Pteridines. III. Synthesis of Some Ketones, Carbinols, and N-Oxides

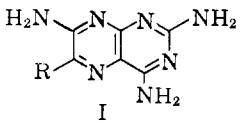
IRWIN J. PACHTER,[1] PIROSKA E. NEMETH, AND ANTHONY J. VILLANI

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

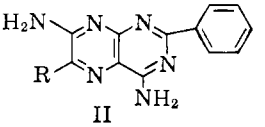
Received October 11, 1962

4-Amino-5-nitrosopyrimidines condense with benzoylacetonitrile, phenacylpyridinium bromide, and acetonylpyridinium chloride in the presence of sodium cyanide to produce 7-amino-6-pteridyl ketones. Reduction of the products with sodium borohydride yields the corresponding carbinols. 7-Substituted pteridine 5-oxides are produced when 4-amino-5-nitrosopyrimidines condense with the aforementioned pyridinium salts in the presence of potassium acetate. The use of α-cyanobenzylpyridinium salts in related reactions results in the formation of 7-amino-6-phenylpteridine 5-oxides.

Many of the pteridines that produce diuresis in animals can be grouped into classes represented by structures I[2] and II.[3] Previous papers in the present series[4,5] dealt with the synthesis for biological evaluation of 6-alkyl and 6-aralkyl compounds in these classes. In pursuit of further information on the relationship of structure to diuretic activity, we have now undertaken the chemically interrelated syntheses of some 6-ketones, 6-carbinols, and 5-oxides of pteridines of classes I and II.



I



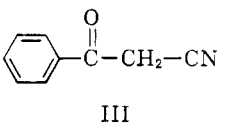
II

Although alkyl-substituted 6-pteridyl ketones were among the first pteridine derivatives to be reported,[6] they have not received recent attention and 7-amino-6-pteridyl ketones, required in the present investigation, have not been reported.

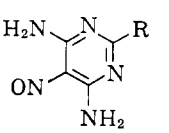
β-Ketonitriles, such as III, may be expected to condense with 4-amino-5-nitrosopyrimidines (IV) in the presence of alkaline catalysts to form pteridines of type V or VI, depending upon whether the cyclization involves nitrile or ketone. It was found that in ethanol in the presence of sodium methoxide or, preferably, sodium cyanide as the alkaline catalyst, pyrimidines IVa and IVb reacted with III to produce only the 6-pteridyl ketones Va and Vb.[7] The less reactive 2,4,6-triamino-5-nitrosopyrimidine did not condense with III in appreciable yield under the same conditions.

Kröhnke[8] has shown that phenacylpyridinium salts (VIIa) and acetonylpyridinium salts (VIIb) condense with nitrosobenzene derivatives the presence of cyanide to give the same products as do β-ketonitriles.

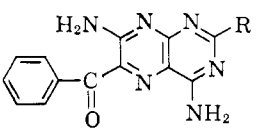
The pyridinium salts were useful in the present work. Compound VIIa reacted with IVa, IVc, and IVd to produce pteridines Va, Vc, and Vd. In the reaction of VIIa with IVa, compound VIa was isolated as a minor by-product; from none of the other reactions described in this paper was a 6-pteridinecarbonitrile isolated.[7]



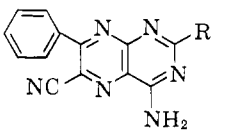
III



IVa, b, c and d



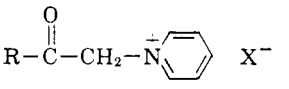
Va, b, c and d



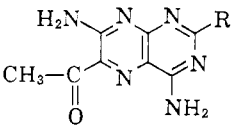
VIa

a. R = phenyl. b. R = hydrogen. c. R = methylthio. d. R = methyl.

Compound VIIb reacted readily with IVa, IVb, and IVc, to produce the methyl ketones VIIIa, VIIIb, and VIIIc.



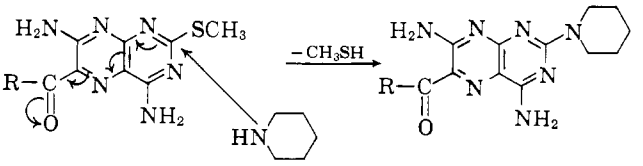
VIIa. R = phenyl, X = bromide
b. R = methyl, X = chloride



VIIIa. R = phenyl
b. R = hydrogen
c. R = methylthio

4,6-Diamino-2-piperidino-5-nitrosopyrimidine and 2,4,6-triamino-5-nitrosopyrimidine did not react satisfactorily with either VIIa or VIIb.

