resistance of disulfides **1** and **13** under the circumstances reported in Table II was determined by the general procedure below, the per cent remaining being determined by glpc analysis for **1** among the reaction products. Glpc was performed much as usual (oven temp for **1**, 92°; for **13**, 122°).[17] Typical retention times for various components, given in sec for 92 or 122° (*) were: dioxane 29, 21*; 1,2,4-trichlorobenzene *ca.* 319, 116*; **1**, 86; **13**, 92*.

Disulfide **1** (1.0013 g) and 1,2,4-trichlorobenzene (0.5103 g) were dissolved in 4 ml of dioxane and 0.3-ml aliquots were sealed in each of several ampules; the same concns were used where other solvents are specified. The ampules were wrapped in Al foil for protection against light and, unless otherwise stated, were heated at 100° in **A**, **B**, **D**, and **E**; in **C**, for light-induced decompn, the samples were placed in 15 × 240 mm Pyrex tubes, which were stoppered and irradiated simultaneously at *ca.* 25° (H_2O cooling) in an Aminco constant-temp apparatus (Cat. No. 4-8600) at a radial distance of 15 cm from a Sylvania 400-W uv lamp. After the time (t) reported, 0.3–1.0 μl from an ampule or from the Pyrex tubes, was injected onto the glpc column. The per cent remaining of **1** or of **13** was calcd from the automatic peak-area output of the instrument by using the expression [(**1** or **13** at time t)/($Cl_3C_6H_3$ at time t)] (100)/[(**1** or **13** at t_0)/($Cl_3C_6H_3$ at t_0)]. The data given below are in order of compd no., per cent of **1** or **13** which remained, and time in days (in parentheses).

A. Thermolysis (100°).—For **1** and **13** in dry dioxane the data are: **1**, 88%(21), 59%(53), and 37%(114); **13**, 93%(21), 88%(53), and 78%(114); without solvent: **1**, 91%(12), 66%(25), and 52%(32).

In the analysis of the reaction mixt from the 9.5-day thermolysis (100° neat) of **1**, an ampule was cooled and its contents were analyzed by glpc–mass spectrometry. Compounds **1** and **29–33** were identified by their molecular ions and by seemingly consistent fragmentations, and **28** was identified by glpc–peak augmentation with authentic **28**.

B. Hydrolysis and Ethanolysis (100°).—For **1** in 100% EtOH the data are: 70%(0.12), 47%(0.33), and 17%(0.87); for 1:1 H_2O–Me_2CO: 93%(0.12), 62%(0.5), and 14%(1.0); for **1** in 1:1 H_2O–Me_2CO at *ca.* 25°: 82%(8), 67%(17), and 63%(24).

C. Irradiation.—In dioxane at *ca.* 25° the data are: **1**, 70%(7), 54%(18), and 40%(32); **13**, 54%(7), 41%(18), and 31%(32). Values for **1** at *ca.* 25° without solvent were: 83%(8), 74%(16), and 59%(32).

D. Catalyzed by Thiol or by Thiolate Ion (100°).—Catalyzed decomps of **1** were done as usual except that 0.0480 g (10 mole %) of thioacetic acid or 0.0618 g (10 mole %) of sodium thioacetate (from thioacetic acid and Na in dry dioxane; the soln remained homogeneous) was added to the proper amts of **1** and internal standard. For thiol-catalyzed decomps of **1** in dioxane the results were: 100%(2.2), 87%(6), and 49%(13); without solvent: 69%(2.2), 41%(6), and 12%(13). For thiolate-catalyzed reactions in dioxane the results were: 23%(0.3) and 13%(0.8).

E. Equilibria.—Reactions and analyses were done as before. Standard solns were prepd by dissolving equimolar portions of pivaloyl disulfide and **28** in dioxane. The per cent survival of pivaloyl disulfide (days) at 100° was: 85%(17), 49%(52), and 29%(114). For irradiated samples the per cent survival was: 95%(7), 72%(18), and 52%(32). The per cent formation of **13** was determined as follows: %**13** = (mole of **13** at time $t/2$) (100)/(mole of pivaloyl disulfide at time t_0). The per cent formation of **13** (days) in dioxane at 100° was: 4%(1.6), 5%(3), 9%(4.6), 12%(9), 12%(17), 18%(52), 17%(84), and 14%(114). For irradiated samples the per cent formation was: 3%(2), 7%(3), 8%(5), 11%(7), 13%(14), 13%(18), 15%(24), and 10%(32).

