reaction mixt was filtered through a Celite bed after addn of H_2O at the end of the oxidn stage.

Procedure D. 4-Iodo-3′-trifluoromethylbenzophenone (28).—The reaction flask was flushed with dry N_2 and cooled by an ice water bath. *n*-BuLi, 22.3 wt % in hexane (Alfa Inorganics, Inc., Beverly, Mass.), 36 ml (approx 0.077 mole), was added dropwise to *m*-bromobenzotrifluoride (15.7 g, 0.07 mole) in 50 ml of dry Et_2O during 20 min. The resultant soln was added dropwise to 13.0 g (0.056 mole) of *p*-iodobenzaldehyde dissolved in 120 ml of dry Et_2O. Refluxing was contd for 0.5 hr, and the mixt was added to 90 g of crushed ice and allowed to stand overnight. The resultant mixt was acidified with HCl, and the Et_2O layer was saved. The H_2O layer was extd 3 times with Et_2O. The combined Et_2O layer and Et_2O exts were dried ($MgSO_4$) and filtered, and the solvent was stripped off. The liquid residue (19.4 g) crystd on standing. A tlc plate showed 5 spots, 1 very large. The crude reaction product was oxidized as described in procedure C.

***p*-Trifluoromethylbenzaldehyde (Modified Procedure).**—This compd was prepd according to ref 6 with the following modifications. *p*-Trifluoromethylbenzyl bromide was prepared by adding 120 g (0.682 mole) of *p*-trifluoromethylbenzyl alcohol to 145 g (0.859 mole) of 48% HBr and 38 g of concd H_2SO_4. The reaction mixt was refluxed for 2 hr and left standing overnight. H_2O (60 ml) was then added to the reaction mixt. The halide layer was sepd, washed once with cold concd H_2SO_4, H_2O, dil $NaHCO_3$ soln, and H_2O, dried ($MgSO_4$), and filtered. The crude product weighed 138.1 g. Distn from a Vigreux-type column yielded 132.5 g of product (81%), mp 31.5° [ref 7 gives bp 65–66° (5 mm), $n^{20}D$ 1.4918]. The bromide had the correct elemental analysis and showed a single spot on tlc. It is a lacrimator and a skin irritant. In the last step a sufficient vol of EtOH was maintained in the EtONa soln so that on addition of 2-nitropropane pptn of the Na salt did not occur. A reaction time greater than 0.5 hr was allowed before the addition of p-$F_3CC_6H_4CH_2Br$. The pure aldehyde was obtained in a 40.7% yield.

Procedure B. 3-Trifluoromethyl-3′,4′-dichlorobenzophenone Guanylhydrazone·HCl (18).—3-Trifluoromethyl-3′,4′-dichlorobenzophenone (5 g, 0.0157 mole), aminoguanidine·HCl (1.7 g, 0.0155 mole), 7 ml of Cellosolve, and 6 drops of concd HCl were refluxed for 15 min. The reaction was monitored by tlc. The reaction mixt was cooled to room temp and some solid material sepd. The reaction material was added to 100 ml of H_2O and stirred for 0.5 hr. The solid material was filtered under suction, washed 3 times with PhH, 3 times with Et_2O, weighed 5.1 g (80%), had mp 294–294.5° dec, was clean in tlc (R_f 0.6), and had the correct elemental anal.

4-Trifluoromethoxy-3′,4′-dichlorobenzophenone Guanylhydrazone·HCl (20).—4-Trifluoromethoxy-3′,4′-dichlorobenzophenone (5.0 g, 0.0134 mole), aminoguanidine·HCl (1.47 g, 0.0133 mole), 7 ml of Cellosolve, and 5 drops of concd HCl were refluxed for 15 min. The reaction mixt was then cooled to room temp, and the solvent was removed under reduced pressure. The residue was partitioned between 200 ml of H_2O and 200 ml of $CHCl_3$. The $CHCl_3$ layer was saved, dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue was stirred for 1 hr with 50 ml of pet ether (bp 30–60°), filtered, weighed 2.4 g, was clean in tlc (R_f 0.8), had mp 235.5–236.5° dec, and had the correct elemental anal.

Acknowledgment.—We thank Drs. B. T. Poon, E. A. Steck, and T. R. Sweeney of the Walter Reed Army Institute of Research for their general help and encouragement. We appreciate the excellent technical assistance of Dee J. Glasby, Arvia Hosking, and June French.

2,4-Diamino-6-arylethylpteridines as *Streptococcus faecium* Growth Inhibitors

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Received March 19, 1971

A synthesis is reported for 2,4-diamino-6-*p*-carboxyphenethylpteridine along with the 3,4,5-trimethoxy and 3,4-dichlorophenyl analogs. The compounds were moderately effective growth inhibitors of an amethopterin-resistant strain of *Streptococcus faecium*. The tetrahydro derivatives were inactive toward this organism.

