effective in rats at daily doses ranging from 62.5 to 125 mg/kg, and thus showed activity comparable with or superior to 7-{[3-(octylamino)propyl]amino}benz[*c*]-acridine dihydrochloride (III).[13] Compounds Va and b and VIa and b killed *T. vaginalis in vitro* at concentrations of 25 μg/ml, but none was active against *L. donovani* in hamsters.

The effects of Va–c, VIb, and VIIa and b against intestinal helminths were assessed in mice infected with *S. obvelata*, *A. tetraptera*, *N. dubius*, and *H. nana*.[2] Four substances (Va–c and VIb) were active against the tapeworm *H. nana* in mice when given at doses of 62.5–125 mg/kg b.i.d. for 1 day and thus showed taeniacidal activity comparable with or superior to quinacrine.[6] Three compounds (Vc, VIb, and VIIb) were also effective against the mouse pinworms *S. obvelata* and *A. tetraptera*. None of the compounds tested was active against *S. mansoni* in mice or *L. carinii* in gerbils.

Each of the heterocyclic aminoalkylhydrazine derivatives caused complete inhibition of *S. pyogenes* (C203) and *S. aureus* (UC-76) *in vitro* at concentrations of 1.25–20 μg/ml.[22] Compounds Va, VIa and b, and VIIa also effected complete inhibition of *M. tuberculosis* ($H_{37}Rv$) at concentrations of 0.63–10 μg/ml, while VIa killed *K. pneumoniae* (AD) at 20 μg/ml. Under comparable experimental conditions, quinacrine was active against *S. pyogenes* (C203) and *M. tuberculosis* ($H_{37}Rv$) *in vitro* at 1.25 and 20 μg/ml, respectively. Three substances (Va, Vc, and VIa) were tested against streptococcus, staphylococcus, and tuberculosis infections in mice,[22] but none was active even at high dose levels.

The over-all results of the present study indicate that the substitution of a hydrazide moiety for an amine function at the distal position of quinacrine, azacrine, and the 7-[(aminoalkyl)amino]benz[*c*]acridines has a deleterious effect on antimalarial activity while potent antiamebic, anthelmintic, and antibacterial properties are maintained.

Experimental Section[23,24]

7-Chloro-2-methoxy-10-({3-[(4-methyl-1-piperazinyl)amino]-propyl}amino)benzo[*b*][1,5]naphthyridine Trihydrochloride (VIIb) (Procedure I).—A solution of 21.0 g (0.12 mole) of 1-[(3-aminopropyl)amino]-4-methylpiperazine[19] in 60 g of phenol was heated on a steam bath *in vacuo* for 20 min at 15 mm. 7,10-Dichloro-2-methoxybenzo[*b*][1,5]naphthyridine[15] (28.0 g, 0.10 mole) was then added and the mixture was stirred and heated on a steam bath for an additional 4 hr. The mixture was cooled and washed into a solution of 25 ml of concentrated HCl in 2 l. of Me_2CO with the aid of a small volume of EtOH. The resulting precipitate was collected by filtration, washed with fresh Me_2CO, and stirred into 1.5 l. of H_2O. A small amount of insoluble material was removed by filtration, and the filtrate was made alkaline with excess concentrated NH_4OH. The resulting mixture was extracted with $CHCl_3$, and the combined $CHCl_3$ extracts were washed with dilute NaOH and H_2O and concentrated on a rotary evaporator. The residue was dissolved in EtOH. The solution was filtered and then treated with excess HCl in *i*-PrOH. The yellow product slowly crystallized from the warm solvent, and was collected by filtration, washed well with *i*-PrOH and Me_2CO, and dried *in vacuo* at 60°. In order to avoid problems associated with hygroscopic, light-sensitive samples, the yellow solid was allowed to equilibrate with atmospheric H_2O in the dark for 24 hr prior to analysis. The hydrated hydrochloride melted at 215–218°.

