solution, and poured into ether. The mixture was filtered to remove NaCl, the layers were separated, and the aqueous phase was extracted with ether. The extracts were combined, dried (anhydrous $K_2CO_3$), and concentrated in vacuo to give 25.1 g (91%) of 95.6% pure (by VPC) $N^4$-(4-chloro-2-quinazolinyl)-$N^1$,$N^1$-diethyl-1,4-pentanediamine as a brown oil. A mixture of 4.1 g (0.012 mol) of this residue, 1.7 g (0.012 mol) of 4-nitrobenzenamine, 4.0 mL of a 25% solution of HCl in *i*-PrOH, and 60 mL of *i*-PrOH was heated under reflux for 6.25 h, concentrated in vacuo to a paste, and added to 1.5 L of $H_2O$. The mixture was made basic with 2 N NaOH and extracted with ether. The extracts were combined, dried (anhydrous $K_2CO_3$), and concentrated in vacuo to an oil. The crude product was dissolved in 200 mL of ether, and HCl was bubbled through the solution for 15 min. The solid which formed was collected and dried to give 5.6 g (84%) of $N^2$-[4-(diethylamino)-1-methylbutyl]-$N^4$-(4-nitrophenyl)-2,4-quinazolinediamine 2.2-hydrochloride 1.7-hydrate (115), mp 125–128 °C with preliminary softening.

Compounds 89, 107, and 113 were of sufficient stability and purity after concentration of the ethereal solution to avoid formation of the hydrochloride salt.

**Acknowledgment.** The authors are indebted to Dr. Leo Rane of the University of Miami and Dr. Paul E. Thompson and co-workers for the antimalarial testing. We also thank C. E. Childs and associates for the microanalyses and Dr. F. MacKellar and co-workers for determination of the spectral data.

# Folate Antagonists. 18. Synthesis and Antimalarial Effects of $N^6$-(Arylmethyl)-$N^6$-methyl-2,4,6-pteridinetriamines and Related $N^6$,$N^6$-Disubstituted 2,4,6-Pteridinetriamines[1-3]

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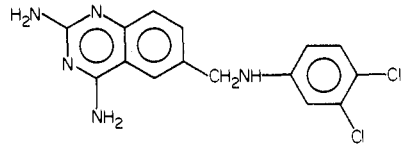
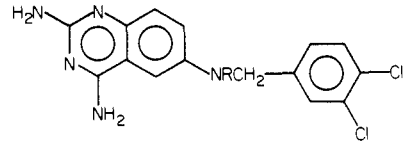
*Received August 4, 1980*

$N^6$-(Arylmethyl)-$N^6$-methyl-2,4,6-pteridinetriamines (1–15) and related $N^6$-substituted 2,4,6-pteridinetriamines (16–20) were obtained by the condensation of 6-chloro-2,4-pteridinediamine with *N*-methylarylmethanamine and other selected secondary amines. The requisite *N*-methylarylmethanamines (21–32) were prepared by the hydrogenation over Pt/C of the corresponding arylcarboxaldehyde in the presence of methanamine. Several of the $N^6$-(arylmethyl)-$N^6$-methyl-2,4,6-pteridinetriamines exhibited exceptional suppressive antimalarial activity against a drug-sensitive line of *Plasmodium berghei* in mice. $N^6$-Methyl-$N^6$-(1-naphthalenylmethyl)-2,4,6-pteridinetriamine (9), the most active of these compounds, was also shown to be curative at 3.16 mg/kg in a single oral dose against *P. cynomolgi* in the rhesus monkey. This compound was also shown to be effective against a chloroquine-resistant line of *P. berghei* in the mouse but showed cross-resistance to a pyrimethamine-resistant strain. Most of the 2,4,6-pteridinetriamines showed strong antibacterial action against *Streptococcus faecalis* and *Staphylococcus aureus*.

Members of a series of 6-[(phenylamino)methyl]-2,4-quinazolinediamines represented by I were reported to be



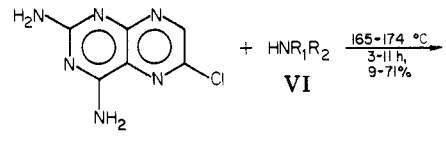
I



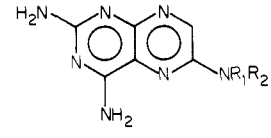
IIa, R = H
b, R = $CH_3$

even more potent as antimalarial agents than the corresponding 6-[(phenylmethyl)amino]-2,4-quinazolinediamines represented by II.[4]

Scheme I

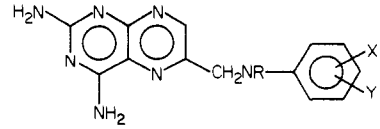


V



VII

We have recently reported[4] that the corresponding 6-[(arylamino)methyl]-2,4-pteridinediamines (IIIa–c) pre-



III

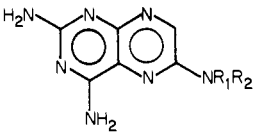
| R | X, Y |
|---|---|
| a $C_2H_5$ | 4-$OCH_3$ |
| b $(CH_2)_2CH_3$ | 3,4-$Cl_2$ |
| c $CH(CH_3)_2$ | 4-Cl |

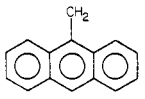
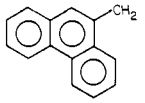
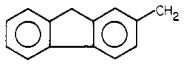
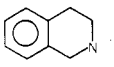
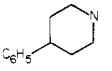
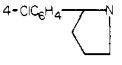
pared as nonclassical analogues of aminopterin and methotrexate, while displaying potent prophylactic effects against *Plasmodium gallinaceum* infections, were generally poorly active against trophozoite-induced *P. berghei* infections in mice.