2-Amino-4-hydroxy-6-arylaminoethylpteridines as Potential Antimalarial Agents

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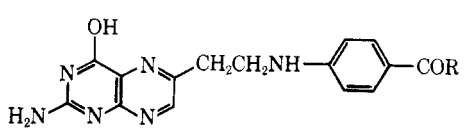
The synthesis of several 2-amino-4-hydroxy-6-arylaminoethylpteridines is described. These compounds, all analogs of homopteroic acid (II), were found to be ineffective in the standard antimalarial screen against *Plasmodium berghei* in rodents.

In recent years there has been a demand for new antimalarial agents to combat resistant strains of the disease. It was of especial interest to develop entirely new classes of compounds to help counteract this resistance problem.

The antifolate and other properties of homofolic acid (I) and its tetrahydro derivative have been reported.[1] We have also found that homopteroic acid (II), an intermediate in the synthesis[2] of I, and its tetrahydro derivative were potent growth inhibitors of *Streptococcus faecium*, a folate-dependent organism. These data, coupled with the observation of Kisliuk, *et al.*,[3] that tetrahydrohomopteroate displayed activity against a pyrimethamine-resistant strain of *Plasmodium cynomolgi* in monkeys, suggested that this area should be further studied in the hope of developing a new type of antimalarial agent.



I, R = NHCH(COOH)CH_2CH_2COOH
II, R = OH

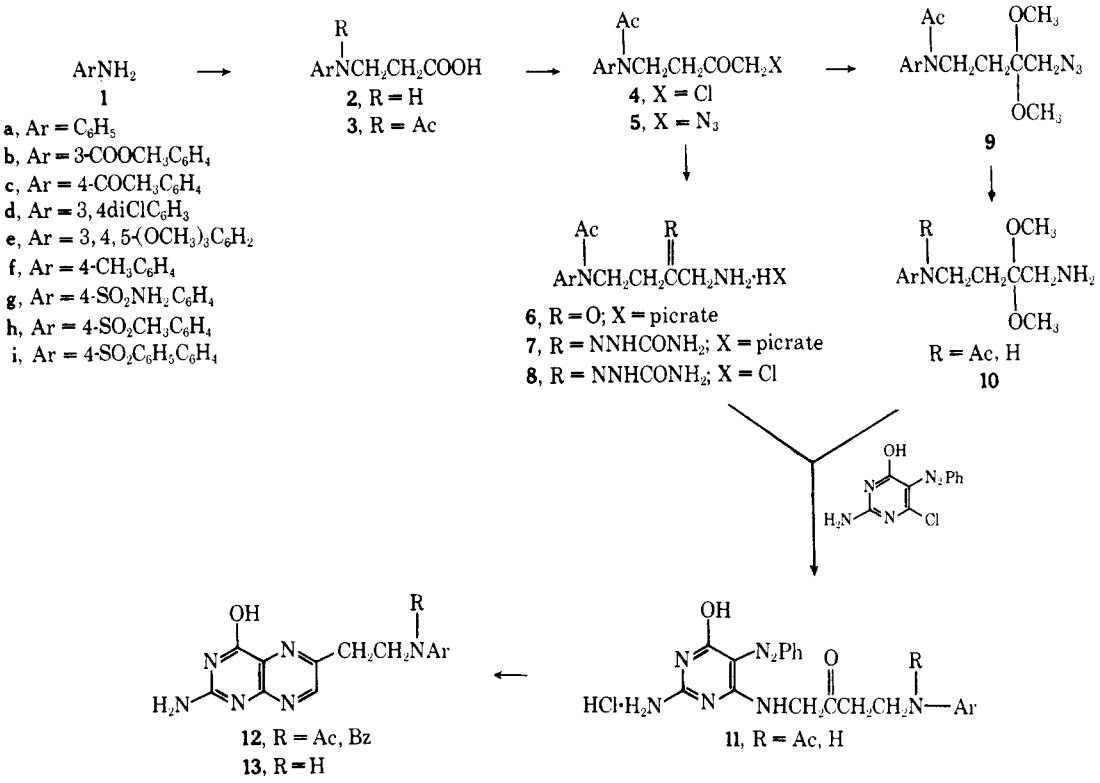
A number of substituted 2-amino-4-hydroxy-6-anilinoethylpteridines related to homopteroic acid (II) were synthesized. These structures, represented in Table

