azopyrimidine in 500 ml of $POCl_3$ was refluxed for 4 hr with stirring. The solvent was removed under vacuum and the residue was extracted with Et_2O. Evaporation of the Et_2O under vacuum gave a residue which was triturated with an ice–water mixture. Filtration gave 21.5 g (65%) of a solid, mp 110–112°, R_f 0.49 (system 4). A small sample recrystallized from hexane had mp 114–115°. *Anal.* ($C_{16}H_{10}Cl_2N_4$) H, N; C: calcd, 58.38; found, 59.03.

4-Amino-2-chloro-6-phenyl-5-phenylazopyrimidine (XIV).—A stream of anhydrous NH_3 was passed into a solution of 10.8 g (0.033 mole) of 2,4-dichloro-6-phenyl-5-phenylazopyrimidine in 500 ml of ether for 1 hr at 0–5°, and the solution was stirred at 0–5° for 1 hr and at room temperature for 1 hr. The precipitate which formed was collected, washed (H_2O), and recrystallized from EtOH to give 7.4 g (72%) of product, mp 239–241°, R_f 0.50 (system 5). *Anal.* ($C_{16}H_{12}ClN_5$) C, H, N.

4,5-Diamino-2-chloro-6-phenylpyrimidine (XV).—A solution of 14.0 g (0.045 mole) of 4-amino-2-chloro-6-phenyl-5-phenylazopyrimidine in 200 ml of DMF containing suspended Raney nickel catalyst was shaken in an H_2 atmosphere at 3.5 kg/cm² pressure until the theoretical quantity of H_2 was taken up (about 1 hr). The catalyst was removed by filtration and the solvent was removed under vacuum. Trituration of the residue with Et_2O gave 8.2 g (88%) of product, mp 193–198°. A sample recrystallized from EtOH–H_2O had mp 205–207°, R_f 0.65 (system 6), 0.82 (system 7). *Anal.* ($C_{10}H_9ClN_4$) C, H, N.

2-Chloro-6,7-dihydroxy-4-phenylpteridine (XVI).—A mixture of 56 g (0.26 mole) of 4,5-diamino-2-chloro-6-phenylpyrimidine and 100 g (0.84 mole) of methyl oxalate in 1 l. of H_2O was refluxed for 20 hr with stirring. Cooling and filtration gave 23.7 g (33%) of product, mp >300°. In other experiments similar to the above, refluxing for 2.5 hr gave a 14.5% yield, for 6 hr a 25% yield, and for 20 hr a 37% yield. A reaction using the same pyrimidine and diethyl oxalate in ethoxyethanol for a 48-hr reflux period gave a 31% yield of the same product. The product was recrystallized by dissolving in dilute NH_4OH and reprecipitating by addition of AcOH to pH 4. This gave a cream-colored solid, mp >300°, R_f 0.80 (system 3). *Anal.* ($C_{12}H_7ClN_4O_2$) C, H, N.

N,N′-(4-Amino-2-chloro-6-phenyl-5-pyrimidinyl)oxamide.—To a stirred solution of 1.1 g (0.005 mole) of 4,5-diamino-2-chloro-6-phenylpyrimidine in 60 ml of $CHCl_3$ was added slowly a solution of 1.26 g (0.01 mole) of oxalyl chloride in 5 ml of $CHCl_3$. Material separated out immediately. The reaction mixture was refluxed with stirring for 2 hr and cooled, and the precipitate was collected. This was washed well with ether and then recrystallized from a DMF–H_2O mixture to give a product, mp >300°, whose ir spectrum differed from 2-chloro-6,7-dihydroxy-4-phenylpteridine; R_f 0.68 (system 8). *Anal.* ($C_{22}H_{16}Cl_2N_8O_2$) C, H; N: 22.63; found, 21.92.

4,6,7-Trichloro-4-phenylpteridine (XVIII).—A mixture of 10.2 g (0.036 mole) of 2-chloro-6,7-dihydroxy-4-phenylpteridine, 39 g (0.19 mole) of PCl_5, and 120 ml of $POCl_3$ was refluxed with stirring for 4 hr. The volatiles were then removed under vacuum and the residue was extracted with four 250-ml portions of Et_2O. The combined extracts were washed quickly with ice water and dried ($MgSO_4$). Evaporation of the Et_2O gave a solid, mp 143–146°. Sublimation of this at 155–160° under vacuum gave 2.2 g (19.5%) of bright yellow crystals, mp 154–156°. *Anal.* ($C_{12}H_5Cl_3N_4$) C, H, N.

In another experiment starting with 3.4 g (0.012 mole) of dihydroxypteridine, the dried etheral extracts were concentrated to small volume on a steam bath (10 ml) and filtration gave 1.4 g (37%) of crystals, mp 153–155°.

2,6,7-Triamino-4-phenylpteridine (IX).—A mixture of 3.3 g (0.011 mole) of 2,6,7-trichloro-4-phenylpteridine and 100 ml of anhydrous NH_3 was allowed to stand in an autoclave at room temperature for several days and then heated at 140° for 6 hr. After evaporation of the NH_3 the residue was taken up in EtOH and allowed to stand at −10° for 3 weeks. Filtration gave a solid which was recrystallized twice from about 200 ml of 60% EtOH–H_2O to give 1.2 g (42%) of product: mp >300°; R_f 0.63, 0.64, 0.70 (system 3). A sample recrystallized from H_2O had mp 298–304° dec; $\lambda_{max}^{1\ N\ NaOH}$ 252 mμ (log ε 4.24), 374 (4.22); $\lambda_{max}^{4.5\%\ HCOOH}$ 263 mμ (log ε 4.36), 400 (4.30); *Anal.* ($C_{12}H_{11}N_7 \cdot 0.25H_2O$) C, H, N.

Acknowledgment.—We wish to thank Mr. Arnold Litt and Mrs. Joyce Carevic for experimental assistance and Dr. J. W. Wilson for his interest and encouragement during the course of this work.