(1) This is paper 49 of a series on antimalarial drugs. For paper 48, see E. F. Elslager, C. Hess, J. Johnson, D. Ortwine, V. Chu, and L. M. Werbel, *J. Med. Chem.*, preceding paper in this issue.
(2) This investigation was supported by the U.S. Army Medical Research and Development Command Contract DA 17-72-C-2077. This is contribution no. 1587 to the Army Research Program on Malaria.
(3) A preliminary report of the work appeared in *Med. Chem., Proc. Int. Symp. Med. Chem., 4th, 1974*, 227 (1974).
(4) D. F. Worth, J. Johnson, E. F. Elslager, and L. M. Werbel, *J. Med. Chem.* 21, 331, 1978.

0022-2623/81/1824-0140$01.00/0 © 1981 American Chemical Society

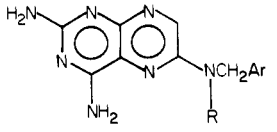
Table I. $N^6,N^6$-Disubstituted 2,4,6-Pteridinetriamines



| no. | $R_1$ | $R_2$ | mp, °C | % yield, purified | reaction conditions: temp, °C | reaction conditions: time, h | crystn solvent | formula | anal. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | $C_6H_5CH_2$ | $CH_3$ | 248-252 dec | 31 | 165 | 3 | 1 N HCl | $C_{14}H_{15}N_7 \cdot HCl \cdot H_2O$ | C, H, N, $Cl^-$, $H_2O$ |
| 2 | $2\text{-}ClC_6H_4CH_2$ | $CH_3$ | 297-300 dec[a] | 47 | 165 | 4 | 1 N HCl | $C_{14}H_{14}ClN_7$ | C, H, N |
| 3 | $4\text{-}ClC_6H_4CH_2$ | $CH_3$ | 300-303 dec[a] | 23 | 165 | 7 | DMF-dil $NH_4OH$ | $C_{14}H_{14}ClN_7$ | C, H, N |
| 4 | $3,4\text{-}Cl_2C_6H_3CH_2$ | $CH_3$ | 303-305 | 42 | 165 | 7 | 33% aq HOAc | $C_{14}H_{13}Cl_2N_7$ | C, H, N |
| 5 | $3\text{-}BrC_6H_4CH_2$ | $CH_3$ | 295-298 dec | 43 | 166-174 | 11 | DMF | $C_{14}H_{14}BrN_7$ | C, H, N |
| 6 | $4\text{-}FC_6H_4CH_2$ | $CH_3$ | 290-292 dec | 31 | 164-169 | 8 | DMF-dil $NH_4OH$ | $C_{14}H_{14}FN_7 \cdot 0.2H_2O$ | C, H, N, $H_2O$ |
| 7 | $3\text{-}CF_3C_6H_4CH_2$ | $CH_3$ | 272 dec | 9 | 167 | 12 | EtOH-$NH_4OH$ | $C_{15}H_4F_3N_7 \cdot 0.2H_2O$ | C, H, N |
| 8 | $3,4,5\text{-}(CH_3O)_3C_6H_2CH_2$ | $CH_3$ | 294-296 dec | 31 | 168-169 | 1 | DMF-dil $NH_4OH$ | $C_{17}H_{21}N_7O_3$ | C, H, N |
| 9 | $1\text{-}C_{10}H_9CH_2$ | $CH_3$ | 301-303 dec | 35 | 165-170 | 5 | DMF | $C_{18}H_{17}N_7$ | C, H, N |
| 10 | $2\text{-}C_{10}H_9CH_2$ | $CH_3$ | 299-301 dec | 33 | 164-169 | 5 | DMF | $C_{18}H_{17}N_7$ | C, H, N |
| 11 | $1\text{-}[(2\text{-}OCH_3)C_{10}H_8]CH_2$ | $CH_3$ | 282-285 dec | 11 | 165 | 2 | DMF | $C_{19}H_{19}N_7O \cdot 0.8H_2O$ | C, H, N |
| 12 | $1\text{-}[(4\text{-}OCH_3)C_{10}H_8]CH_2$ | $CH_3$ | 289-291 dec | 37 | 170 | 4 | DMF-dil $NH_4OH$ | $C_{19}H_{19}N_7O$ | C, H, N |
| 13 |  | $CH_3$ | 277-281 dec | 5 | 170 | 8 | DMF-dil $NH_4OH$ | $C_{22}H_{19}N_7 \cdot 0.7H_2O$ | C, H, N, $H_2O$ |
| 14 |  | $CH_3$ | >300 | 13 | 170 | 4.5 | DMF | $C_{22}H_{19}N_7 \cdot 0.6H_2O \cdot 0.3C_3H_7NO$[b] | C, H, N, $H_2O$ |
| 15 |  | $CH_3$ | 289-291 dec | 17 | 170 | 7 | EtOH | $C_{21}H_{19}N_7 \cdot HCl$ | C, H, N, $Cl^-$ |
| 16 | $C_6H_5(CH_2)_2$ | $CH_3$ | 235 | 33 | 167 | 2 | DMF-dil $NH_4OH$ | $C_{15}H_{17}N_7 \cdot 1.6H_2O$ | C, H, N, $H_2O$ |
| | $NR_1R_2$ | | | | | | | | |
| 17 |  | | 295-298 dec | 37 | 167 | 0.25 | DMF | $C_{15}H_{15}N_7 \cdot 2H_2O$ | C, H, N, $H_2O$ |
| 18 |  | | 281-285 dec | 67 | 165 | 3 | DMF-dil $NH_4OH$ | $C_{17}H_{19}N_7 \cdot 0.5HCl \cdot 0.1H_2O$ | C, H, N, $Cl^-$, $H_2O$ |
| 19 |  | | 292-300 dec | 18 | 165 | 8.5 | EtOH-$NH_4OH$ | $C_{16}H_{16}ClN_7$ | C, H, N |
| 20 | c-$NC_5H_{10}$ | | >300 | 71 | 106 | 21 | 1 N HCl | $C_{11}H_{15}N_7 \cdot HCl \cdot 1.8H_2O$ | C, H, N, $Cl^-$, $H_2O$ |