(1) L. Goodman, J. DeGraw, R. L. Kisliuk, M. Friedkin, E. J. Pastore, E. J. Crawford, L. T. Plante, A. Al-Nahas, J. F. Morningstar, G. Kwok, L. Wilson, E. F. Donovan, and J. Ratzlan, *J. Amer. Chem. Soc.*, **86**, 308 (1964); R. L. Kisliuk and M. Friedkin, Abstracts of the 6th International Congress Biochemistry, Vol. I, 1964, p 65; R. L. Kisliuk, M. Friedkin, V. Reid, E. J. Crawford, L. H. Schmidt, R. Rossan, D. Lewis, J. Harrison, and R. Sullivan, *J. Pharm. Exp. Ther.* **159**, 416 (1968).

(2) J. I. DeGraw, J. P. Marsh, E. M. Acton, O. P. Crews, C. W. Mosher, A. Fujiwara and L. Goodman, *J. Org. Chem.*, **30**, 3404 (1965).

(3) R. L. Kisliuk, M. Friedkin, L. H. Schmidt, and R. Rossan, *Science*, **156**, 1616 (1967).

SCHEME I



VII, had the *p*-carboxyl group of II replaced by other groups. Also, the *m*-homopteroic acid (**13b**) was prepared. We were unable to obtain the *p*-SO_2NH_2, -SO_2CH_3, or -$SO_2C_6H_5$ substituted analogs, as is discussed further in the chemistry section.

Initially, our biological evaluations were confined to the standard *Plasmodium berghei* screen in rats and the growth inhibition of *S. faecium*. None of the pteridines, including homopteroic acid itself, were active as antimalarials in the *P. berghei* screen as shown in Table I. Obvious questions are raised as to whether such compounds are transported well in the host animal and of their ability to penetrate the cells of the *Plasmodium*. We suspect that cell permeability is poor for these compounds as it is for most aminohydroxypteridines. We expect to report on their action against the monkey *P. cynomolgi* strain in a future communication. It would also be desirable to evaluate the tetrahydro derivatives, but their serious instability to oxidation would probably preclude development of a practical drug.

TABLE I

BIOLOGICAL DATA

No.	Antimalarial bioassay result[a] 40 mg/kg	160 mg/kg	640 mg/kg	*S. faecium* growth inhibition[b] Before hydrogenation	After hydrogenation[c]
13a	0.6	1.0	2.0	>20,000	>20,000
b	0.8	1.0	1.0	12,000	80
c				>20,000	1,000
d	0.1	0.1	0.3	>20,000	>20,000
e				>20,000	>20,000
f	0.1	0.1	0.3	>20,000	1,000
II (Homopteroic acid)	0.1	0.1	0.1	400	0.3

[a] Increase in survival time (days) of treated mice beyond that of untreated controls after single sc dosages (3 days post infection) of 40, 160, and 640 mg/kg. Average survival time of untreated controls was 7.0 ± 0.5 days. The infecting organism was *P. berghei*. [b] *Streptococcus faecium* (ATCC 8043). Values expressed are substrate concns (ng/ml) required for 50% growth inhibition; the folate concn was 1 ng/ml. [c] Hydrogenation in aq medium over PtO_2 at 1 atm. Uv spectral changes were consistent with the tetrahydropteridine form.