Pteridines. X.[1] Some Pyrimidopyrimidine Isomers of Triamterene

HAROLD GRABOYES, GERALD E. JAFFE, IRWIN J. PACHTER, JOANNE P. ROSENBLOOM, ANTHONY J. VILLANI, JAMES W. WILSON, AND JOSEPH WEINSTOCK[2]

Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101

Received January 6, 1968

2,4,7-Triamino-5-phenylpyrimido[4,5-*d*]pyrimidine was prepared by the condensation of guanidine with 2,6-diamino-5-cyano-4-phenylpyrimidine. Similar reactions gave 5-alkyl analogs of this compound. An attempt to use 4-amino-5-cyano-2,6-dimethylpyrimidine in this reaction gave 2,4,7-triamino-5-methylpyrimido[4,5-*d*]-pyrimidine in contrast to the diphenyl analog which gave the expected product. 2,4,5-Triamino-7-phenylpyrimido[4,5-*d*]pyrimidine was prepared by the fusion of guanidine carbonate with 4-amino-5-cyano-6-methylmercapto-2-phenylpyrimidine. 2,4,8-Triamino-6-phenylpyrimido[5,4-*d*]pyrimidine was prepared by condensation of methyl 2,4,5-triaminopyrimidine-6-carboxylate with benzamidine to form 2,4-diamino-8-hydroxy-6-phenylpyrimido[5,4-*d*]pyrimidine followed by deoxychlorination and amination.

Several of the pteridine isomers of triamterene (2,4,7-triamine-6-phenylpteridine) are interesting diuretic agents.[3] This suggested that other similarly substituted polyaza heterocyclic compounds might also have useful diuretic properties. Our interest was first directed to the pyrimido[4,5-*d*]pyrimidine ring system by the report[4] that certain 2,5- and 2,4,7-polyaminopyrimido[4,5-*d*]pyrimidines showed interesting diuretic activity in dogs when given orally at low doses, and we hoped that a phenyl triamino analog would have superior activity.

The previously used method[4–6] for the preparation of 4-aminopyrimido[4,5-*d*]pyrimidines is the reaction of the appropriately substituted 4-amino-5-cyanopyrimidine with the proper amidine or guanidine. This method was adapted for the synthesis of 2,4,7-triamino-

(1) Previous paper in this series: J. Weinstock and R. Y. Dunoff, *J. Med. Chem.*, **11**, 565 (1968).

(2) To whom inquiries should be addressed.

(3) J. Weinstock, J. W. Wilson, V. D. Wiebelhaus, A. R. Maass, F. T. Brennan, and G. Sosnowski, *J. Med. Chem.*, **11**, 573 (1968), paper XII of this series.

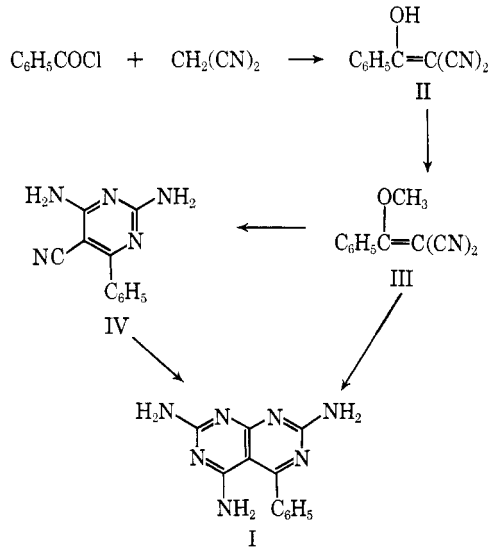
(4) E. C. Taylor, R. J. Knopf, R. F. Meyer, A. Holmes, and M. L. Hoefle, *J. Am. Chem. Soc.*, **82**, 5711 (1960).

(5) J. Druey, P. Schmidt, K. Eichenberger, and M. Wilhelm, U. S. Patent 3,055,900 (1962).

(6) (a) S. K. Chatterji and N. Anand, *J. Sci. Ind. Res.* (India), **17B**, 63 (1958); (b) *ibid.*, **18B**, 272 (1959).

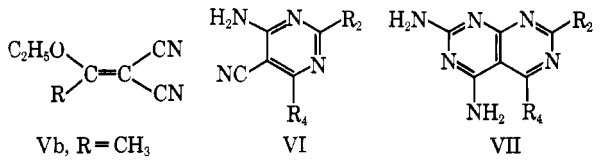
5-phenylpyrimido[4,5-*d*]pyrimidine (I) as shown in Scheme I. 2,6-Diamino-5-cyano-4-phenylpyrimidine (IV) had been prepared[7] by the reaction of benzoyl cyanide with malonitrile to give 1,1-dicyano-2-hydroxy-2-phenylethylene (enol of benzoylmalonitrile) (II) which was converted to the enol ether (III) by dimethyl sulfate and sodium bicarbonate.

SCHEME I



Reaction of III with guanidine had given IV. Since benzoyl cyanide is not readily available in quantity, an alternative synthesis of II was desired. The reaction of benzoyl chloride with malononitrile and triethylamine in tetrahydrofuran gave II in 67% yield. Condensation of III with guanidine gave IV as reported, and reaction of this with guanidine in refluxing Ethyl Cellosolve gave I. This product could also be obtained directly from III by condensation with 4 moles of guanidine and 9 moles of sodium methoxide in refluxing Ethyl Cellosolve.

Diuretic testing of I showed it to have interesting activity,[3] and this prompted the synthesis of a number of related compounds. By methods similar to those outlined above, III was condensed with formamidine to



Vb, R = CH_3
c, R = C_2H_5

VI

VII

a, R_2 = H; R_4 = C_6H_5
b, R_2 = NH_2; R_4 = CH_3
c, R_2 = NH_2; R_4 = C_2H_5
d, R_2 = R_4 = CH_3
e, R_2 = R_4 = C_6H_5

give 4-amino-5-cyano-6-phenylpyrimidine (VIa) (Table I) which on treatment with guanidine gave 2,4-diamino-5-phenylpyrimido[4,5-*d*]pyrimidine (VIIa) (Table II). 1,1-Dicyano-2-ethoxypropene (Vb) on reaction with guanidine in refluxing ethanol gave 2,4-diamino-5-cyano-6-methylpyrimidine, and in refluxing Ethyl Cellosolve gave 2,4,7-triamino-5-methylpyrimido[4,5-*d*]pyrimidine (VIIb). The preparation of 2,4-diamino-5-cyano-6-ethylpyrimidine (VIc) from 1,1-dicyano-2-ethoxy-1-butene (Vc) and its conversion to 2,4,7-triamino-5-ethylpyrimido[4,5-*d*]pyrimidine proceeded similarly.

(7) A. Dornow and E. Schleese, *Ber.*, **91**, 1830 (1958).