[a] With preliminary shrinking. [b] The NMR spectrum ($Me_2SO$-$d_6$) demonstrated the presence of 0.3 mol of DMF.

We now report that, surprisingly, the 6-[(aralkyl)-amino]-2,4-diaminopteridines IV possess extremely potent suppressive antimalarial effects against drug-sensitive lines of *P. berghei* in mice.



IV

**Chemistry.** The $N^6,N^6$-disubstituted 2,4,6-pteridinetriamines (Table I, 1–20) were prepared by allowing 6-chloro-2,4-pteridinediamine (V) to react with a variety of secondary amines (VI), including *N*-methylarylmethanamines, piperidines, and 2-(4-chlorophenyl)pyrrolidine, at 165–174 °C (Scheme I). The reaction generally proceeded with difficulty, and purification of the products was complicated by the presence of unchanged starting materials as well as decomposition products. Utilization of the presumably more reactive 6-bromo-2,4-pteridinediamine in the preparation of 2 and 8 resulted in no marked improvement. No product could be isolated from the reaction of 6-chloro-2,4-pteridinediamine with the primary amine, 3,4-dichlorobenzenemethanamine. A similar observation has been reported by Taylor and Kobylecki.[5]

(5) E. C. Taylor and R. Kobylecki, *J. Org. Chem.*, **43**, 680 (1978).

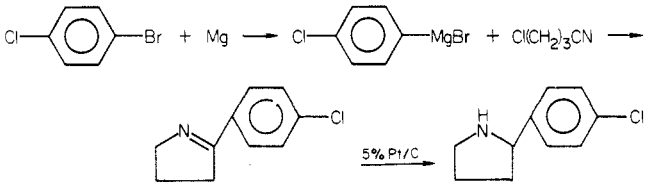
Table II. *N*-Methylarylmethanamines

$ArCH_2NHCH_3$

| no. | name | Ar | bp (mp), °C | yield purified, % | formula | anal. |
|---|---|---|---|---|---|---|
| 21 | 3,4-dichloro-*N*-methylbenzenemethanamine[a] | 3,4-$Cl_2C_6H_3$ | 146 (47 mm) | 68 | $C_8H_9Cl_2N$ | C, H, N |
| 22 | 3-bromo-*N*-methylbenzenemethanamine[b] | 3-$BrC_6H_4$ | 115–123 (38–39 mm) | 64 | $C_8H_{10}BrN$ | C, H, N |
| 23 | 4-fluoro-*N*-methylbenzenemethanamine hydrochloride[c] | 4-$FC_6H_4$ | 73–75 (9 mm), HCl: 193–195 | 66.5 | $C_8H_{10}FN\cdot HCl$ | C, H |
| 24 | *N*-methyl-3-(trifluoromethyl)benzenemethanamine hydrochloride[d] | 3-$CF_3C_6H_4$ | 68–72 (9 mm), HCl: 170–172 | 41 | $C_9H_{10}F_3N\cdot HCl$ | C, H, N |
| 25 | 3,4,5-trimethoxy-*N*-methylbenzenemethanamine 0.25-hydrate[e] | 3,4,5-$(OCH_3)_3C_6H_2$ | 91 (0.05 mm) | 90 | $C_{11}H_{17}NO_3\cdot 0.25H_2O$ | C, H, N, $H_2O$ |
| 26 | *N*-methyl-1-naphthalenemethanamine[f] | 1-$C_{10}H_7$ | 139–150 (17–18 mm) | 79 | $C_{12}H_{13}N$[g] | C, H, N |
| 27 | *N*-methyl-2-naphthalenemethanamine | 2-$C_{10}H_7$ | 125–135 (17 mm) | 75 | $C_{12}H_{13}N$[g] | C, H, N |
| 28 | 2-methoxy-*N*-methyl-1-naphthalenemethanamine | 1-(2-$OCH_3C_{10}H_6$) | 123–129 (0.6 mm) | 80 | $C_{13}H_{15}NO$ | C, H, N |
| 29 | 4-methoxy-*N*-methyl-1-naphthalenemethanamine | 1-(4-$OCH_3C_{10}H_6$) | 131–136 (0.6 mm)[h] | 57 | $C_{13}H_{15}NO$ | C, H, N |
| 30 | *N*-methyl-9-anthracenemethanamine | | 45–48[i] | 38 | $C_{16}H_{15}N$ | C, H, N |
| 31 | *N*-methyl-9-phenanthrenemethanamine | | 57–59[i] | 61 | $C_{16}H_{15}N$ | C, H, N |
| 32 | *N*-methyl-9*H*-fluorene-2-methanamine | | 48–92[j] | 81 | $C_{15}H_{15}N$ | C, H, N |