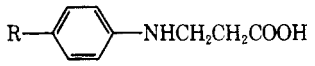
In Table I the data for the growth inhibition of *S. faecium* are also presented. In the fully aromatic form only homopteroic acid (II) showed significant activity. After reduction to the tetrahydropteridines, the *m*-carboxy isomer **13b** also showed significant activity. Likewise the 4-acetyl (**13c**) and 4-methyl (**13f**) compounds were considerably increased in potency after reduction. It is interesting that the analogs lacking a C-containing substituent on the Ph ring (**13a,d,e**) were completely inactive in either form. This would seem to indicate that hydrophobic binding by the Ph ring to a lipoid region of an enzyme is not an important factor. The mechanism by which homofolate (I) inhibits *S. faecium* growth is still unclear, but it is believed to act by blocking folic acid uptake.[4]

Syntheses of the pteridine compounds were accomplished by the same general procedure that was used for homopteroic acid.[2] The method is outlined in Scheme I and began with the condensation of an appropriately substituted aniline (**1**) and propiolactone.[5] The resulting β-anilino acid (**2**), after acylation of the NH group, was converted into the chloromethyl ketone **4** *via* the acid chloride–CH_2N_2 process. This procedure failed for the *N*-acetyl 3,4,5-trimethoxyanilino compound (**3e′**), but the use of the *N*-Bz blocking group overcame

(4) R. L. Kisliuk, G. Strait, and E. J. Crawford, 156th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept 1968.
(5) C. D. Hurd and S. Hayao, *J. Amer. Chem. Soc.*, **74**, 5889 (1952).

Table II

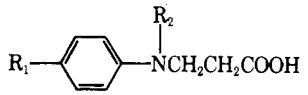
β-Alanines



No.	R	Yield, %	Mp, °C	Formula
2b	3-$COOCH_3$	45	115–117	$C_{11}H_{13}NO_4$
c	4-$COCH_3$	80	155–157	$C_{11}H_{13}NO_3$
d	3,4-Cl_2	47	103–105.3	$C_9H_9Cl_2NO_2$
h	4-SO_2CH_3	42	152.5–154	$C_{10}H_{13}NO_4S$
i	4-$SO_2C_6H_5$	67	147–148.5	$C_{15}H_{15}NO_4S$

Table III

N-Acyl-β-alanines



No.	R_1	R_2	Method	Yield, %	Mp, °C	Formula
3b	3-$COOCH_3$	Ac	A	87	117–118	$C_{13}H_{15}NO_5$
c	4-$COCH_3$	Ac	A	69	119–120	$C_{13}H_{15}NO_4$
d	3,4-Cl_2	Ac	A	64	136–137	$C_{11}H_{11}Cl_2NO_3$
e	3,4,5-$(OCH_3)_3$	Bz	B	53	130–132	$C_{19}H_{21}NO_6$
e′	3,4,5-$(OCH_3)_3$	Ac	B	41	165–168.5	$C_{14}H_{19}NO_6$
f	4-CH_3	Ac	B	25	105–107	$C_{12}H_{15}NO_3$
g	4-SO_2NH_2	Ac	A	92	131–132	$C_{11}H_{14}N_2O_5S$
h	4-SO_2CH_3	Ac	A	75	165.5–167	$C_{12}H_{15}NO_5S$
i	4-$SO_2C_6H_5$	Ac	A	78	187–190.5	$C_{17}H_{17}NO_5S$

the difficulty. The sulfonamido intermediate **3g** could not be successfully carried through this step.

Displacement of Cl by NaN_3 afforded the azido ketone **5**, which could be hydrogenated in acid solution to yield the amino ketone **6**, isolated as the picrate salt. The amino ketone picrate was directly treated with semicarbazide·HCl to give the semicarbazone **7** as the picrate. Exchange with Dowex 2(Cl^-) resin in aq MeOH readily afforded the amino semicarbazone·HCl (**8**). Condensation of **8** with 2-amino-4-hydroxy-5-phenylazo-6-chloropyrimidine[6] in DMF, followed by acid hydrolysis of the semicarbazone group afforded the phenylazo pyrimidinylamino ketone **11**. Catalytic reduction of the phenylazo moiety was accompanied by ring closure to the 7,8-dihydropteridine which could be easily aromatized by oxidation *in situ* with dil H_2O_2.