It was found possible to replace the 2-methylthio groups of Vc and VIIIc with piperidine under reflux and thus obtained derivatives (Ve and VIIId) with basic groups at positions 2, 4, and 7. In these reactions, the 6-carbonyls serve as activating groups. 4,7-Diamino-6-methyl-2-methylthiopteridine,[4] a related compound in which the activating effect is lacking, fails to react at an appreciable rate under the same conditions.



Vc. R = phenyl
VIIIc. R = methyl

Ve. R = phenyl
VIIId. R = methyl

Pure products were not obtained from the reactions of Vc and VIIIc with ammonia.

Triamino-5-nitrosopyrimidines react well under alkaline conditions only with strongly nucleophilic anions such as those derived from phenylacetonitrile and cyanoacetamide. The reactions generally require elevated temperatures. These nitrosopyrimidines are

(1) Present address: Endo Laboratories, Richmond Hill 18, N. Y.

(2) V. D. Wiebelhaus, J. Weinstock, F. T. Brennan, G. Sosnowsky, and T. J. Larsen, *Fed. Proc.*, **20**, 409 (1961).

(3) (a) E. C. Taylor and J. Weinstock, U. S. Patent 2,963,480 (1960); (b) T. S. Osdene and E. C. Taylor, U. S. Patent 2,975,180 (1961).

(4) I. J. Pachter and P. E. Nemeth, Part I, *J. Org. Chem.*, **28**, 1187 (1963).

(5) I. J. Pachter, Part II, *ibid.*, **28**, 1191 (1963).

(6) F. Sachs and G. Meyerheim, *Ber.*, **41**, 3957 (1908).

(7) As we shall describe elsewhere, VIa is the major product when brominated benzoylacetonitrile reacts with 4,5,6-triamino-2-phenylpyrimidine (XX).

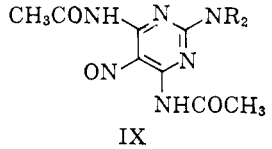
(8) F. Kröhnke, *Angew. Chem.*, **65**, 605 (1953).

less reactive as a consequence of resonance interactions involving the nitroso and three amino groups.

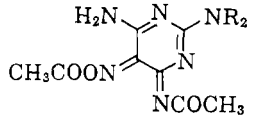
In an attempt to render the molecules more reactive, they were subjected to acetylation. It was expected that competing interactions of amino and acetyl groups would decrease interactions of amino and nitroso groups and hence serve to activate the latter.

2,4,6-Triamino-5-nitrosopyrimidine reacted with acetic anhydride in acetic acid under mild conditions to produce a blue diacetyl compound. More prolonged reaction at higher temperature gave a green triacetyl derivative. 4,6 - Diamino - 5 - nitroso - 2 - piperidinopyrimidine reacted readily to form a green diacetyl compound.

The nature of the acetylated products is presently not certain. One possible structure for the diacetyl compounds is IX. Another is X[9]; infrared absorption data in the 5.5–6.1-μ region (Table I) are not inconsistent with ester formulations.



IX



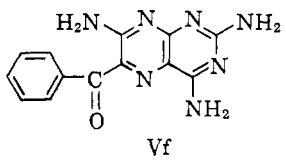
X

TABLE I

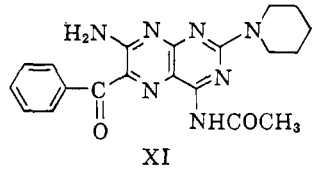
INFRARED ABSORPTION MAXIMA (NUJOL)

5-Nitrosopyrimidine	Wave length, μ
2,4,6-Triamino-	5.93, 6.02 (s), 6.05 (s), 6.08
Diacetylated 2,4,6-triamino-	5.68, 5.84, 5.93
Triacetylated 2,4,6-triamino-	5.69, 5.79, 5.90
4,6-Diamino-2-piperidino-	6.02 (s), 6.08
Diacetylated 4,6-diamino-2-piperidino-	5.78, 5.85

Diacetylated 2,4,6-triamino-5-nitrosopyrimidine reacted rapidly when heated with benzoylacetonitrile (III) in the presence of aqueous ethanolic sodium cyanide to produce a yellow pteridine. The product, a monoacetyl derivative, gave phenyl 2,4,7-triamino-6-pteridyl ketone (Vf) in good yield when treated with cold aqueous sodium hydroxide.