[a] E. F. Elslager et al. *J. Med. Chem.*, 15, 1138; bp 119–121 °C (10 mm). [b] Previously isolated as the HCl salt, mp 159–160 °C: S. L. Shapiro et al. *J. Am. Chem. Soc.*, 81, 3728 (1959). [c] Lit.[18] reports bp 80–82 °C (14 mm). [d] The material still contained 15% of an impurity after distillation. Purification was accomplished by treating a solution of the material with 2-propanol saturated with hydrogen chloride to afford the product as the hydrochloride salt. [e] A. Sonn, *Ber. Dtsch. Chem. Ges.*, 58, 1103 (1925), reports bp 92 °C (17 mm). [f] Previously isolated as the HCl salt, mp 190 °C: R. C. Hutton et al. *J. Chem. Soc. A*, 1573 (1966). [g] Purest fraction according to VPC submitted for analysis. [h] The literature[8] reports 158–163 °C (0.5 mm). [i] Recrystallized from hexane. [j] The material was homogeneous by VPC and spectral data were consistent with the structure.

Scheme II




33

The 6-chloro-2,4-pteridinediamine (V) was prepared according to a six-step synthesis described by Jones and Cragoe[6] and the 6-bromo-2,4-pteridinediamine by a similar method.[7] Taylor and Kobylecki[5] recently have described a more convenient three-step synthesis of 6-chloro-2,4-pteridinediamine.

Most of the *N*-methylarylmethanamines (VI, Table II, compounds **21–32**) utilized which were not commercially available were prepared by the hydrogenation of the corresponding arylcarboxaldehyde in the presence of methanamine[8] over platinum on carbon. One exception was 4-fluoro-*N*-methylbenzenemethanamine (Table II, **23**), which was obtained by the reaction of 1-(chloromethyl)-4-fluorobenzene with methanamine in a sealed vessel.[9]

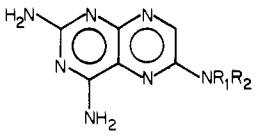
2-(4-Chlorophenyl)pyrrolidine[10] (**33**) was prepared by the catalytic (Pt/C) reduction of 5-(4-chlorophenyl)-3,4-dihydro-2*H*-pyrrole, which was obtained from the reaction[11] of 4-chlorophenylmagnesium bromide with 4-chlorobutanenitrile (Scheme II).

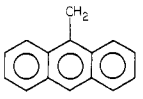
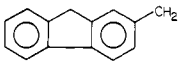
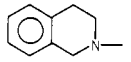
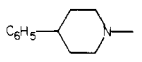
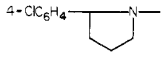
**Suppressive Antimalarial Screening in Mice.** The $N^6$,$N^6$-disubstituted 2,4,6-pteridinetriamines listed in Table I, with the exception of compound **14**, were tested initially against a normal drug-sensitive strain of *P. berghei* in mice by the parenteral route.[12,13] The compounds were dissolved or suspended in sesame or peanut oil and were administered to mice in a single subcutaneous dose 72 h postinfection. Extension of the mean survival time of the treated mice is interpreted as evidence of antimalarial activity.

Many of the compounds tested showed impressive activity against *P. berghei* in mice. The most potent compound, $N^6$-methyl-$N^6$-(1-naphthalenylmethyl)-2,4,6-pteridinetriamine (compound **9**, Table III) was curative from 640 through 5 mg/kg. This phenomenal activity is completely eradicated by either the addition of a methoxy group at the 2 position of the naphthalene ring (compound **11**) or the attachment of another aromatic ring (compound **13**). However, considerable activity is retained when the methoxy group is inserted at the 4 position instead (compound **12**, minimum curative dose, MCD = 40) or when the attachment of the methylene is moved to the 2 position

(6) J. H. Jones and E. J. Cragoe, *J. Med. Chem.*, 11, 322 (1968).
(7) E. J. Cragoe and J. H. Jones, U.S. Patent 3 487 082, Dec. 30, 1969.
(8) This procedure is similar to that described by Z. Horii, I. Ninomiya, and Y. Tamura, *Chem. Pharm. Bull.*, 7, 444 (1959).
(9) We thank Dr. Donald Butler of these laboratories for preparing this compound.
(10) J. P. Wibaut and J. Dhont, *Recl. Rev. Trav. Chim. Pays-Bas*, 62, 272 (1943).
(11) Procedure according to L. Craig, H. Bulbrook, and R. M. Hixon, *J. Am. Chem. Soc.*, 53, 1831 (1931).
(12) The parenteral antimalarial screening in mice and chicks was carried out in the laboratory of Dr. Leo Rane of the University of Miami. Test results were provided through the courtesy of Drs. T. R. Sweeney and E. A. Steck of the Walter Reed Army Institute of Research.
(13) For a description of the test method, see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, 10, 431 (1967).