Some of the azido ketones were not compatible with the hydrogenation conditions required for reduction to the amino ketone. The azido ketone was then blocked as the ketal derivative **9**, which could be reduced to the amino ketal **10** with $NaBH_4$ in boiling *i*-PrOH. This procedure was especially useful for the synthesis of the *p*-Ac compound **13c**, since both keto groups could be blocked as ketals. In the weakly basic anilines the Ac blocking group was displaced by *i*-PrO^- during the $NaBH_4$ reductions. The resultant anilines did not compete with the α-amino group for displacement of Cl in the reaction with the chlorophenylazo pyrimidine. However, when the phenylazo pyrimidinyl ketones (**11**, R = H) were hydrogenated the resulting dihydropteridines suffered loss of the anilino portion of the side chain. Reacetylation of the 3,4-dichloro compound **11d** followed by reductive cyclization, etc., proceeded successfully to the pteridine **13d**. The sulfones **11h** and **i** could not be reacetylated without significant decomposition and the syntheses had to be abandoned at this stage.

(6) W. R. Boon and T. Leigh, *J. Chem. Soc.*, 1497 (1951).

Experimental Section

All new compounds in Tables II–VII and those followed by empirical formulas below were analyzed for C, H, N with values within ±0.4% of theoretical.

4-Acetamidophenyl Methyl Sulfone.—A soln of 223 g of 4-methylthioaniline in 1866 ml of HOAc–Ac_2O (1:1) was heated 1 hr on the steam bath. The soln was cooled to 0° with an ice–salt bath and maintained at *ca.* 0° while 433 ml of ice-cold 30% H_2O_2 was slowly added. The soln was kept at room temp for 2.5 days and then diluted with 15 l. of H_2O. The mixt was chilled and the light yellow cryst ppt was collected, washed with H_2O, and dried to afford 244 g (71%), mp 186–187°. A portion was recystd from PhH to provide an anal. sample, mp 187–189°. *Anal.* ($C_9H_{11}NO_3S$).

Acid hydrolysis (6 *N* HCl) afforded the amino sulfone **1h**.[7]

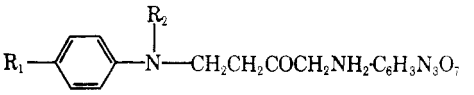
β-Alanines (2) (Table II).—Except for **2a**,[8] these compds were synthesized by the general procedure of Hurd and Hayao,[5] whereby an appropriately substd aniline (**1**) is allowed to react with propiolactone. The anilines were commercially available except for **1h** above and **1i**.[9] The *p*-aminosulfones (**1h** and **i**) required heating at 150° with propiolactone and MeCN in a steel bomb for 15 hr; with subsequent saponification of an acrylate ester formed.

***N*-Acyl-β-alanines (3) (Table III). Method A.**—A mixt of 3 g of β-arylaminopropionic acid, 5 ml of Ac_2O, and 5 ml of HOAc was heated on the steam bath for 2.5 hr and evapd *in vacuo;* the residue was taken up in excess satd $NaHCO_3$ and warmed on the steam bath for 30 min. The aq soln was decanted from a small amt of insol material, chilled, and acidified (pH 2) with 6 *N* HCl. The acidic mixt was extd with $CHCl_3$ and the ext was dried ($MgSO_4$) and evapd *in vacuo* to leave the *N*-Ac acid. Compound **3a**[10] was also prepd in this manner.

Method B.—The crude syrup obtained from 10 g of 3,4,5-trimethoxyaniline and 4.1 ml of propiolactone was partitioned between $CHCl_3$ and 10% K_2CO_3. The aq portion was treated with

Table IV

Aminomethyl Ketone Picrates

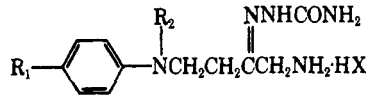


No.	R_1	R_2	Yield, %	Mp, °C	Formula
6a	H	Ac	33	157–161	$C_{15}H_{19}N_5O_9$
b	3-$COOCH_3$	Ac	31	163–164	$C_{20}H_{21}N_5O_{11}$
e	3,4,5-$(OCH_3)_3$	Bz	29	173–176	$C_{26}H_{27}N_5O_{12}$

(7) E. A. Fehnel and M. Carmack, *J. Amer. Chem. Soc.*, **72**, 1292 (1950).
(8) A. F. Bekhli, *Z. Obsch. Khim.*, **21**, 86 (1951).
(9) E. Knusli, *Gazz. Chim. Ital.*, **79**, 621 (1949).
(10) J. Braunholtz and F. Mann, *J. Chem. Soc.*, 4166 (1957).