6-Chloro-2-methoxy-9-{[3-(piperidinoamino)propyl]amino}-acridine Dihydrochloride (Vb) (Procedure II).—A mixture of 10.0 g (0.064 mole) of 1-[(3-aminopropyl)amino]piperidine[19] and 18.0 g (0.064 mole) of 6,9-dichloro-2-methoxyacridine in 50 g of phenol was stirred and heated on a steam bath for 3 hr. A red-brown solid slowly precipitated from the deep red solution. This hot mixture was then poured into a well-stirred solution of 27 ml of concentrated HCl in 1.5 l. of Me_2CO to give 27.0 g of a yellow solid which was collected by filtration and washed well with Et_2O. Recrystallization from MeOH gave 20.0 g of a bright yellow powder which did not analyze correctly. The crude product was stirred into hot H_2O, and a small amount of insoluble material was removed by filtration. The filtrate was poured into cold H_2O containing excess NH_4OH, and the liberated free base was extracted into $CHCl_3$. The $CHCl_3$ solution was washed with H_2O and dried (K_2CO_3). Dilution with Et_2O followed by the addition of excess HCl gave a precipitate which upon crystallization from EtOH yielded 12.1 g of pure product as bright yellow crystals, mp 132–135°.

7-{[3-(Piperidinoamino)propyl]amino}benz[*c*]acridine Dihydrochloride (VIa) (Procedure III).—A solution of 10.0 g (0.064 mole) of 1-[(3-aminopropyl)amino]piperidine[19] and 16.0 g (0.064 mole) of 7-chlorobenz[*c*]acridine[12–14] in 50 g of phenol was heated on a steam bath for 3 hr. The hot solution was poured into a cooled solution of 5 ml of concentrated HCl in 500 ml of Me_2CO. The Me_2CO was decanted, and the tarry residue was triturated twice with Et_2O and then dissolved in EtOH. This solution was poured into Et_2O, and the yellow deliquescent precipitate was collected and dried in an evacuated desiccator. This material was stirred into warm H_2O and treated with decolorizing charcoal, and the filtrate was chilled and treated with excess dilute NaOH. The sticky base was collected by filtration and washed with H_2O. An Et_2O solution of this base was dried over anhydrous K_2CO_3 and treated with excess HCl. The hygroscopic solid thus formed was collected by filtration and dried in an evacuated desiccator to obtain 16.0 g of yellow powder, mp >100°.

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(23) Melting points (corrected) were taken on a Thomas–Hoover capillary melting point apparatus.

(24) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4 % of the theoretical values. Water determinations were by the Karl Fischer method.

Trifluoromethylbenzanilides as Anticoccidial Agents

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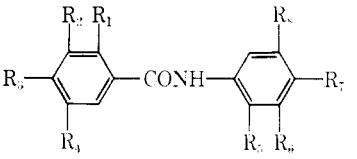
As part of a program directed toward the use of trifluoromethyl compounds as antiprotozoal agents, we wish to report our investigation of a series of trifluoromethylbenzanilides. Our interest in trifluoromethyl compounds was prompted by the discovery that, in anticoccidial benzamides bearing a nitro group, the nitro group and a trifluoromethyl group could be exchanged without loss of activity.[1] This work was underway when other reports appeared relating to anti-

(1) D. E. Welch, R. R. Baron, and B. A. Burton, *J. Med. Chem.*, **12**, 299 (1969).