Table III. Parenteral Antimalarial Effects of $N^6,N^6$-Disubstituted 2,4,6-Pteridinetriamines against *Plasmodium berghei* in Mice



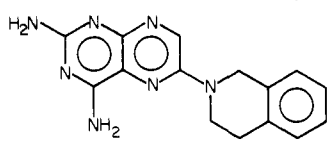
| no. | $R_1$ | $R_2$ | MST, C or T[a] after single sc mg/kg dose | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 640 | 320 | 160 | 80 | 40 | 20 | 10 |
| 1 | $C_6H_5CH_2$ | $CH_3$ | 0.3 | | 0.1 | | 0.1 | | |
| 2 | $2\text{-}ClC_6H_4CH_2$ | $CH_3$ | C5, T5 | C3, T2 | C6/10 | C3/5 | C4/10 | 9.5 | |
| 3 | $4\text{-}ClC_6H_4CH_2$ | $CH_3$ | | C10/10 | C5/5 | C7/10 | C3/5 | C4/10 | 4.3 |
| 4 | $3,4\text{-}Cl_2C_6H_3CH_2$ | $CH_3$ | C10/10 | C5/5 | C10/10 | C3/5 | C6/15 | 10.6 | 2.5 |
| 5 | $3\text{-}BrC_6H_4CH_2$ | $CH_3$ | C4/10 | C1/5 | 12.8 | 10.7 | 10.2 | 6.9 | |
| 6 | $4\text{-}FC_6H_4CH_2$ | $CH_3$ | C10/10 | C4/5 | C8/10 | C3/5 | C5/10 | 8.5 | |
| 7 | $3\text{-}CF_3C_6H_4CH_2$ | $CH_3$ | | | C5/5 | C5/5 | 15.4 | 12.2 | 8.8 |
| 8 | $3,4,5\text{-}(CH_3O)_3C_6H_2CH_2$ | $CH_3$ | C10/10 | C4/5 | C8/10 | C3/5 | C6/10 | 5.5 | |
| 9 | $1\text{-}C_{10}H_9CH_2$ | $CH_3$ | C10/10 | C5/5 | C10/10 | C5/5 | C15/15 | C5/5 | C4/5[b] |
| 10 | $2\text{-}C_{10}H_9CH_2$ | $CH_3$ | C10/10 | C5/5 | C10/10 | C5/5 | C4/5 | C2/5 | 5.9 |
| 11 | $1\text{-}(2\text{-}OCH_3C_{10}H_8)CH_2$ | $CH_3$ | | 0.2 | | 0.2 | | 0.2 | |
| 12 | $1\text{-}(4\text{-}OCH_3C_{10}H_8)CH_2$ | $CH_3$ | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 6.5 | |
| 13 |  | $CH_3$ | | 1.3 | | 0.1 | | 0.1 | |
| 15 |  | $CH_3$ | | 5/5 | 5/5 | 2/5 | 8.1 | 6.3 | 3.5 |
| 16 | $C_6H_5(CH_2)_2$ | $CH_3$ | 3.9 | 1.7 | 0.7 | 0.1 | 0.1 | 0.1 | |
| | $NR_1R_2$ | | | | | | | | |
| 17 |  | | 0.5 | | 0.3 | | 0.1 | | |
| 18 |  | | 0.1 | | 0.1 | | 0.1 | | |
| 19 |  | | | C3/5 | C3/5 | C2/5 | 12.1 | 10.1 | 7.9 |
| 20 | c-$NC_5H_{10}$ | | | 0.9 | | 0.3 | | 0.3 | |
| IIb | | | C5/5 | C10/10 | C10/10 | C10/10 | C15/15 | C8/15 | 8.7 |
| cycloguanil hydrochloride | | | T5 | C3, T2 | C5 | C2/5 | C1/5 | 7.9 | |

[a] MST is the mean survival time (days) of treated mice (MSTT) minus the mean survival time (days) of control mice (MSTC). In the present study the MSTC ranged from 6.1 to 6.3 days. T signifies the number of toxic deaths, occurring on days 2–5 after infection, which are attributed to drug action. C indicates the number of mice surviving at 60 days postinfection and termed "cured"; data to establish parasitological cure based on subinoculation are unavailable. Each compound was administered as a single sc dose. Each entry at each dose level represents results with a five-animal group. [b] Continuation of data: 5 mg/kg, C2/5; 2.5 mg/kg, 9.7; 1.25 mg/kg, 4.5.

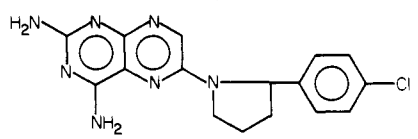
of the naphthalene ring (compound **10**, MCD = 20).

$N^6$-(9*H*-Fluoren-2-ylmethyl)-$N^6$-methyl-2,4,6-pteridinetriamine (compound **15**) and the $N^6$-methyl-$N^6$-[(substituted-phenyl)methyl]-2,4,6-triamines (compounds **2**–**8**) also possessed curative activity. The 4-chloro substituted analogue (compound **3**) was the most active of the phenyl series, being equal in potency to the quinazoline analogue IIb (MCD = 20 mg/kg).

6-[2-(4-Chlorophenyl)-1-pyrrolidinyl]-2,4-pteridinediamine (compound **19**), which one may envision as an



**17**



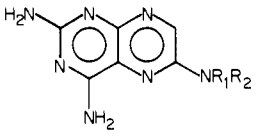
**19**

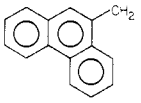
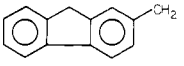
analogue of **3** wherein an ethyl bridge extends between the $N^6$-methyl and the $N^6$-methylene, was also curative through 80 mg/kg. Compound **17**, wherein the aromatic ring of the benzyl group is fused back to the nitrogen at position 6, was inactive. It is difficult to determine whether this was due to steric constraint, since the unsubstituted parent compound (compound **1**) was also inactive. Similar uncertainty surrounds the inactivity of **16** which contains an additional methylene group between $N^6$ and the phenyl ring. The 6-(1-piperidinyl)-2,4-pteridinediamines (**18** and **20**) were also inactive.