TABLE I

PREPARATION OF 4-AMINO-5-CYANOPYRIMIDINES (VI)[f]

Product	Reactants[a]	Yield, %	Recrystn solvent	Mp, °C	Formula[g]
VIa	FA + III	51	EtOH	193–194.5	$C_{11}H_8N_4$
VIb	GC + Vb	50	EC[b]	285–287	$C_6H_7N_5$
VIc	GC + Vc	83	EtOH	194–196	$C_7H_9N_5$
VId	AH + Vb	76	EtOH	226–228[e]	$C_7H_8N_4$
VIe	BH + III	80[d]	*c*	211–213	$C_{17}H_{12}N_4$

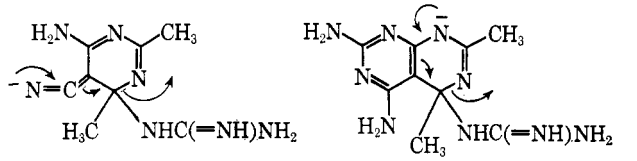
[a] FA is formamidine AcOH; GC, guanidine carbonate; AH, acetamidine HCl; BH, benzamidine HCl. [b] Ethyl Cellosolve. [c] Crude product washed with H_2O. [d] Reference 8a reports 26% yield, mp 211°. [e] Reference 8b reports a 58% yield of product, mp 220.5°. [f] See preparation of VIb in Experimental Section for general procedure. [g] All compounds were analyzed for C, H, N and analytical results were within ±0.4% of calculated values unless noted.

An attempt to prepare VId as previously described[8a] by the condensation of acetamidine and malononitrile gave as the only product isolated 1,1-dicyano-2-iminopropane (VIII). Its structure was suggested by elemental analysis and its reaction with guanidine to give VIIb. Apparently under the specified conditions

$$CH_3C(=NH)NH_2 + CH_2(CN)_2 \longrightarrow CH_3C(=NH)CH(CN)_2 \longrightarrow \text{VIIb}$$
$$\text{VIII}$$

only the first step of the required sequence to give VId could be accomplished. The condensation of Vb with acetamidine gave the pyrimidine VId in an unambiguous manner.[8b] It was hydrolyzed by concentrated sulfuric acid to 4-amino-2,6-dimethylpyrimidine-5-carboxamide (Table III).

Attempts to condense VId with guanidine to form VIId failed, with the only product isolated (in 14% yield) from the reaction being VIIb. This could be rationalized by assuming that either VId or VIId reacted with guanidine in a ring-opening reaction and eliminated acetamidine. The first intermediates in these reactions would be IX and X which should be



IX X

stable anions.[9] In contrast to this, 4-amino-5-cyano-2,6-diphenylpyrimidine (VIe) reacted with guanidine to give the expected 2,4-diamino-5,7-diphenylpyrimido-[4,5-*d*]pyrimidine (VIIe). The pyrimidine VIe was obtained in 26% yield by condensation of benzamidine and malononitrile,[8] and in 80% yield by reaction of III with benzamidine in refluxing ethanol.

(8) (a) G. W. Kenner, B. Lythgoe, A. R. Todd, and A. Topham, *J. Chem. Soc.*, 388 (1943); (b) W. Huber and H. A. Hölscher, *Ber.*, **71**, 87 (1938).

(9) Similar ring opening reactions have been postulated in the aminolysis of pteridines: E. C. Taylor and C. K. Cain, *J. Am. Chem. Soc.*, **73**, 4384 (1951); E. C. Taylor, *ibid.*, **74**, 1651 (1952). For some arguments disputing ring-opened intermediates see M. D. Potter and T. Henshall, *J. Chem. Soc.* 2000 (1956).

TABLE II

PREPARATION OF 2,4-DIAMINOPYRIMIDO[4,5-*d*]PYRIMIDINES

Product	Reactants[a]	Recrystn solvent	Yield, %	Mp, °C	R_f (system)	Solvent	Ultraviolet spectral data, λ_{max}, mμ (log ε)	Formula[f]
I·H_3PO_4·0.5H_2O	GC + III	H_2O	59	>300[b]	0.53 (1)	1 *N* HCl	226 (4.53), 249 (4.47), 318 (4.10)	$C_{12}H_{11}O_7$·H_3PO_4·0.5H_2O
						1 *N* NaOH	235 (4.70), 322 (4.09)	
I	GC + IV		37[c]	>300				
VIIa	GC + Vb	*d*	64	>300		1 *N* HCl	251 (4.30), 276 (4.11)	$C_{12}H_{10}N_6$[j]
						1 *N* NaOH	251 (4.42), 320 (3.79)	
VIIb·HCl·0.5H_2O	GC + Vb	*e*	39	>300	0.37 (1)	1 *N* HCl	226 (4.60), 234 (sh) (4.57), 300 (4.07)	$C_7H_9N_7$·HCl·0.5H_2O
VIIb·HCl	GC + VId		14		0.33 (1)	1 *N* NaOH	233 (4.73), 310 (4.21)	
VIIb	GC + VIII		42		0.30 (1)			
VIIc	GC + VIc	*f*	17	>300		1 *N* HCl	226 (4.71), 238 (sh) (4.57), 305 (4.21)	$C_8H_{11}N_7$[k]
						1 *N* NaOH	233 (4.83), 312 (4.31)	
VIIe	GC + VIe	*g*	37	>300	0.85 (1)	1 *N* HCl[h]	234, 258, 314	$C_{18}H_{14}N_6$
						1 *N* NaOH[h]	258, 334	

[a] GC is guanidine carbonate. [b] Sulfate and free base melt >300°. Satisfactory elemental analyses obtained in each case. [c] 48-hr reaction time; 20-hr reaction gave 23% of I and 75 hr gave 80%. [d] Dissolve in dilute HCl and liberate with dilute NH_4OH. [e] Concentrated HCl. [f] Dissolve in 15% AcOH and precipitate with NH_4OH. [g] Dissolve in 50% AcOH and precipitate with concentrated NH_4OH. [h] Spectra qualitative due to insolubility of compound. [i] See footnote *g*, Table I. [j] C: calcd, 60.49; found, 59.99. [k] N: calcd, 47.78; found, 47.23

TABLE III

4-AMINOPYRIMIDINE-5-CARBOXAMIDES BY HYDROLYSIS OF 4-AMINO-5-CYANOPYRIMIDINES[a]

R_2	R_4	Yield, %	Recrystn solvent	Mp, °C	Formula[c]
NH_2	NH_2	96	EC[b]	211–213	$C_5H_8N_6O$
CH_3	CH_3	83	EC	212–214	$C_7H_{11}N_4O$
H	C_6H_5	85	EC–H_2O	256–257	$C_{11}H_{10}N_4O$
C_6H_5	NH_2	71	EtOH	240–241	$C_{11}H_{11}N_5O$

[a] See preparation of XXa in Experimental Section for general procedure. [b] Ethyl Cellosolve. [c] See footnote *g*, Table I.