TABLE V

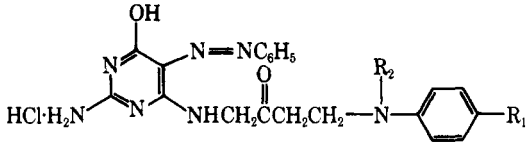
AMINO SEMICARBAZONES



No.	R_1	R_2	X	Yield, %	Mp, °C	Formula
7a	H	Ac	Picrate	81	176–180	$C_{19}H_{22}N_8O_9 \cdot 0.5EtOH$
8a	H	Ac	Cl	79	140–145	$C_{13}H_{19}N_5O_2 \cdot HCl$
7b	3-$COOCH_3$	Ac	Picrate	38	134–136	$C_{21}H_{24}N_8O_{11} \cdot H_2O$
8b	3-$COOCH_3$	Ac	Cl	88	202–204	$C_{15}H_{21}N_5O_4 \cdot HCl$
7e	3,4,5-$(OCH_3)_3$	Bz	Picrate	83	177–178.5	$C_{27}H_{30}N_8O_{12}$
8e	3,4,5-$(OCH_3)_3$	Bz	Cl	53	192–195	$C_{21}H_{27}N_5O_5 \cdot HCl \cdot H_2O$

TABLE VI

2-AMINO-4-HYDROXY-5-PHENYLAZO-6-PYRIMIDINYLAMINO KETONE HYDROCHLORIDES

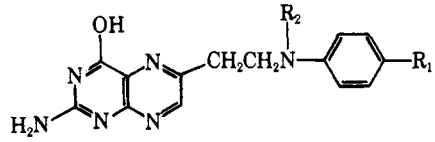


No.	R_1	R_2	Method	Yield, %	Mp, °C	Formula
11a	H	Ac	A	83	225–230	$C_{22}H_{23}N_7O_3 \cdot HCl$
b	3-$COOCH_3$	Ac	A	92	153–155	$C_{24}H_{25}N_7O_5 \cdot HCl \cdot CH_3OH$
c	4-$COCH_3$	Ac	B	29	215–218 dec	$C_{24}H_{25}N_7O_4 \cdot HCl \cdot H_2O$
d	3,4-diCl	H	B	48	158–161	$C_{20}H_{19}Cl_2N_7O_2 \cdot HCl$
d′	3,4-diCl	Ac	*a*	58	205–207.5	$C_{22}H_{21}Cl_2N_7O_3 \cdot HCl$
e	3,4,5-$(OCH_3)_3$	Bz	A	78	173–178	$C_{30}H_{31}N_7O_6 \cdot HCl \cdot H_2O$
f	4-CH_3	Ac	B	30	219–224	$C_{23}H_{25}N_7O_3 \cdot HCl \cdot 0.5H_2O$
h	4-SO_2CH_3	H	B	14	205–220 dec	$C_{21}H_{23}N_7O_4S \cdot HCl$
i	4-$SO_2C_6H_5$	H	B	67	170–175	$C_{26}H_{25}N_7O_4S \cdot HCl \cdot H_2O$

[a] From treatment of **11d** with Ac_2O at 135° for 2 hr.