TABLE I

TRIFLUOROMETHYLBENZANILIDES



No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Mp, °C[a] (recrystn solvent)	% yield	Formula[b]	Min effect. dose, % in feed
1	H	CF_3	H	NO_2	H	H	H	H	206.5–207[c]	94	$C_{14}H_9F_3N_2O_3$	0.05
2	H	CF_3	H	NO_2	H	H	NO_2	H	182–183[c]	80	$C_{14}H_8F_3N_3O_5$	
3	H	CF_3	H	NO_2	NO_2	H	H	H	175–175.5[d]	67	$C_{14}H_8F_3N_3O_5$	
4	H	CF_3	H	NO_2	H	NO_2	H	H	196.5–197.5[c]	80	$C_{14}H_8F_3N_3O_5$	
5	H	CF_3	H	NO_2	H	CF_3	NO_2	H	180–181[c]	82	$C_{15}H_7F_6N_3O_5$	
6	H	CF_3	H	NO_2	CF_3	H	H	H	149–149.5[c]	72	$C_{15}H_8F_6N_2O_3$	
7	H	CF_3	H	NO_2	H	CF_3	H	H	190–191[c]	78	$C_{15}H_8F_6N_2O_3$	
8	H	CF_3	H	NO_2	CF_3	H	NO_2	H	135–136[c]	19	$C_{15}H_7F_6N_3O_5$	
9	H	CF_3	H	NO_2	H	H	Cl	H	188–191[c]	84	$C_{14}H_8ClF_3N_2O_3$	
10	H	CF_3	H	NO_2	H	CF_3	H	CF_3	218–218.5[c]	80	$C_{16}H_7F_9N_2O_2$	0.025
11	H	CF_3	H	NO_2	NO_2	H	CF_3	H	144–144.5[c]	32	$C_{15}H_7F_6N_3O_5$	
12	H	CF_3	H	NO_2	H	CF_3	Cl	H	188–189.5[c]	49	$C_{15}H_7ClF_6N_2O_3$	
13	H	CF_3	H	NO_2	CF_3	H	Cl	H	156.5–157[c]	86	$C_{15}H_7ClF_6N_2O_3$	
14	H	CF_3	H	NO_2	H	H	F	H	209–209.5[c]	83	$C_{14}H_8F_4N_2O_3$	
15	H	CF_3	H	NO_2	NO_2	H	NO_2	H	141–141.5[c]	48	$C_{14}H_7F_3N_4O_7$	
16	H	CF_3	H	NO_2	H	CF_3	F	H	197.5–198[c]	90	$C_{15}H_7F_7N_2O_3$	
17	H	CF_3	H	NO_2	H	H	CH_3	H	218–219[c]	97	$C_{15}H_{11}F_3N_2O_3$	
18	H	CF_3	H	NO_2	Cl	H	Cl	H	164.5–165[c]	87	$C_{14}H_7Cl_2F_3N_2O_3$	
19	H	CF_3	H	NO_2	Cl	H	NO_2	H	150–151[c]	40	$C_{14}H_7ClF_3N_3O_5$	
20	H	CF_3	H	NO_2	H	Cl	Cl	H	212–213[c]	70	$C_{14}H_7Cl_2F_3N_2O_4$	
21	H	CF_3	H	NO_2	H	NO_2	H	NO_2	210–211[c]	89	$C_{14}H_7F_3N_4O_7$	
22	H	CF_3	H	CF_3	H	CF_3	NO_2	H	171–172[c]	91	$C_{16}H_7F_9N_2O_5$	
23	H	CF_3	H	CF_3	H	CF_3	H	CF_3	219–219.5[c]	89	$C_{17}H_7F_{12}NO$	0.05
24	H	NO_2	H	H	H	CF_3	H	CF_3	229–229.5[c]	72	$C_{15}H_8F_6N_2O_3$	
25	H	NO_2	H	H	H	CF_3	NO_2	H	196–198[c]	72	$C_{14}H_8F_3N_3O_5$	
26	H	CF_3	H	H	H	CF_3	H	CF_3	197–197.5[c]	91	$C_{16}H_8F_9NO$	
27	H	CF_3	H	H	H	CF_3	NO_2	H	160–161[c]	61	$C_{15}H_8F_6N_2O_3$	
28	H	CF_3	H	H	NO_2	H	NO_2	H	138–138.5[c]	25	$C_{14}H_8F_3N_3O_5$	
29	H	CF_3	H	H	H	Cl	Cl	H	131.5–132[c]	84	$C_{14}H_7Cl_2F_3NO$	
30	H	CF_3	H	H	H	NO_2	H	NO_2	181–181.5[c]	80	$C_{14}H_7F_3N_4O_7$	
31	CF_3	H	NO_2	H	H	CF_3	NO_2	H	171–172.5[c]	81	$C_{15}H_7F_6N_3O_5$	
32	H	CF_3	NO_2	H	H	CF_3	H	CF_3	216–216.5[c]	89	$C_{16}H_7F_9N_2O_3$	
33	H	NO_2	H	NO_2	H	CF_3	H	CF_3	210–211[c]	76	$C_{15}H_7F_6N_3O_5$	

[a] Melting points are uncorrected and were taken in open capillaries using a Thomas–Hoover apparatus. [b] All compounds were analyzed for C, H, N, using an F & M Model 185 analyzer; analytical results obtained were within ±0.4% of the theoretical values. Ir spectra were consistent with the structure and were determined in KBr disks with a Beckman IR4 spectrophotometer. [c] EtOH. [d] EtOH–$CHCl_3$. [e] EtOH–H_2O.