The only possible pyrimido[4,5-*d*]pyrimidine isomer of I is 2,4,5-triamino-7-phenylpyrimido[4,5-*d*]pyrimidine (XI). Our first approach to this involved the condensation of 4,6-diamino-5-cyano-2-phenylpyrimidine (XII) with guanidine. The reported preparation[10] of XII involved the condensation of benzamidine with 1-amino-1-chloro-2,2-dicyanoethylene. Our attempts to repeat this procedure failed and subsequently[11] it was reported that the product of this reaction is actually benzamidinium tricyanomethanide (XIII), and that sublimation of this at 155° (1 mm) for 28 hr gave XII in 21% yield. We found that XII could be prepared more conveniently in about the same yield by heating XIII slowly to 215° in DMF. However, reaction of XII with guanidine under the usual conditions did not give the desired XI in an acceptable yield. The low reactivity of this pyrimidine was also demonstrated by lack of satisfactory reactions by fusion with guanidine carbonate, urea, or thiourea. In addition, hydrolysis of XII with nitrous acid in 2 *N* HCl at reflux for 23 hr gave only 6-amino-5-cyano-4-hydroxy-2-phenylpyrimidine (XIV) (Scheme II). However, XII was converted

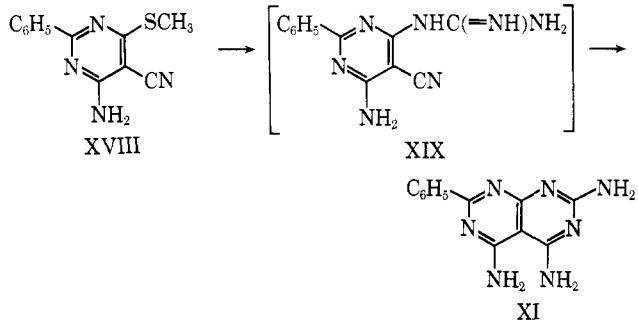
SCHEME II

(10) W. J. Middleton and V. A. Engelhardt, *J. Am. Chem. Soc.*, **80**, 2829 (1958).

(11) S. Trofimenko, E. L. Little, Jr., and H. F. Mower, *J. Org. Chem.*, **27**, 433 (1962).

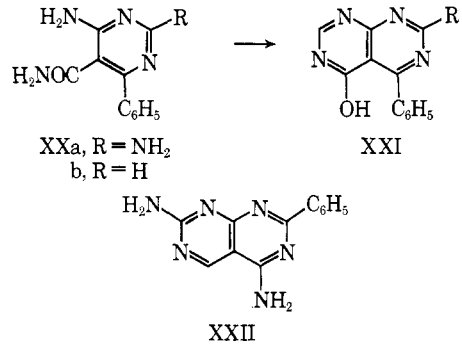
to the corresponding amide XV in good yield by hydrolysis in concentrated sulfuric acid. Fusion of XV with thiourea quite unexpectedly gave 4,6-diamino-2-phenylpyrimidine (XVI).[12] Fusion of XV with urea gave 4-amino-5,7-dihydroxy-2-phenylpyrimido[4,5-*d*]pyrimidine (XVII), but attempts to convert this to the corresponding 5,7-dichloro analog by treatment with PCl_5 in $POCl_3$ in our hands gave a product which could not be purified for analysis.

One rationalization of the inertness of XII is that the flanking amino groups sterically hinder the nitrile. This suggested that the cyclizing moiety be attached first to the pyrimidine ring, and then the proximity would facilitate cyclization. A suitable intermediate for such an approach was 4-amino-5-cyano-6-methylmercapto-2-phenylpyrimidine (XVIII). Repetition of the reported[10] synthesis gave a product, mp 180–182°, rather than the reported mp 163–165°. In addition, an incorrect empirical formula and analytical data had been presented for this compound. The product obtained by repetition of the reported procedure gave correct analytical data for XVIII. Fusion of XVIII with guanidine carbonate at 200° gave XI directly without isolation of an intermediate such as XIX.



XVIII XIX XI

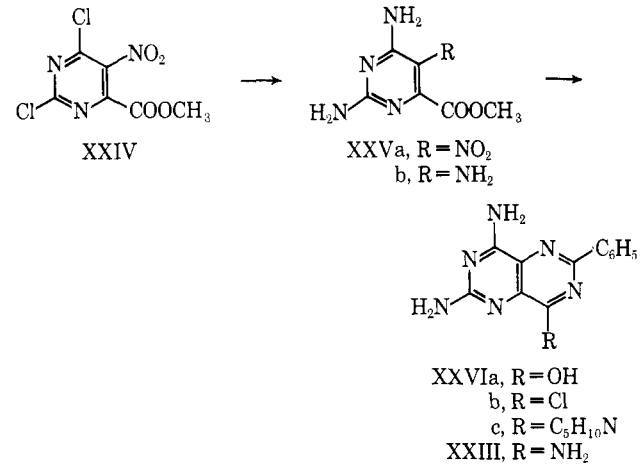
In order to prepare some less highly substituted pyrimido[4,5-*d*]pyrimidines, I was hydrolyzed to give 2,4-diamino-6-phenylpyrimidine-5-carboxamide (XXa) which on reflux in formamide gave 2-amino-5-hydroxy-4-phenylpyrimido[4,5-*d*]pyrimidine (XXIa). A similar sequence starting from VIa gave XXb and XXIb. Finally, treatment of 2,4-diamino-5-cyanopyrimidine[6a] with benzamidine under the usual conditions gave 4,7-diamino-2-phenylpyrimido[4,5-*d*]pyrimidine (XXII).