In the preceding paper of this series[1] we reported the potent growth inhibitory activity of 10-deazapteroic acid (**1**) and its tetrahydro derivative against *Streptococcus faecium*, a folate-dependent organism. It was observed that the activity of the pteroic analog was greatly enhanced by reduction to the tetrahydro compound. Since 2,4-diamino pteridines should be more capable of cell penetration[2] it was of interest to extend the investigation to 2,4-diamino analogs of I. Accordingly 2,4-diamino-6-*p*-carboxy- (**8d**), 3,4-dichloro- (**8a**), and 3,4,5-trimethoxyphenethylpteridine (**8b**) (Table I) were synthesized and evaluated.

The synthesis of the compds is outlined in Scheme I and the general method has been well discussed previously.[1,3,4] 2,4-Diamino-5-nitro-6-chloropyrimidine was condensed with the appropriate α-amino ketone blocked as the ketal or semicarbazone. An improvement in the process was the use of CF_3COOH for hydrolysis of the blocking group. It was also of interest that the use of 5% NaOH in $2\text{-}MeOC_2H_4OH$ permitted rapid hydrolysis (30 min) of the ester **8c** without concurrent hydroxylic displacement of the pteridine 4-amino group.

As shown in Table II the compds were good inhibitors of *S. faecium* growth, being of the same order of magnitude as aminopterin. Three were moderately active against an amethopterin-resistant strain of *S. faecium* and activity was noted also against *Lactobacillus casei*. Activity against *Pediococcus cerevisiae* was low. Reduction to the tetrahydropteridine derivatives markedly decreased activity against all of the organisms tested.

The carboxylic acid **8d** appeared to be the most active of these compds. However, when tested for antima-

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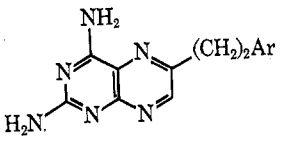
Table I

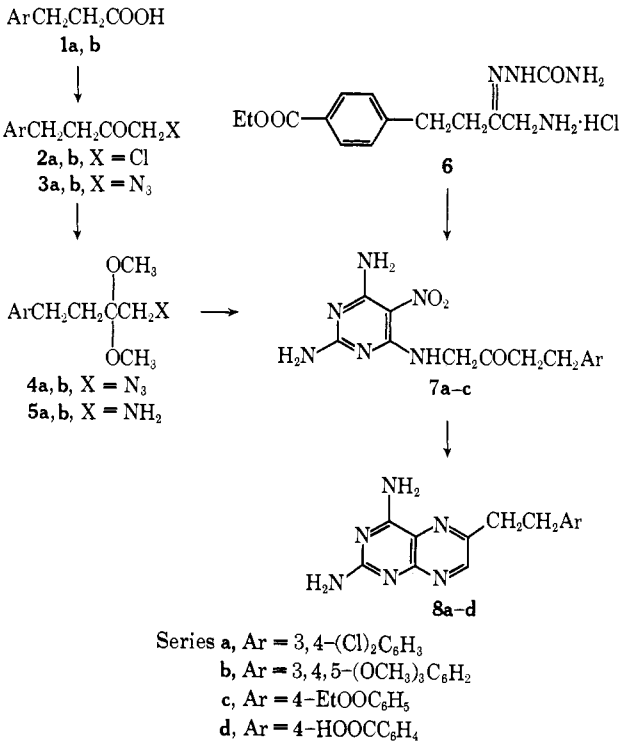
2,4-Diamino-6-arylethylpteridines



Compd	Ar	pH	Uv, mμ (ε)	Formula[a]
8a	3,4-$(Cl)_2C_6H_3$	1	244 (16,200), 340 (8470)	$C_{14}H_{12}Cl_2N_6$
b	3,4,5-$(OCH_3)_3C_6H_2$	1	243 (24,600), 340 (13,000)	$C_{17}H_{20}N_6O_3$
c	4-$EtOOCC_6H_4$	13	256 (20,200), 370 (4870)	$C_{17}H_{18}N_6O_2 \cdot 0.25H_2O$
d	4-$HOOCC_6H_4$	13	256 (22,200), 372 (5750)	$C_{15}H_{14}N_6O_2 \cdot H_2O$
		1	243 (25,800), 338 (8600)	

[a] All compds were anal. for C, H, N.

Scheme I



Series **a**, Ar = 3,4-$(Cl)_2C_6H_3$
b, Ar = 3,4,5-$(OCH_3)_3C_6H_2$
c, Ar = 4-$EtOOC_6H_5$
d, Ar = 4-$HOOCC_6H_4$

larial activity against *P. berghei* in mice, **8d** was completely inactive.

Experimental Section

Compounds followed by empirical formulas were analyzed for the elements indicated with values within ±0.4% of theoretical.