**Drug-Resistance Studies.**[14] $N^6$-Methyl-$N^6$-(1-naphthalenylmethyl)-2,4,6-pteridinetriamine (compound **9**), which exhibited the highest activity against the normal drug-sensitive strain of *P. berghei* in mice, was tested against chloroquine- and pyrimethamine-resistant lines. The $SD_{90}$ for the sensitive line (P line) was 45 mg/kg and the $SD_{90}$ for the chloroquine-resistant line (C line) was 48 mg/kg, whereas that for the pyrimethamine-resistant line was greater than 250 mg/kg. Thus, **9** was fully active against the chloroquine-resistant strain but was cross-re-

(14) Testing against resistant strains of *P. berghei* was carried out by Dr. Arba L. Ager, Jr., at the University of Miami, and test results were supplied through the courtesy of Col. D. E. Davidson and Dr. E. A. Steck of the Walter Reed Army Institute of Research.

Table IV. In Vitro Antibacterial Effects of $N^6$,$N^6$-Disubstituted 2,4,6-Pteridinetriamines



| | | | min inhibitory concn, μg/mL[a] | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| no. | $R_1$ | $R_2$ | *S.f.* MGH-2[b] | *S.a.* UC-76[c] | *S.a.* S18713[c] | *P.a.* 28[d] | *E.c.* Vogel[e] | *S.s.* C-10[f] | *M.t.* $H_{37}R_V$[g] |
| 1 | $C_6H_5CH_2$ | $CH_3$ | <0.25 | <0.25 | <0.25 | >25 | 10 | >25 | 10 |
| 2 | $2\text{-}ClC_6H_4CH_2$ | $CH_3$ | <0.25 | <0.25 | <0.25 | >25 | >25 | >25 | 5 |
| 4 | $3,4\text{-}Cl_2C_6H_3CH_2$ | $CH_3$ | <0.25 | <0.25 | <0.25 | >25 | >25 | >25 | 10 |
| 6 | $4\text{-}FC_6H_4CH_2$ | $CH_3$ | <0.25 | <0.25 | <0.25 | >25 | >25 | >25 | 2.5 |
| 7 | $3\text{-}CF_3C_6H_4CH_2$ | $CH_3$ | <0.25 | <0.25 | <0.25 | >25 | >25 | >25 | 10 |
| 8 | $3,4,5\text{-}(CH_3O)_3C_6H_2CH_2$ | $CH_3$ | <0.25 | <0.25 | <0.25 | >25 | >25 | >25 | >25 |
| 9 | $1\text{-}C_{10}H_9CH_2$ | $CH_3$ | <0.25 | <0.25 | <0.25 | >25 | >25 | >25 | >25 |
| 10 | $2\text{-}C_{10}H_9CH_2$ | $CH_3$ | <0.25 | <0.25 | <0.25 | >25 | >25 | >25 | >25 |
| 12 | $1\text{-}(4\text{-}OCH_3C_{10}H_8)CH_2$ | $CH_3$ | <0.25 | <0.25 | <0.25 | >25 | >25 | >25 | 2.5 |
| 14 |  | $CH_3$ | <0.25 | <0.25 | <0.25 | >25 | >25 | >25 | 2.5 |
| 15 |  | $CH_3$ | <0.25 | <0.25 | <0.25 | >25 | >25 | >25 | 5 |
| 16 | $C_6H_5(CH_2)_2$ | $CH_3$ | <0.25 | <0.25 | <0.25 | >25 | >25 | >25 | >25 |
| 18 | $4\text{-}C_6H_5\text{-}c\text{-}NC_5H_{10}$ | | <0.25 | >25 | >25 | >25 | >25 | >25 | 10 |
| | trimethoprim | | <0.25 | <0.25 | <0.25 | >25 | <0.25 | <0.25 | >25 |

[a] Gradient plate test. [b] *S.f.* = *Streptococcus faecalis*. [c] *S.a.* = *Staphylococcus aureus*. [d] *P.a.* = *Pseudomonas aeruginosa*. [e] *E.c.* = *Escherichia coli*. [f] *S.s.* = *Shigella sonnei*. [g] *M.t.* = *Mycobacterium tuberculosis*.

sistant with the pyrimethamine-resistant strain by greater than fivefold.

**Antimalarial Testing in Primates.**[15] The 1-naphthalenyl analogue (compound 9) was tested against a trophozoite-induced *P. cynomolgi* infection in rhesus monkeys at single oral doses of 10, 3.16, and 1 mg/kg. Both monkeys were cured with the 10 mg/kg dose. Only one of two monkeys was cured with the 3.16 mg/kg dose, although the other showed marked suppression of parasitemia. The 1 mg/kg dose led to a slight suppression of parasitemia in one monkey and was ineffective in the other.

**Antibacterial Studies.** Thirteen of the pteridinetriamines (compounds 1, 2, 4, 6–10, 12, 14–16, and 18) were tested in vitro against a spectrum of pathogenic bacteria, including *Streptococcus faecalis* (MGH-2), normal (UC-76) and drug-resistant (S18713) *Staphylococcus aureus*, *Escherichia coli* (Vogel), *Shigella sonnei* (C-10), and *Mycobacterium tuberculosis* ($H_{37}Rv$) (Table IV). A modification of the gradient plate procedure of Szybalski[16] and Webb and Washington[17] was employed throughout. All but one compound (18) inhibited the growth of *S. faecalis* MGH-2, *S. aureus* UC-76, and *S. aureus* S18713 at drug concentrations of <0.25 μg/mL, and all but one (1) were completely ineffective against *P. aeruginosa* 28, *E. coli* (Vogel), and *S. aureus* (C-10). Nine compounds (2, 4, 6, 7, 12, 14, 15, and 18) exhibited moderate activity against *M. tuberculosis*, with 6, 12, and 14 inhibiting growth at levels as low as 2.5 μg/mL.