TABLE VII

2-AMINO-4-HYDROXY-6-SUBSTITUTED PTERIDINES



No.	R_1	R_2	Yield, %	Uv $\lambda_{max}^{pH\ 13}$ (mμ) (ε)	Formula
12a	H	Ac	59	257 (16,200) 370 (4,900)	$C_{16}H_{16}N_6O_2$
b	3-$COOCH_3$	Ac	78	256 (22,000) 368 (5,850)	$C_{18}H_{18}N_6O_4$
c	4-$COCH_3$	Ac	64	255 (21,500) 375 (4,060)	$C_{18}H_{18}N_6O_3 \cdot 0.5H_2O$
d	3,4-$(Cl)_2$	Ac	62	253 (20,100) 375 (5,020)	$C_{16}H_{14}Cl_2N_6O_2$
e	3,4,5-$(OCH_3)_3$	Bz	56	255 (21,300) 369 (4,560)	$C_{24}H_{24}N_6O_5$
f	4-CH_3	Ac	66	255 (20,900) 375 (6,440)	$C_{17}H_{18}N_6O_2 \cdot 0.5H_2O$
13a	H	H	68	254 (22,700) 370 (5,800)	$C_{14}H_{14}N_6O$
b	3-COOH	H	70	253 (28,200) 368 (6,930)	$C_{15}H_{14}N_6O_3 \cdot 1.5H_2O$
c	4-$COCH_3$	H	60	253 (20,550)[a] 337 (19,800)	$C_{16}H_{16}N_6O_2$
d	3,4-$(Cl)_2$	H	93	252 (29,100) 370 (5,820)	$C_{14}H_{12}Cl_2N_6O$
e	3,4,5-$(OCH_3)_3$	H	22	252 (23,500) 371 (5,340)	$C_{17}H_{20}N_6O_4$
f	4-CH_3	H	56	251 (24,600) 368 (6,000)	$C_{15}H_{16}N_6O$

[a] 370-mμ band masked by intense peak at 337 seen in $RNHC_6H_4COCH_3$ compounds.

BzCl at 0–5°, stirred for 1.5 hr, and acidified (pH 2). After extn into $CHCl_3$, the soln was dried ($MgSO_4$) and evapd to leave a dark gum which crystd from $(i\text{-Pr})_2O$ to afford 10.4 g (53%) of *N*-Bz acid (**3e**). Ac_2O was similarly employed for **3e′** and **3f**.

Chloromethyl Ketones (4).—A soln of 1 equiv of the appropriate acid chloride in Et_2O was added dropwise to 2.7 equiv of CH_2N_2 in Et_2O at 0–5°. After 1 hr the mixt was treated with dry HCl for 30–60 min at 0–5° and evapd to dryness. The residue was redissolved in warm Et_2O and filtered to remove any polymethylene. The filtrate was evapd to afford the chloro ketone in 50–80% yield, usually as a syrup except for the 4-Me compd **4f**, mp 121–125°, $C_{13}H_{16}ClNO_2$ and *N*-benzoyl-3,4,5-trimethoxy compd **4e**, mp 100–104°, $C_{20}H_{22}ClNO_5$.

Azidomethyl Ketones (5).—A mixt of 1 g of chloromethyl ketone (**4**), 8 g of NaN_3, and 30 ml of 83% MeOH was stirred 4 hr at room temp. The MeOH was removed *in vacuo*, and the residue partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 ext was dried ($MgSO_4$) and evapd to leave the azidomethyl ketone in 70–80% yield as a syrup possessing a strong 4.75-μ band in the ir.

Aminomethyl Ketones (6) (Table IV).—A mixt of azidomethyl ketone (**5**), PtO_2, and EtOH contg 1 equiv of HCl was stirred for 24 hr under 1 atm of H_2. The catalyst was removed by filtration and the filtrate evapd *in vacuo*. The residue was dissolved in a little H_2O and treated with 1 equiv of picric acid in warm H_2O. The yellow picrates were collected and recrystd from EtOH.

Amino Semicarbazone Picrates and Hydrochlorides (7,8) (Table V).—To a warm soln of 1 equiv of aminomethyl ketone picrate (**6**) in 50% EtOH (60 ml/g) was added a 10% semicarbazide·HCl soln (3 equiv). After 24 hr the yellow crystals were collected to afford the amino semicarbazone picrate. Occasionally a second treatment was necessary to obtain complete conversion.

