ΔST, days	Toxicity[e]
12	3-CF_3	1	0	163–166	A	C, H, N, F		5
13	3,5-$(CF_3)_2$	1	0	194.5–195	A	C, H, N		
14	3-CF_3, 4-CH_3O	1	0	198–200	A	C, N, F; H[f]	2	0
15	4-CF_3O	1	0	174–175	A	C, H, N	7.2A	0
16	4-CF_2ClO	1	0	170–172	B	C, H, N, F	3.9	3
17	4-CF_2ClO	1	2	189–190	C	H, N; C[g]		
18	3-CF_3O	1	0	122.5–123.5	B	C, H, N; F[h]	1.4	3
19	3-CF_3O	1	2	179.5–181	C	C, H, N	0.3[i]	0
20	3-CF_2ClO	1	0	119.5–120	B	C, H, N, F	*i*	5
21	3-CF_2ClO	1	2	188.5–189.5	C	C, H, N	0.9	3
22	4-CF_3O[j]	0	0	206.5–207	B	C, H, N, F	12.4A	3
23	4-CF_3O[j]	0	1	280–282	C	C, H, N, F		
Pyrimethamine							3C[i,k]	2

[a]Solvents are A, benzene; B, benzene–hexane; C, THF. [b]See footnote *b* in Table I. [c]Mice were treated 3 days postinfection sc with a single dose of the compound being screened. The change in survival time (ΔST) is an indication of activity against *P. berghei* (see ref 8). [d]Dosage, 320 mg/kg. [e]Number of deaths per five test animals. [f]H: calcd, 4.36; found, 5.08. [g]C: calcd, 34.11; found, 34.57. [h]F: calcd, 20.05; found, 19.60. [i]Dosage, 160 mg/kg. [j]C_2H_5 at the pyrimidine ring 6 position. [k]Biological data for pyrimethamine were made available through the courtesy of Dr. E. A. Steck of the Walter Reed Army Medical Center. See ref 2b for additional data on the activity of pyrimethamine in the rodent screen.

SbF_3, and 2.5 g of $SbCl_5$ were added to a flask equipped for vacuum distillation. After the initial exothermic reaction subsided the pressure was reduced to 90 mm and the reaction heated to effect distillation (overhead temperature 90–100°). Redistillation at atmospheric pressure yielded 34.7 g of 3-(α,α,α-trifluoro)anisoyl fluoride, bp 165–166°.

The acyl fluoride (34.7 g) in 500 ml of Et_2O was reduced with 158 ml (1.27 *M*) of $LiAlH_4$ in Et_2O at −78°. Isolation of product by standard techniques gave 26.8 g of 3-trifluoromethoxybenzyl alcohol, bp 97–98° (11 mm).

To a solution of 25.8 g of the benzyl alcohol in 400 ml of anhydrous pyridine was added 55 g of $Pb(OAc)_4$. After 2–3 hr at 70–80° the $Pb(OAc)_4$ had completely dissolved and the blood red solution became pale yellow in color. By the usual isolation procedures there was obtained 16.6 g of 3-(α,α,α-trifluoro)anisaldehyde, bp 83–86° (24 mm).

Method C. 3-(α,α,α-Trichloro)anisoyl chloride (54.4 g) and 53.6 g of SbF_3 were allowed to react as described in method B. The reaction was heated at 110–120° (bath temperature) and the material collected up to 104° (22 mm) was redistilled, yielding 20.3 g of 3-(α-chloro-α,α-difluoro)anisoyl fluoride, bp 105–115° (50 mm).

The acyl fluoride was reduced with $LiAlH_4$ according to method B to give 3-chlorodifluoromethoxybenzyl alcohol, bp 114–117° (10 mm).

Oxidation of the benzyl alcohol with $Pb(OAc)_4$ yielded 3-(α-chloro-α,α-difluoro)anisaldehyde, bp 93–96° (10 mm).

4-Bromo-2-trifluoromethylanisole. To a slurry of 100 g of 4-bromo-2-trifluoromethylphenol and 172 g of K_2CO_3 in DMF was added 105 g of Me_2SO_4. After the initial exothermic reaction the mixture was heated on a steam bath for 30 min. Filtration, dissolution of the filtrate in pentane, H_2O washing, drying, and distillation gave 70 g of the titled compound, bp 120° (20 mm).