## Conclusion

Interest in related antifol types[19] which appear to have greater potency against both sensitive and resistant strains of malaria has led us to discontinue further effort with the pteridinetriamines reported herein.

## Experimental Section

Melting points (corrected) were taken on a Thomas-Hoover capillary melting point apparatus. The progress of the condensations between 6-chloro-2,4-pteridinediamine and the secondary amines was followed by TLC using silica gel plates (Eastman) and the solvent mixtures of MeOH–EtOAc–$Et_3N$ (25:75:1) and EtOAc–HOAc (4:1). The 2,4,6-pteridinetriamine products displayed bright-green fluorescence under UV light (254 nm), whereas the starting material, 6-chloro-2,4-pteridinediamine, displayed a blue fluorescence. Spectral data were obtained with a Beckman IR-9 spectrophotometer (IR) and a Varian A60 spectrophotometer (NMR) and were consistent with the assigned structures.

**$N^6$,$N^6$-Disubstituted 2,4,6-Pteridinediamines.** The following three preparations are presented as examples of the purification techniques used to isolate these compounds. Compounds 2, 3, 5–12, 14, and 16–19 were purified using variations of these examples.

**$N^6$-Methyl-$N^6$-(phenylmethyl)-2,4,6-pteridinetriamine Hydrochloride Hydrate (1, Table I).** A mixture of 1.5 g (0.0076 mol) of 6-chloro-2,4-pteridinediamine and 12 mL of *N*-methylbenzenemethanamine was stirred at 165 °C for 3 h, cooled, and poured into ether. The precipitate that formed was collected, washed with ether, and then taken up in 150 mL of hot 1 N HCl. The mixture was filtered hot to remove insoluble material, and the filtrate was cooled to afford 0.8 g (31.3%) of the title compound, mp 248–252 °C dec.

**$N^6$-[(3,4-Dichlorophenyl)methyl]-$N^6$-methyl-2,4,6-pteridinetriamine (4, Table I).** A mixture of 2.0 g (0.0102 mol) of 6-chloro-2,4-pteridinediamine and 30 mL of 3,4-dichloro-*N*-methylbenzenemethanamine was stirred at 145–152 °C for 7 h, then at 152–155 °C for 2 h, and finally at 158–162 °C for 6 h. The reaction mixture was cooled to approximately 100 °C and filtered to collect 2.7 g of orange solid, which was triturated with 30 mL

(15) Primate test data were provided by Col. D. Davidson of the Walter Reed Army Institute of Research.
(16) W. Szybalski, *Microb. Genet. Bull.*, **5**, 16 (1951).
(17) A. H. Webb and L. Washington, *Bacterial. Proc.*, **52**, M88 (1966).
(18) J. V. Braun and A. Friedsam *Ber. Dtsch. Chem. Ges.*, **63B**, 2407 (1930).
(19) E. F. Elslager, P. Jacob, J. Johnson, L. M. Werbel, D. F. Worth, and L. Rane, *J. Med. Chem.*, **21**, 1059 (1978).

of warm 1 N HCl. The remaining solid was dissolved in hot DMF, treated with decolorizing charcoal, filtered through supercell, treated with about 15 mL of 3.5 N $NH_4OH$, and chilled to give 0.84 g of crude product. Recrystallization from 33% aqueous HOAc afforded 0.7 g (19.5%) of the desired product, mp 303-305 °C dec.

**$N^6$-(9-Anthracenylmethyl)-$N^6$-methyl-2,4,6-pteridinetriamine 0.7-Hydrate (13, Table I).** A mixture of 2.5 g (0.0127 mol) of 6-chloro-2,4-pteridinediamine and 9.6 g (0.0434 mol) of *N*-methyl-9-anthracenemethanamine was stirred at 170 °C for 8 h, allowed to cool, and triturated first with ether, then with MeOH, and finally with warm 0.5 N HCl. The resulting dark solid was extracted 3 times with 150-mL portions of boiling EtOH. The extracts were combined, concentrated to 200 mL, and cooled to afford 1.36 g of precipitate. This material was triturated with warm DMF and then recrystallized from DMF containing a few drops of concentrated $NH_4OH$ to give 0.25 g (5%) of the title compound, mp 277-281 °C dec.

**6-(1-Piperidinyl)-2,4-pteridinediamine Hydrochloride 1.8-Hydrate (20, Table I).** A mixture of 0.4 g (0.002 mol) of 6-chloro-2,4-pteridinediamine and 6 mL (7 g, 0.082 mol) of piperidine was heated under relux for 21 h, cooled, and diluted with about 30 mL of ether. The precipitate that formed was washed with water and recrystallized from 1 N HCl to give 0.45 g (71.4%) of the product, mp >300 °C.

**4-Methoxy-*N*-methyl-1-naphthalenemethanamine (29, Table II).** A mixture of 50.53 g (0.272 mol) of 4-methoxy-1-naphthaldehyde and 28 mL (0.36 mol) of 40% aqueous methanamine in 500 mL of MeOH was hydrogenated at room temperature over 2 g of 5% platinum on carbon for 0.7 h at an initial pressure of 50.5 psi. The decrease in pressure was 22 psi (100% of theoretical). The mixture was filtered and the solvent removed in vacuo from the filtrate. The resulting oil was distilled to give 31.15 g (57%) of the product, bp 131-136 °C (0.6 mm). Compounds **21**, **22**, **24-28**, and **30** were prepared similarly.