Vf

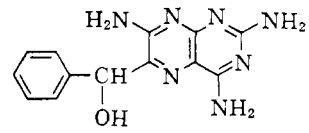


XI

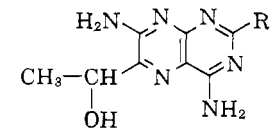
Similarly, diacetylated 4,6-diamino-5-nitroso-2-piperidinopyrimidine produced a pteridine to which structure XI is assigned. Upon brief alkaline hydrolysis the product gave Ve, identical with the compound previously derived from Vc.

Sodium borohydride in methanol reduced the ketones to the corresponding carbinols (XII and XIII). Four carbinols were prepared in this manner.

(9) E. C. Taylor, C. W. Jefford, and C. C. Cheng, *J. Am. Chem. Soc.*, **83**, 1261 (1961), reported that 4,6-diamino-2-dimethylamino-5-nitrosopyrimidine and related molecules underwent rearrangement to substituted 4-cyano-*s*-triazines when heated under reflux with acetic anhydride. They suggested that oximino esters related to X are intermediates in the process.

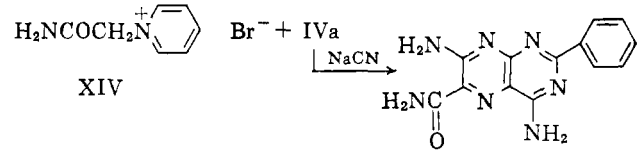


XII



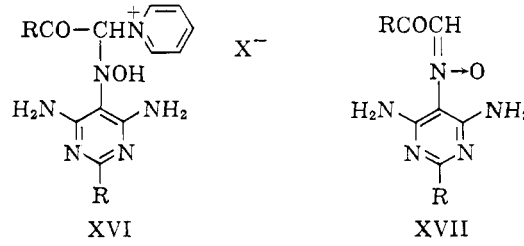
XIIIa. R = phenyl
b. R = hydrogen
c. R = piperidino

Pteridine syntheses from pyridinium salts are not limited to the preparation of pteridyl ketones. The salt XIV reacted with IVa in the presence of sodium cyanide to produce 4,7-diamino-2-phenyl-6-pteridinecarboxamide (XV).



XIV XV

In the syntheses of pteridines from pyridinium salts, hydroxylamines (XVI) and nitrones (XVII)[8] are probable intermediates.

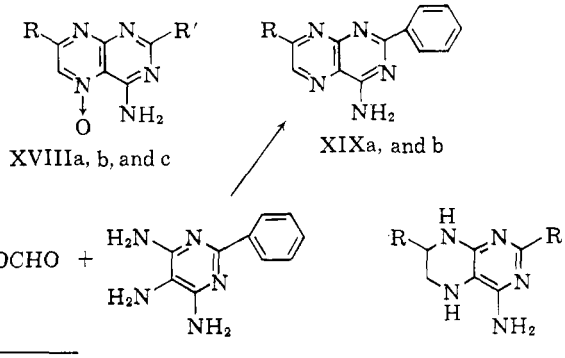


XVI XVII

In the absence of cyanide, the nitrones might be expected to cyclize to the corresponding pteridine 5-oxides. Authentic pteridine N-oxides have thus far not been reported in the literature.

When VIIa and VIIb were condensed with IVa in the presence of potassium acetate in place of sodium cyanide, the N-oxides XVIIIa and XVIIIb were produced. Compound VIIb reacted with IVb in similar fashion to produce XVIIIc.