coccidial and antibacterial activity of certain trifluoromethylbenzamides and -anilides.[2–4]

The compounds prepared for testing are listed in Table I. They were prepared by treating the appropriate acid chloride and aniline in pyridine at 25–50° and subsequent precipitation in water. All starting materials were commercially available or prepared by reported routes.[1,5]

The efficacy data in Table I show that optimal activity was obtained with 3,3′,5′-tris(trifluoromethyl)-5-nitrobenzanilide (**10**). Only two other compounds in the series displayed anticoccidial activity. It is of interest to note that the benzoyl moiety must apparently possess a 3,5-trifluoromethylnitro or 3,5-bis(trifluoromethyl) configuration.

(2) J. W. Baker, G. L. Bachman, L. Schumacher, D. P. Roman, and A. L. Tharp, *J. Med. Chem.*, **10**, 93 (1967).

(3) W. Zerweck, O. Työsken, and K. Hinrermeier, U. S. Patent 3,332,996 (July 25, 1967).

(4) J. W. Baker, U. S. Patent 3,426,049 (Feb. 4, 1969).

(5) Pierce Chemical Co., Rockford, Ill.

Experimental Section

General Synthesis Scheme.—The chloride of the appropriate acid (0.10 mol) was prepared by heating at reflux for 3–4 hr in excess $SOCl_2$. The $SOCl_2$ was then removed under vacuum and the residue was slowly added to the appropriate aniline (0.10 mol) in 50 ml of pyridine. After heating and stirring at 50° for 1 hr, the mixture was poured into 500 ml of ice–H_2O. After standing overnight, the solid was removed by filtration, washed with dilute HCl and H_2O, dried, and recrystallized.

Biological Methods.—Chicks used in the coccidiosis efficacy trials were either broiler-type heavy breed or hybrid leghorn-type birds raised in batteries during the growing period using special precautions to ensure freedom from coccidiosis infection. At 3–5 weeks of age, the chicks were transferred to individual cages with hardware cloth floors where the efficacy experiments were conducted.

The *Eimeria tenella* cultures used in these experiments were serially propagated in our laboratory over a period of several years. These cultures were isolated by single oocyst inoculation of coccidiosis-free birds to ensure the purity of the cultures. Infection was accomplished by depositing a predetermined volume of calibrated oocyst suspension directly into the crop of each chick.

The compounds tested in these trials were incorporated into a standard ration and fed to the birds for 2 days prior to infection and continued for the duration of the test.

The anticoccidial efficacy in these experiments was based on three factors: (1) mortality, (2) weight gain or loss, and (3) droppings scores. The primary criterion of efficacy was the mortality produced in the medicated-infected chicks as compared to the nonmedicated-infected chicks. Droppings scores and ratios of mean weight gains, medicated-infected *vs.* nonmedicated-noninfected, were used as indicators of morbidity.[6]

Acknowledgment.—The authors wish to acknowledge Mrs. Carol Barker and Mr. Marvin Carr for obtaining the analytical data and assisting with the experiments.

(6) R. R. Baron, M. W. Moeller, and N. F. Morehouse, *Poultry Sci.*, **45**, 411 (1966).

New Compounds

Synthesis of 3,5-Dihydroxy-4-methoxy-α-methylphenethanolamine and Analogs

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Numerous endogenous amines were synthesized by this laboratory during the past several years.[1] 3,5-Dihydroxy-4-methoxy-α-methylphenethylamine and its phenethanolamine analog were found recently to be among the most active releasing agents for cardiac norepinephine-3H.[2] Such results have prompted us to report our syntheses.

Experimental Section[3]

3,5-Dibenzyloxy-4-methoxy-β-methyl-β-nitrostyrene.—A mixture of 2.40 g of NH_4OAc, 0.73 ml of Ac_2O, and 2.40 ml of AcOH was heated to 60° for 15 min. To the mixture was added 1.40 g (4.0 mmoles) of 3,5-dibenzyloxy-4-methoxybenzaldehyde, 15 ml of AcOH, and 40 ml of $EtNO_2$. The mixture was stirred and heated to reflux, using a Dean–Stark water separator. After the addition of 1.75 g of NaOAc and 6 ml of AcOH, the distilled $EtNO_2$ was replaced three times in the 2-hr reflux period. The separator was removed and excess $EtNO_2$ was removed under vacuum. The mixture was cooled and washed with H_2O. A semisolid resulted which was crystallized from MeOH to give 4.30 g (45.8%), mp 97–99°. *Anal.* ($C_{24}H_{23}NO_5$) C, H, N.