4-Trifluoromethoxybenzyl Alcohol. BuLi (0.415 mol) was added to 100 g of 4-bromo(α,α,α-trifluoro)anisole in 1 l. of Et_2O at −10°. After 1 hr at 0° 24.8 g of paraformaldehyde, slurried in 200 ml of THF, was added. The titled compound was isolated in 45% yield, bp 98–101° (10 mm). *Anal.* ($C_8H_7F_3O_2$) H; C: calcd, 50.00; found, 50.44.

4-Trifluoromethoxybenzyl Bromide. A mixture of 34 g of 4-trifluoromethoxybenzyl alcohol, 85 ml of 48% HBr, and 12.5 ml of concentrated H_2SO_4 was stirred and heated on a steam bath for 3–4 hr. The cooled mixture was extracted with Et_2O and distilled: yield 38.7 g; bp 82–84° (10 mm) *Anal.* ($C_8H_6BrF_3O$) C, H.

4-Trifluoromethoxybenzyl Cyanide. A solution of 21.3 g of NaCN in 75 ml of H_2O and 74 ml of DMF was added to 37 g of 4-trifluoromethoxybenzyl bromide in 74 ml of DMF. The reaction was stirred at ambient temperature for several days, poured into 600 ml of H_2O, extracted with pentane, and distilled: yield 24.7 g; bp 118–121° (11 mm). *Anal.* ($C_9H_6F_3NO$) C, H.

2,4-Diamino-6-ethyl-5-(4-trifluoromethoxyphenyl)pyrimidine (22). 4-Trifluoromethoxybenzyl cyanide was converted to the titled compound according to the general procedure reported for the preparation of this class of pyrimidines.[7]

2,4-Diamino-6-ethyl-5-(4-trifluoromethoxyphenyl)pyrimidine Methanesulfonate (23). To 1 g of 22 in 180 ml of THF was added 0.96 g of $MeSO_3H$ in 100 ml of THF. After stirring at room temperature for several hours the precipitated product was filtered and washed with Et_2O.

Acknowledgment. The author wishes to thank Dr. E. A. Steck for his encouragement and discussion during the course of this program. This work was supported by the U. S. Army Medicinal Research and Development Command under Contract No. DADA 17-68-C-8103. This is Contribution No. 1180 from the Army Research Program on Malaria.

References

(1) (a) F. Y. Wiselogle, Ed., "A Survey of Antimalarial Drugs, 1941–1945," J. W. Edwards, Ann Arbor, Mich., 1946; (b) P. B. Russel in "Medicinal Chemistry," A. Burger, Ed., Interscience, New York, N. Y, 1960, p 814; (c) E. A. Steck, "The Chemotherapy of Protozoan Diseases," Vol. III, Division of Medicinal Chemistry, Walter Reed Army Institute of Research, p 23.1.

(2) (a) J. R. DoAmaral, E. J. Blanz, Jr., and F. A. French, *J. Med. Chem.*, **12**, 21 (1969); (b) R. W. A. Rees, P. B. Russell, T. J. Foell, and R. E. Bright, *ibid.*, **15**, 859 (1972); (c) P. Chien, D. J. McCaustland, W. H. Burton, and C. C. Cheng, *ibid.*, **15**, 28 (1972); (d) B. P. Das, J. A. Campbell, F. B. Samples, R. A. Wallace, L. K. Whisenant, R. W. Woodard, and D. W. Boykin, Jr., *ibid.*, **15**, 570 (1972).

(3) P. Stenbuck and R. Baltzly, *J. Org. Chem.*, **28**, 1982 (1963).

(4) L. M. Yagupol'skii and V. I. Troitskaya, *Zh. Obshch. Khim.*, **30**, 3192 (1960).

(5) W. A. Sheppard, *J. Org. Chem.*, **29**, 1 (1964).

(6) N. N. Yarovenko and A. S. Vasil'eva, *Zh. Obshch. Khim.*, **28**, 2502 (1958).

(7) (a) P. B. Russell and G. H. Hitchings, *J. Amer. Chem. Soc.*, **73**, 3763 (1951); (b) R. Baltzly and P. B. Russell, *J. Org. Chem.*, **21**, 912 (1956).

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