**4-Fluoro-*N*-methylbenzenemethanamine[18] (23).** A mixture of 289 g (2 M) of 1-(chloromethyl)-4-fluorobenzene and 290 g (9.6 M) of methanamine in 400 mL of THF was placed in a sealed vessel at room temperature and under 30 psi. The temperature and pressure of the mixture rapidly increased to 88 °C and 135 psi. After 2 h, the mixture was diluted with MeOH and filtered to collect 77 g of solid. The filtrate was diluted with ether, again filtered to collect 100 g of solid, and then concentrated to dryness. The residue was combined with the solids and dissolved in water. The solution was made basic with NaOH and extracted with ether. The extract was dried over magnesium sulfate, filtered, concentrated under vacuum, and distilled to afford 185 g (66.5%), bp 73-75 °C (9 mm). A 10-g sample was converted to its HCl salt and recrystallized from 2-propanol-MeOH/ether (charcoal) to afford 10 g, mp 193-195 °C.

**2-(4-Chlorophenyl)pyrrolidine.[10]** To a stirring mixture of 24.3 g (1.0 mol) of magnesium turnings and a crystal of iodine in 75 mL of anhydrous ether was added dropwise a solution of 191.5 g (1.0 mol) of 1-bromo-4-chlorobenzene in 1 L of ether. After the addition was complete, the mixture was stirred for 0.5 h. A solution of 103.6 g (1.0 mol) of 4-chlorobutanenitrile in 100 mL of ether was added dropwise to the 4-chlorophenylmagnesium bromide, and the mixture was stirred under reflux for 1 h. Then, the reflux condenser was reversed and the ether allowed to distill off, keeping the volume constant by addition of xylene. When the temperature of the mixture reached 135 °C, the mixture was heated under reflux for 2 h and allowed to cool overnight. To the stirred mixture was added dropwise 130 mL of saturated $NH_4Cl$ solution. The mixture was filtered and the filter cake was washed with xylene and water. The filtrate and washes were combined and the layers separated. The water layer was extracted with xylene. The xylene fractions were combined, washed with water, dried over anhydrous $K_2CO_3$ in the presence of decolorizing charcoal, filtered through supercell, and evaporated to dryness under vacuum. The residue was recrystallized from petroleum ether to give 72.6 g (40.5%) of 5-(4-chlorophenyl)-3,4-dihydro-2*H*-pyrrole, mp 64-66 °C.

A mixture of 72.5 g (0.403 mol) of 5-(4-chlorophenyl)-3,4-dihydro-2*H*-pyrrole and 2 g of 5% platinum on carbon in 350 mL of toluene was hydrogenated under an initial pressure of 50.5 psi and an average temperature of 28 °C for 21.8 h. An additional gram of 5% platinum on carbon was added and hydrogenation was continued for 23.1 h. The total decrease in pressure was 29.0 psi, 90% of theoretical. The reaction mixture was filtered and the solvent was removed under vacuum. The residual oil was distilled to yield 66.7 g, bp 130 °C (7 mm). VPC demonstrated a 15% contamination with starting material. The hydrogenation was repeated using 59.1 g of this mixture. After filtration and removal of the toluene, distillation gave two fractions: 16.2 g (25% yield), bp 144-151 °C (14 mm) 91% by VPC), and 26.7 g (41% yield), bp 150-151 °C (14 mm) (97% by VPC).

**Acknowledgment.** The authors are indebted to Dr. M. W. Fisher and Dr. C. L. Heifitz of Warner-Lambert Co. for the antibacterial studies. We also thank William Pearlman for conducting the hydrogenations, C. E. Childs and associates for the microanalyses, Dr. J. M. Vandenbelt and co-workers for the determination of spectral data, and Ms. Jeanne Hoftiezer and Ms. Georgianna Hill for preparing many of the intermediates.

# Synthesis and Antidepressant Activity of Substituted (ω-Aminoalkoxy)benzene Derivatives

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A series of substituted (ω-aminoalkoxy)benzene derivatives has been synthesized and screened for potential antidepressant activities. The effect of structural variation of these molecules has been systematically examined. Antidepressant activity was clearly displayed by 2-benzyl-1-[4-(methylamino)butoxy]benzene (**7**), 2-(2-hydroxybenzyl)-1-[4-(methylamino)butoxy]benzene (**19**), 1-[4-(methylamino)butoxy]-2-phenoxybenzene (**29**), and 1-[4-(methylamino)butoxy]-2-(phenylthio)benzene (**31**) in further pharmacological studies. These compounds did not possess the anticholinergic, antihistaminic, and muscle-relaxant side effects common to tricyclic antidepressants.

In spite of their clinical usefulness, the tricyclic antidepressants, such as amitriptyline and imipramine, cause varying degrees of side effects mainly originating from anticholinergic actions.[1-3] Routine pharmacological screening in our laboratories of compounds, directed toward new psychotropic agents, has shown that some 1-(4-aminobutoxy)-2-phenylbenzene derivatives antagonize the reserpine-induced hypothermia in mice. These observations prompted us to synthesize a wide variety of related compounds to find a new type of antidepressant

(1) B. Blackwell, J. O. Lipkin, J. H. Meyer, R. Kuzma, and W. V. Boulter, *Psychopharmacologia*, **25**, 205 (1972).
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(3) F. Von Hoffmeister, *Arzneim.-Forsch.*, **19**, 458 (1969).

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