Similarly, other substituted β-nitrostyrenes have been prepared and the results are summarized in Table I.

1-(3,5-Dibenzyloxy-4-methoxyphenyl)-2-methyl-2-nitroethanol.—To a solution of 10.5 g (30 mmoles) of 3,5-dibenzyloxy-4-methoxybenzaldehyde in 354 ml of EtOH at 5° was added 6.7 g (89 mmoles) of $EtNO_2$. The temperature was maintained at 5° and with stirring a solution of 1.75 g (31 mmoles) of NaOH in 6.5 ml of H_2O was added dropwise over 10 min. The mixture was stirred at 5° for 1 hr and then poured into 820 ml of 2% AcOH at 0° very slowly. The product was extracted [$(ClCH_2)_2$], dried (Na_2SO_4), concentrated to dryness, and crystallized from C_6H_6–C_6H_{14} to yield in two crops 3.25 g (25.7%) of product, mp 110–113°. *Anal.* ($C_{24}H_{23}NO_6$) C, H, N.

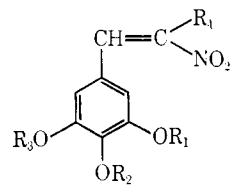
Other β-nitrophenethanols are listed in Table II.

3,5-Dihydroxy-4-methoxy-α-methylphenethanolamine Hydrochloride.—To a Parr shaker were charged 3.25 g (7.7 mmoles) of 1-(3,5-dibenzyloxy-4-methoxyphenyl)-2-methyl-2-nitroethanol dissolved in 140 ml of EtOH, 0.75 g of PtO_2, and 2.1 kg/cm² of H_2. The mixture was shaken for 25 min, the catalyst was filtered and replaced with 1.10 g of 10% Pd–C, and the mixture again was shaken under 2.1 kg/cm² for 27 min. The catalyst was filtered and washed with EtOH and the combined filtrates were made acidic with alcoholic HCl and taken to dryness. The residue was crystallized from EtOH–Et_2O to yield in three crops 0.160 g (8.34%) of product, mp 252–254° dec. *Anal.* ($C_{10}H_{15}NO_4 \cdot HCl$) C, H, N.

Similarly, other substituted phenethanolamines have been prepared and the results are summarized in Table III.

3,5-Dihydroxy-4-methoxy-β-methylphenethylamine Hydrochloride.—To a solution of 4.0 g (100 mmoles) of LAH dissolved

TABLE I
SUBSTITUTED β-NITROSTYRENES



R_1	R_2	R_3	R_4	Mp, C°	Yield, %	Formula	Analyses
CH_3	$C_6H_5CH_2$	CH_3	H	133	79	$C_{17}H_{17}NO_5$	C, H, N[a]
CH_3	CH_3	$C_6H_5CH_2$	H	103–105	49.4	$C_{17}H_{17}NO_5$	C, H, N[b]
CH_3	CH_3	CH_3	H	115–119	67	$C_{11}H_{13}NO_5$	C, H, N[c]
$C_6H_5CH_2$	CH_3	$C_6H_5CH_2$	CH_3	97–99	45.8	$C_{24}H_{23}NO_5$	C, H, N

[a] K. Ratzl, T. Horejachi, and G. Gillek, *Monatsh.*, **85**, 1154 (1954). [b] E. Späth and H. Röder, *ibid.*, **43**, 93 (1922). [c] E. Späth, *ibid.*, **40**, 129 (1919).

(1) This investigation was supported by the Psychopharmacology Research Branch, National Institute of Mental Health, Contract SA-43-ph-3021.

(2) C. R. Creveling, J. W. Daly, and B. Witkop, *J. Med. Chem.*, **11**, 595 (1968).

(3) Melting points are corrected. Where analyses are indicated by symbols of the elements, analytical results obtained were within ±0.4% of the theoretical values. Spectral data were in agreement with assigned structures.