XXa, R = NH_2; b, R = H XXI XXII

Another pyrimidopyrimidine isomer of triamterene is 2-phenyl-4,6,8-triaminopyrimido[5,4-*d*]pyrimidine (XXIII). It was prepared by the procedure outlined in Scheme III. Treatment of methyl 2,6-dichloro-5-nitropyrimidine-4-carboxylate (XXIV)[13] with NH_4OH on a steam bath gave methyl 2,6-diamino-5-nitropyrimidine-4-carboxylate (XXVa). Hydrogenation of XXVa gave methyl 2,5,6-triaminopyrimidine-4-carboxylate (XXVb) which on heating with benzamidine at 100° furnished 2-phenyl-4-hydroxy-6,8-diaminopyrimido[5,4-*d*]pyrimidine (XXVIa). Refluxing XXVIa with PCl_5 in $POCl_3$ produced 6,8-diamino-4-chloro-2-phenylpyrimido[5,4-*d*]pyrimidine (XXVIb) which was used without purification. Reflux of XXVIb in piperidine gave XXVIc, and reaction of XXVIb with liquid ammonia at 150° gave 4,6,8-triamino-2-phenylpyrimido[5,4-*d*]pyrimidine (XXIII) which is the desired analog of triamterene.

SCHEME III



XXIV XXVa, R = NO_2; b, R = NH_2 XXVIa, R = OH; b, R = Cl; c, R = $C_5H_{10}N$; XXIII, R = NH_2

An attempt was made to prepare XXIII *via* 2,4,8-trihydroxy-6-phenylpyrimido[5,4-*d*]pyrimidine, but the synthesis of this from pyrimidine precursors was unsuccessful. Also, an attempt was made to prepare 2,4,5-triamino-6-cyanopyrimidine in order to condense it with benzamidine to obtain XXIII directly, but this was also not successful. The synthesis of the pyrimidines involved in these alternate approaches is included in the Experimental Section.

Pharmacology.—The diuretic structure–activity relationships of the compounds described in this paper will be reported in an accompanying paper.[3]

Experimental Section[14]

Benzoylmalononitrile.—A solution of 1.98 kg (30.0 mole) of malononitrile, 6.06 kg (60 mole) of Et_3N, and 36 l. of THF was cooled to 5° in a jacketed 80-l. reactor and a solution of 4.23 kg (30 moles) of benzoyl chloride in 3 l. of THF was added maintaining the temperature below 35°. After complete addition, the precipitated $Et_3N \cdot HCl$ was removed by filtration and the filtrate was poured into 50 kg of an ice–water mixture. The resulting solution was treated with a solution of 2 l. of concentrated H_2SO_4 in 10 l. of H_2O. An oil layer separated which was drawn off. The aqueous solution was extracted twice with 5 l. of ether and the combined organic phase was washed (H_2O) and dried (Mg-

(12) We wish to thank Dr. E. C. Taylor of Princeton University for carrying out a comparison with an authentic sample.

(13) J. Clark and G. R. Ramage, *J. Chem. Soc.*, 2821 (1958).

(14) We wish to thank Miss Margaret Carroll and her staff for microanalytical data, Dr. Walter Thompson and Mr. Richard J. Warren for spectral data, and Mr. Alex Post and Mr. E. L. Haines for chromatographic data. Melting points are uncorrected and were determined in open capillary tubes. Ir spectra were determined on a Perkin-Elmer Infracord and uv spectra on a Cary Model 14 spectrophotometer. Paper chromatography (circular) was carried out on 3 MM Whatman paper. The systems used were (1) HCOOH–H_2O–BuOH (1:5:5); (2) EtOH–H_2O (2:1) on castor oil–mineral oil (1:1) pretreated paper. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

SO_4). Evaporation of the solvent left 4.35 kg of a solid which on recrystallization from $CHCl_3$–MeCN with concentration gave 3.37 kg (67%) of crystals, mp 124–126°, lit.[7] mp 129–130°. The ir spectra of the products prepared as described above and from benzoyl cyanide[7] were identical. A somewhat similar procedure has been reported since the completion of our work.[15]

2,4-Diamino-5-cyano-6-methylpyrimidine (VIb).—To a solution of NaOMe (11.9 g, 0.22 mole) in EtOH (150 ml) were added guanidine carbonate (18 g, 0.1 mole) and 1,1-dicyano-2-ethoxy-2-methylethylene[16] (13.6 g, 0.1 mole). The resulting mixture was refluxed with stirring for 3 hr and cooled and the resulting solid was removed by filtration. This material was washed (H_2O) and 7.6 g (51%) of yellow compound, mp 285–287°, was obtained which was recrystallized from Ethyl Cellosolve to give yellow crystals, mp 285–287°.

4,6-Diamino-5-cyano-2-phenylpyrimidine.—A mixture of 200 g (0.95 mole) of the benzamidinium salt of tricyanomethane[11] and 100 ml of DMF was heated slowly to 215° and then slowly allowed to cool to room temperature. The resulting dark red solution was diluted with 1.4 l. of H_2O and 0.6 l. of 10% HCl. The solution was brought to reflux, treated with activated carbon, and filtered. The pH of the filtrate was brought to 8 by the addition of 40% NaOH while cooling to hold the solution below 25°. The resulting solid was collected by filtration and recrystallized again in a similar manner from dilute HCl. This gave 54 g (23.5%) of a colorless solid, mp 233–235°. Recrystallization of a small sample from a large volume of PhMe gave a colorless solid, mp 238–240°, lit.[11] mp 238–240. *Anal.* ($C_{11}H_9N_5$) C, H, N.

1,1-Dicyano-2-iminopropane.—Acetamidine hydrochloride (47.5 g, 0.5 mole) was added to a solution of NaOMe (27 g, 0.5 mole) in 300 ml of EtOH and the mixture was treated with 33 g (0.5 mole) of malononitrile and refluxed for 3 hr and chilled. The solid product was isolated by filtration and washed (H_2O) to give 31 g (58%) of tan crystals, mp 210–214°. A recrystallization from 500 ml of EtOH which included treatment of the solution with charcoal gave 24 g of white crystals, mp 213–216°. *Anal.* ($C_5H_5N_3$) C, H, N.