The picrate (1 g) was stirred with 10 g of Dowex 2 (Cl^-) resin and 30 ml of 83% MeOH for 24 hr. The resin was removed and the soln again treated with 1 g of resin. Removal of the solvent *in vacuo* afforded the hydrochloride salt, recrystd from EtOH.

Azido Ketals (9).—A mixt of 1 g of azidomethyl ketone (**5**), 10 ml of MeOH, 5 ml of $HC(OMe)_3$, and 0.15 g of *p*-TsOH was refluxed 10–15 hr. The soln was evapd *in vacuo* and the residue was taken up in CH_2Cl_2 and added slowly to satd $NaHCO_3$ with stirring. The CH_2Cl_2 layer was dried ($MgSO_4$) and evapd to leave the ketal as a syrup. The ir spectra showed N_3 at 4.75 μ, ketal (9.5) and loss of C=O at 5.8 μ. The 4-$COCH_3$ case (**9c**) required use of HCl rather than *p*-TsOH to achieve conversion of the acetophenone moiety to ketal.

Amino Ketals (10).—The crude azido ketal **9** was refluxed with an equal wt of $NaBH_4$ in 20 vol of *i*-PrOH for 24 hr. The solvent was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 ext was dried ($MgSO_4$) and evapd to leave the amino ketal as a syrup in 60–80% yield, with loss of the 4.75-μ azide band in the ir.

2-Amino-4-hydroxy-5-phenylazo-6-pyrimidinylamino Ketal·HCl (11) (Table VI). Method A.—To a soln of 0.44 g (19.0 mg-atoms) of Na in 80 ml of EtOH was added 6.18 g (19.8 mmoles) of 1-amino-4-(*N*-acetylanilino)-2-butanone semicarbazone·HCl (**8a**). After stirring for 1 hr a soln of 4.73 g (18.9 mmoles) of 2-amino-4-hydroxy-5-phenylazo-6-chloropyrimidine[6] in 47 ml of DMF was added, followed by 3.8 ml (28.4 mmoles) of *s*-collidine. The mixt was stirred at ambient temp for 72 hr and diluted with 700 ml of H_2O and the orange solid was collected. After washing with H_2O and EtOH the material was dried to give 6.34 g (68%). The crude semicarbazone was stirred with 60 ml of HOAc and 300 ml of 2 *N* HCl for 3 hr. The yellow crystals were collected, washed with 30 ml of 1 *N* HCl, and dried to leave the phenylazopyrimidinylamino ketone·HCl (**11a**), 5.00 g (83%).

Method B.—One equivalent of amino ketal **10** was stirred with 1 equiv of 2-amino-4-hydroxy-5-phenylazo-6-chloropyrimidine and 1.5 equiv of *s*-collidine in DMF for 3 days. After dilution with ice water, the pptd product was hydrolyzed with HOAc–2 *N* HCl as described in method A.

2-Amino-4-hydroxy-6-substituted Pteridines (12, 13) (Table VII).—The appropriate phenylazopyrimidinyl ketone·HCl (**11**) was stirred with 5% Pd/C and 50% MeOH (20 ml/g) under 1 atm of H_2 for 20 hr. Dil HCl was added and the mixt was warmed until all pptd product was dissolved. The catalyst was removed by filtration and the filtrate was treated with 2 equiv of 30% H_2O_2. After 1 hr the pH was adjusted to 6–7 with NH_4OH and the pptd pteridine was collected and washed with H_2O. The crude material was stirred briefly with warm DMF and filtered. The cake was washed with DMF and H_2O and dried. The blocking groups were hydrolyzed with 10% NaOH for 3 hr at 100° under N_2, with two exceptions. The toluidino intermediate **12f** required 4 hr at 150° (bomb tube) for removal of the *N*-Ac, while the *N*-Bz in the trimethoxy series (**12e**) required 6 hr at 150°. The hydrolysates were adjusted to pH 6–7 to ppt the deblocked pteridines. However, in the *N*-Bz case, acidification to pH 1–2 followed by Et_2O extn, before pptn of the pteridine at pH 6–7, was necessary to ensure removal of benzoic acid.

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