β-3,4,5-Trimethoxyphenylpropionic Acid (1b).—A mixt of 47.5 g of 3,4,5-trimethoxyphenylcinnamic acid, 1.0 g of 5% Rh/C, and 370 ml of 95% EtOH was shaken under 3 atm of H_2 for 3 hr. After filtration the solvent was evapd *in vacuo*, and the residue was crystd from cyclohexane, 44.0 g, mp 105–107°; lit.[5] mp 98°, by NaHg reduction.

Chloromethyl Ketones (2).—A mixt of 15.0 g of **1b**, 9.0 ml of $SOCl_2$, and 135 ml of C_6H_6 was heated at 65–70° for 4 hr. The solvent was removed *in vacuo*, and the residual acid chloride was taken up in Et_2O (100 ml). The soln was added to CH_2N_2 (0.2 mole in 270 ml of Et_2O) at 0–5°. After 30 min the soln was gassed with dry HCl for 30 min, and the Et_2O was evapd. The residue was redissolved in 20 ml of warm Et_2O and filtered, and the Et_2O was evapd to leave **2b** as a white solid (100%), recrystd from Et_2O, mp 72.5–74.5°. *Anal.* ($C_{13}H_{17}ClO_4$) C, H.

The 3,4-dichlorophenyl compd **2a** was similarly obtd as a syrup (73%) from 3,4-dichlorophenylpropionic acid (**1a**).[6]

2,4-Diamino-5-nitro-6-pyrimidinylamino Ketones (7).—To 12 ml of 0.22 *M* NaOEt in EtOH was added 0.87 g (2.64 mmoles) of the semicarbazone·HCl **6**.[1] The mixt was stirred 1 hr and evapd *in vacuo*, and the residue was treated with 0.50 g (2.64 mmoles) of 2,4-diamino-5-nitro-6-chloropyridine[7] and 0.35 ml (2.64 mmoles) of *s*-collidine in 15 ml of DMF. The mixt was stirred 0.5 hr at 85–90°, cooled, and dild with an equal vol of H_2O. The solid was collected and washed with H_2O and EtOH, 0.85 g (73%).

The intermediate semicarbazone (0.39 g) was hydrolyzed with 90% CF_3COOH (10 ml) at room temp (18 hr). The solvent was removed, and the residue was dild with H_2O and taken to pH 9 (15% K_2CO_3). The solid *p*-carbethoxyphenyl ketone **7c** was collected, 0.30 g (89%). Anal. sample had mp 207–210° (2-Me-OC_2H_4OH). *Anal.* ($C_{17}H_{20}N_6O_5$) C, H, N.

The 3,4-dichlorophenyl ketone **7a** and the trimethoxy analog **7b** were similarly obtd in 30 and 50% yield, resp, by condn of the aminomethyl ketals **5a, b** with the nitrochloropyrimidine, followed by hydrolysis. The syrupy ketals **5** were prepd from the chloromethyl ketones **2** by the previously described method,[1] all intermediates being syrups also.

Ketones **7a** had mp 187–190° (2-$MeOC_2H_4OH$). *Anal.* ($C_{14}H_{14}Cl_2N_6O_3$) C, H, N. Ketone **7b** had mp 185–187° (MeOH). *Anal.* ($C_{17}H_{22}N_6O_6$) C, 49.6; H, N.

2,4-Diamino-6-substituted Pteridines (8, Table I).—A mixt of 1.0 g of the appropriate nitropyrimidinyl ketone (7) and 3–5 ml of HOAc was warmed into soln. Then at 90–100° an equal wt of Zn dust was added over 30 min. The hot sol was decanted, and the Zn was washed with hot 50% HOAc. The combined, cooled soln was treated with 30% H_2O_2 (3 equiv) for 1 hr. The solvent was evapd *in vacuo*, and the residue was treated with H_2O and 6 *N* NH_4OH to pH 5–6. The pptd pteridine was collected, H_2O washed, and dried.

Hydrolysis of the ester **8c** to the acid **8d** was done with 5% NaOH in 2-$MeOC_2H_4OH$ for 30 min at 100°.

Table II

Bacterial Growth Inhibition[a]

Compd	*S. faecium* ATCC 8043	*S. faecium* (amethopterin resistant)	*L. casei* ATCC 7469	*P. cerevisiae* ATCC 8081
Amethopterin	0.15	>6000	0.01	60
Aminopterin	1.0		0.03	210
8a	6.0	600	600	>2000
8b	3.0	300	40	1600
8c	4.0	2000	28	>2000
8d	2.0	200	13	2000
Tetrahydro[b]-8a	17	1600		>2000
Tetrahydro-8b	21	2000		>2000
Tetrahydro-8c	17	>2000		>2000
Tetrahydro-8d	12	>2000		>2000

[a] Expressed as ng/ml for 50% inhibition. [b] Hydrogenated 3 mg of compd over 10 mg of PtO_2 at pH 11; uv corresponded to tetrahydropteridine.

Acknowledgment.—This work was supported by the U. S. Army Medical Research and Development Command under Contract No. DADA 17-67-C-7129. This is Contribution No. 906 from the Army Research Program on Malaria.

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