4-Amino-5-cyano-6-methylthio-2-phenylpyrimidine.—To a solution of benzamidine hydrochloride (9.3 g, 0.06 mole) and NaOH (2.0 g, 0.05 mole) in H_2O (25 ml) was added 1,1-dimethylmercapto-2,2-dicyanoethylene[17] (8.5 g, 0.05 mole). The reaction mixture was heated on a steam bath for 0.5 hr during which time solution followed by separation of a new solid occurred. The mixture was diluted with H_2O (25 ml) and cooled, and the solid was removed by filtration. The crude product was recrystallized from EtOH giving 3.8 g (30%) of white needles, mp 180–182°, R_f 0.51 (system 2). *Anal.* ($C_{12}H_{10}N_4S$) C, H, N.

2,4-Diamino-6-phenylpyrimidine-5-carboxamide (XXa).—To concentrated H_2SO_4 (100 ml) was added in small portions 2,4-diamino-5-cyano-6-phenylpyrimidine[7] (21.1 g, 0.1 mole) keeping the temperature below 30°; cooling was required. The mixture was warmed on a steam bath for 1.5 hr while gradual solution occurred. The solution was cooled and poured over ice (500 g) causing the separation of the sulfate salt. Basification (NH_4OH) of the solid and mother liquor separately gave 22.1 g (96%) of the free base. After recrystallization from Ethyl Cellosolve the material melted 211–213°. *Anal.* ($C_{11}H_{11}N_5O$) C, H, N.

4-Amino-5-cyano-6-hydroxy-2-phenylpyrimidine.—To a solution of $NaNO_2$ (7 g, 0.1 mole) in concentrated HCl (22 ml) and H_2O (100 ml) was added 2-phenyl-4,6-diamino-5-cyanopyrimidine (4.22 g, 0.22 mole). The yellow suspension was refluxed for 23 hr and cooled and the solid was collected. The material was reprecipitated three times from NaOH–AcOH to give yellow needles, 1.2 g (17%), mp >300°. *Anal.* ($C_{11}H_8N_4O$) C, H, N.

2,4,7-Triamino-5-phenylpyrimido[4,5-*d*]pyrimidine Phosphate. (I).—A mixture of $NaOCH_3$ (970 g, 18.0 mole), Ethyl Cellosolve (8 l.), guanidine carbonate (1.47 kg, 8.16 mole), and 1-phenyl-1-methoxy-2,2-dicyanoethylene (383 g, 2.04 mole) was refluxed with stirring for 3 days. The hot suspension was filtered and the insoluble product was washed with Cellosolve and then with four 3-l. portions of hot H_2O. The solid was suspended in 8 l. of H_2O and heated to reflux, and 85% H_3PO_4 (1.2 l.) was added dropwise. The hot solution was filtered and cooled. The salt was collected and recrystallized from H_2O (9 l.) to give 411 g (59%) of product, mp >300°.

(15) J. Fleury and B. Libis, *Bull. Soc. Chim. France*, 413 (1964).
(16) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **21**, 1240 (1956).
(17) R. Gompper, E. Kutter, and W. Töpfl, *Ann.*, **659**, 90 (1962).

2,5-Diamino-7-phenylpyrimido[4,5-*d*]pyrimidine.—To a solution of $NaOCH_3$ (6 g, 0.11 mole) in Ethyl Cellosolve (400 ml) were added benzamidine hydrochloride (15.6 g, 0.1 mole) and 2,4-diamino-5-cyanopyrimidine (13.5 g, 0.1 mole). The reaction mixture was heated under reflux for 20 hr. The solution was charcoaled, filtered, and concentrated under vacuum to a brown syrup. Water was added (100 ml) causing separation of a gummy solid which gradually crystallized. The crude product was removed by filtration, suspended in refluxing EtOH, collected, and recrystallized from Ethyl Cellosolve to give 1 g (4.2%) of white granules: mp >300°; R_f 0.65 (system 1); $\lambda_{max}^{1\ N\ HCl}$ 252 mμ (log ε 4.61), 298 (4.49); $\lambda_{max}^{1\ N\ NaOH}$ 248 mμ (log ε 4.68), 326 (4.16). *Anal.* ($C_{12}H_{10}N$) C, H, N.

2-Amino-5-hydroxy-4-phenylpyrimido[4,5-*d*]pyrimidine.—A mixture of 2,4-diamino-6-phenylpyrimidine-5-carboxamide (7.5 g, 0.033 mole) and formamide (30 ml) was refluxed 0.5 hr during which time solution followed by separation of a new compound occurred. The mixture was cooled and filtered to give 4.7 g (56%) of product. The material was recrystallized from dilute AcOH to give crystals, mp >300°, R_f 0.71 (system 1). *Anal.* ($C_{12}H_9N_5O$) C, H, N.

4-Hydroxy-5-phenylpyrimido[4,5-*d*]pyrimidine.—Repeating the procedure outlined for 2-amino-5-hydroxy-4-phenyl-pyrimido-[4,5-*d*]pyrimidine using 4-amino-6-phenylpyrimidine-5-carboxamide and formamide under reflux for several hours and recrystallizing the crude material from DMF gave 8 g (56%) of white needles: mp >300°; R_f 0.76 (system 1); $\lambda_{max}^{4.5\%\ HCOOH}$ 262 mμ (log ε 4.06), 284 (3.99); $\lambda_{max}^{1\ N\ NaOH}$ 268 mμ (sh) (log ε 4.01), 312 (3.90). *Anal.* ($C_{12}H_8N_4O$) C, H, N.

4-Amino-5,7-dihydroxy-2-phenylpyrimido[4,5-*d*]pyrimidine.—4,6-Diamino-2-phenylpyrimidine-5-carboxamide (21 g, 0.0915 mole) and urea (55 g, 0.915 mole) were mixed and then heated at 180–190° for 2.5 hr. After cooling, the solid mass was dissolved in 5% NaOH solution, charcoaled, and reprecipitated by acidification with AcOH. The collected material was recrystallized from DMF–H_2O to give 16 g (68%) of product, mp >320°. *Anal.* ($C_{12}H_9N_5O_2$) C, H, N.

2,4,5-Triamino-7-phenylpyrimido[4,5-*d*]pyrimidine Diphosphate.—A mixture of 4-amino-5-cyano-6-methylthio-2-phenylpyrimidine (7.2 g, 0.03 mole) and guanidine carbonate (27 g, 0.15 mole) were heated in an oil bath at an internal temperature of 200° for 1 hr during which time some melting and resolidification occurred. The mixture was diluted (H_2O, 100 ml), heated on a steam bath 15 min, and filtered. The insoluble material was recrystallized from dilute H_3PO_4 to yield 3.5 g (25%) of yellow material: mp >300°; R_f 0.68 (system 1); $\lambda_{max}^{4.5\%\ HCOOH}$ 257 mμ (log ε 4.39), 300 (4.21); $\lambda_{max}^{1\ N\ NaOH}$ 241 mμ (log ε 4.66), 258 (sh) (4.37), 294 (sh) (3.93). *Anal.* ($C_{12}H_{11}N \cdot 2H_3PO_4$) C, H, N, P.

Methyl 2,6-Diamino-5-nitropyrimidine-4-carboxylate.—Methyl 2,6-dichloro-5-nitropyrimidine-4-carboxylate (110 g, 0.435 mole) was added to a cold solution of 27% NH_4OH. The mixture was stirred for 1 hr causing solution, followed by separation of a new material. The suspension was heated on a steam bath 10 min with stirring and then cooled. The solid was collected, washed (H_2O, EtOH), and dried to give 81 g (84%) of product, mp >300°. A portion was recrystallized (MeOH). *Anal.* ($C_6H_7N_5O_4$) C, H, N.

Methyl 2,5,6-Triaminopyrimidine-4-carboxylate.—Methyl 2,6-diamino-5-nitropyrimidine-4-carboxylate (1.0 g) with $CaCO_3$ (0.2 g) and Raney nickel in MeOH (65 ml) was reduced under an initial pressure of H_2 at 3.5 kg/cm². The mixture was filtered, the filtrate was decolorized by charcoal and then taken to dryness under vacuum. The yellow solid was triturated with Me_2CO and then recrystallized from MeOH to give 0.6 g of compound, mp 217° dec. *Anal.* ($C_6H_9N_5O_2$) C, H, N.

2,4-Diamino-8-hydroxy-6-phenylpyrimido[5,4-*d*]pyrimidine.—Benzamidine (96.5 g, 0.8 mole) was mixed with methyl 2,5,6-triaminopyrimidine-4-carboxylate (30 g, 0.16 mole) and heated at 100–105° for 20 hr. The crude material was dissolved in glacial AcOH, charcoaled, filtered, and left to stand causing deposit of the acetate salt. This was suspended in hot water, treated with concentrated NH_4OH, and cooled. The solid was collected and recrystallized from DMF yielding 11.3 g (38%) of crystals: mp 272–273°; R_f 0.51 (system 1); $\lambda_{max}^{4.5\%\ HCOOH}$ 284 mμ (log ε 4.32), 325 (sh) (4.03); $\lambda_{max}^{1\ N\ NaOH}$ 238 mμ (log ε 4.49), 316 (4.27). *Anal.* ($C_{12}H_{10}N_6O$) C, H, N.

2-Phenyl-4,6,8-triaminopyrimido[5,4-*d*]pyrimidine.—2-Phenyl-4-hydroxy-6,8-diaminopyrimido[5,4-*d*]pyrimidine (2.6 g, 0.01 mole) was refluxed 16 hr in a mixture of $POCl_3$ (225 ml) and PCl_5 (13.5 g). Removal of the excess solvent *in vacuo* followed by

trituration with ice water yielded 3.4 g of **2-phenyl-4-chloro-6,8-diaminopyrimido[5,4-*d*]pyrimidine.** This (2.9 g) was treated with liquid NH_3 (25 ml) in a bomb at 150° for 6 hr. The solid residue was washed (H_2O, EtOH). It was recrystallized from DMF–MeOH yielding 0.8 g (31%) of crystals: mp 354–356° dec; R_f 0.69 (system 1); $\lambda_{max}^{4.5\%\ HCOOH}$ 248 mμ (log ε 4.44), 294 (4.27), 336 (sh) (3.85), 354 (sh) (3.72). *Anal.* ($C_{12}H_{11}N_7 \cdot 0.5H_2O$) C, H, N.

2-Phenyl-4-piperidino-6,8-diaminopyrimido[5,4-*d*]pyrimidine.—2-Phenyl-4-chloro-6,8-diaminopyrimido[5,4-*d*]pyrimidine (1.0 g) and piperidine (60 ml) were refluxed 16 hr. The mixture was filtered and the filtrate was concentrated to dryness *in vacuo*. The residue was dissolved in hot aqueous AcOH, decolorized, and filtered, and then the solution was made basic with concentrated NH_4OH. The pale yellow solid was collected (0.4 g) and recrystallized from MeOH–H_2O to give a solid, mp 215°, R_f 0.55 (system 2). *Anal.* ($C_{17}H_{19}N_7$) H; C: calcd, 63.53; found, 64.00.

Methyl 5-Amino-2,6-dihydroxypyrimidine-4-carboxylate.—Methyl 2,6-dihydroxy-5-nitropyrimidine-4-carboxylate (5.0 g, 0.027 mole) was added to a solution of 12.1 g (0.07 mole) of sodium dithionate at 10° and then stirred at room temperature for 15 min. A solid precipitated which was washed with hot MeOH (2.85 g, 66%) and recrystallized twice from DMF to give pale yellow crystals, mp 254–255° dec. *Anal.* ($C_6H_7N_3O_4$) C, H, N.

2,6-Dihydroxy-5-nitropyrimidine-4-carboxamide.—A mixture of methyl 2,6-dihydroxy-5-nitropyrimidine-4-carboxylate (35 g, 0.16 mole), MeOH (720 ml), and liquid NH_3 (72 ml) was heated at 100° for 6 hr in an autoclave. On cooling a solid was obtained which was recrystallized from 540 ml of H_2O to give 21 g (60%) of a yellow solid, mp 269–270°, which on analysis proved to be the ammonium salt of the desired product. *Anal.* ($C_5H_7N_5O_5$) C, H, N.

A portion of the above was treated with aqueous acid and recrystallized from MeOH to give crystals, mp 285° dec. *Anal.* ($C_5H_4N_4O_3$) C, H, N.

2,5,6-Triaminopyrimidine-4-carboxamide.—A suspension of 5.3 g (0.027 mole) of 2,6-diamino-5-nitropyrimidine-6-carboxamide and 300 mg of PtO_2 in 200 ml of glacial AcOH was shaken under 2.8 kg/cm² of H_2 for 2.5 hr. The catalyst was removed by filtration and the solvent was evaporated under vacuum. The residue was washed with MeOH to give 3.8 g (83%) of product which was dissolved in dilute NH_4OH and treated with charcoal, and the solution was filtered. Chilling gave 1.2 g (26%) of white needles, mp 285° dec. A sample was boiled with MeOH to give yellow needles, mp 286–288° *Anal.* ($C_5H_8N_6O$) C, H, N.

2,6-Diamino-5-nitropyrimidine-4-carboxamide.—A suspension of 18 g (0.071 mole) of methyl 2,6-dichloro-5-nitropyrimidine-4-carboxylate in 720 ml of 10% MeOH–NH_3 was heated in a steel bomb at 100° for 2 hr. The product was dissolved in excess MeOH, filtered, and taken to dryness under vacuum. The residue was washed (H_2O) and recrystallized (MeOH) to give 3.2 g (22%) of prisms, mp >285°. *Anal.* ($C_5H_6N_6O_3$) C, H, N.

4,6-Diamino-2-phenylpyrimidine.—A mixture of 3 g (0.013 mole) of 4,6-diamino-2-phenylpyrimidine-5-carboxamide and 9.9 g (0.13 mole) of thiourea was heated at 180° for 5 hr and cooled. Addition of 90 ml of 5% NaOH and warming caused the separation of a yellow-green solid, mp 180–188°. This was dissolved in hot H_2O and acidified with HCl to give a yellow solid, mp 258–260°, which is the hydrochloride of the product. This was dissolved (H_2O), treated with charcoal, and made basic with NH_4OH to give white crystals, mp 193–195°. Repeating the acid–base cycle gave 0.45 g of crystals, mp 194.5–196°, whose ir spectra were identical with that of an authentic sample; lit.[18] mp 195–196°. *Anal.* ($C_{10}H_{10}N_4$) C, H, N.

(18) G. A. Howard, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 476 (1944).

Pteridines. XII.[1] Structure–Activity Relationships of Some Pteridine Diuretics

JOSEPH WEINSTOCK,[2a] JAMES W. WILSON,[2a] VIRGIL D. WIEBELHAUS,[2b] ALFRED R. MAASS,[2b] FRANCIS T. BRENNAN,[2b] AND GENEVIEVE SOSNOWSKI[2b]

Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania

Received January 6, 1968

The diuretic activity of pteridines related to 2,4,7-triamino-6-phenylpteridine (triamterene), 2,4-diamino-6,7-dimethylpteridine (I), and 4,7-diamino-2-phenylpteridine-6-carboxamide (II) was studied in the saline-loaded and sodium-deficient rat. A limited number of related pyrimidopyrimidines were similarly studied. Some of the compounds related to triamterene and I not only cause Na^+ excretion but also conserve K^+. All of the 2-phenylpteridines we have studied which are active natriuretic agents also cause K^+ excretion. In the triamterene series, replacement of any of the amino groups by either a large amine or a nonbasic group other than hydrogen leads to reduction of diuretic activity. Replacement of the phenyl by a small, nonbasic group gives active diuretic agents, but an aromatic (or heteroaromatic) group seems desirable for highest activity. Some variation in the substitution pattern on the pteridine ring is permissible as demonstrated by the activity of the triamterene isomers. The 7-phenyl isomer is outstanding as a blocker of K^+ excretion.

The presently known diuretic pteridines[3] may be grouped into three principle classes based on structural features and electrolyte excretion pattern. In order of their discovery these are (1) the 2,4-diamino-6,7-dialkylpteridines, (2) the 2-aryl-4,7-diaminopteridine-6-carboxamides, and (3) the 2,4,7-triamino-6-arylpteridines. In this paper we will discuss the structure–activity relationships within each of these classes and compare these classes to each other. In addition we will discuss the diuretic activity of some related pyrimidopyrimidines. The prototype for the first class is 2,4-diamino-6,7-dimethylpteridine (I), for the second class, 4,7-diamino-2-phenylpteridine-6-carboxamide (II), and for the third class, 2,4,7-triamino-6-phenylpteridine (triamterene, III).

(1) Previous papers in this series: (a) I. J. Pachter and P. E. Nemeth, *J. Org. Chem.*, **28**, 1187 (1963); (b) I. J. Pachter, *ibid.*, **28**, 1191 (1963); (c) I. J. Pachter, P. E. Nemeth, and A. J. Villani, *ibid.*, **28**, 1197 (1963); (d) I. J. Pachter and P. E. Nemeth, *ibid.*, **28**, 1203 (1963); (e) J. Weinstock, R. Y. Dunoff, and J. G. Williams, *J. Med. Chem.*, **11**, 542 (1968); (f) J. Weinstock, R. Y. Dunoff, B. Sutton, B. Trost, J. Kirkpatrick, F. Farina, and A. S. Straub, *ibid.*, **11**, 549 (1968); (g) J. Weinstock, I. J. Pachter, P. E. Nemeth, and G. Jaffe, *ibid.*, **11**, 557 (1968); (h) J. Weinstock, H. Graboyes, G. Jaffe, I. J. Pachter, K. Snader, C. B. Karash, and R. Y. Dunoff, *ibid.*, **11**, 560 (1968); (i) J. Weinstock and R. Y. Dunoff, *ibid.*, **11**, 565 (1968); (j) H. Graboyes, G. E. Jaffe, I. J. Pachter, J. P. Rosenbloom, A. J. Villani, J. W. Wilson, and J. Weinstock, *ibid.*, **11**, 568 (1968); (k) J. Weinstock, R. Y. Dunoff, J. Carevic, J. G. Williams, and A. J. Villani, *ibid.*, **11**, 618 (1968).

(2) (a) Medicinal Chemistry Section. (b) Biochemistry Section.

(3) For a brief discussion of the discovery of useful diuretic activity in the pteridines see J. Weinstock and V. D. Wiebelhaus in "Pteridine Chemistry," W. Pfleiderer and E. C. Taylor, Ed., Pergamon Press, Oxford, 1964, p 37. For discussion of other biological properties of pteridines and related compounds see (a) elsewhere in the above reference; (b) "Chemistry and Biology of Pteridines," G. E. W. Wolstenholme and M. P. Cameron, Ed., Little, Brown and Co., Boston, Mass., 1954; (c) S. Kaufman, *Ann. Rev. Biochem.*, **36**, 171 (1967); (d) G. H. Hitchings and J. J. Burchall, *Advan. Enzymol.*, **27**, 417 (1965).