Upon hydrogenation of XVIIIa and XVIIIb with Raney nickel as catalyst, the pteridines XIXa and XIXb were produced. These were identical with the products derived from the reactions of phenylglyoxal and methylglyoxal with 4,5,6-triamino-2-phenylpyrimidine (XX). More prolonged hydrogenation of the N-oxides XVIIIb and XVIIIc or the pteridine XIXb yielded the 5,6,7,8-tetrahydro compounds XXIb and



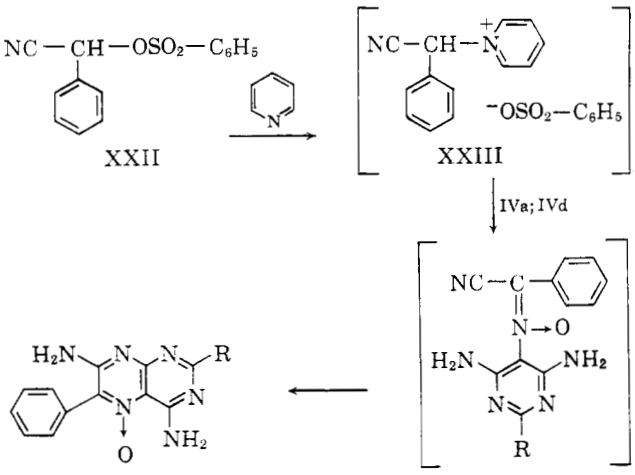
XVIIIa, b, and c XIXa, and b

XX XXIb and c

a. R = phenyl, R′ = phenyl. b. R = methyl, R′ = phenyl. c. R = methyl, R′ = hydrogen.

XXIc. Compound XIXa was resistant to further hydrogenation under the same conditions.

α-Cyanobenzyl benzenesulfonate (XXII), derived from benzaldehyde, benzenesulfonyl chloride and sodium cyanide,[10] was converted into the pyridinium compound XXIII. Without purification, the latter was treated with nitrosopyrimidines IVa and IVd in the presence of alkali to produce the N-oxides XXVa and XXVb in good yield.



XXVa and b XXIVa and b

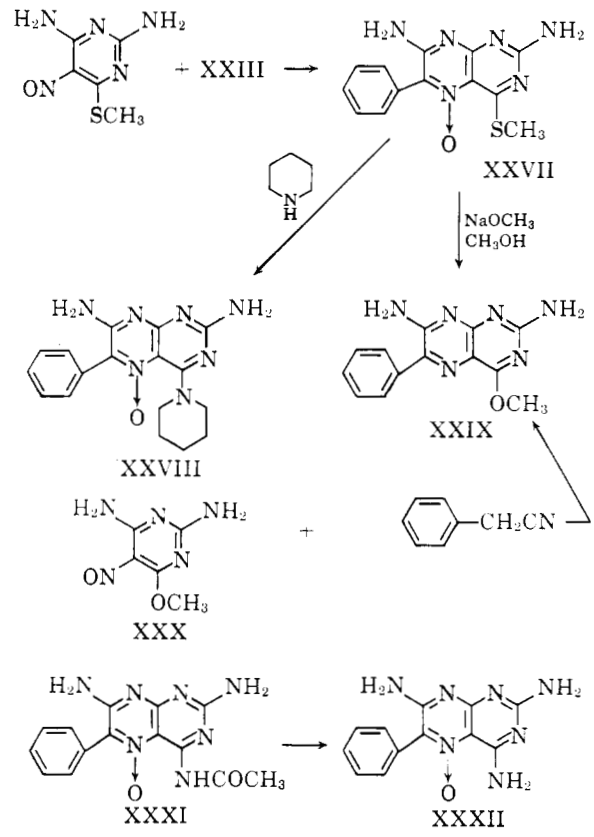
a. R = phenyl. b. R = methylthio.

In the preparation of XXVa and XXVb, sodium cyanide was found to be a most effective alkaline catalyst. Apparently, intermediates of type XXIV cyclize to N-oxides rapidly and show little, if any, tendency to add cyanide and lose cyanate.[4]

Compound XXVb did not react at an appreciable rate with refluxing piperidine. This is not surprising, for the net effect of an oxide at N-5 on nucleophilic displacement should be marked activation of C-6 but only limited activation of C-2, C-4, and C-7.[11]

2,6 - Diamino - 4 - methylthio - 5 - nitrosopyrimidine (XXVI) reacted with XXIII to produce 2,7-diamino-4-methylthio-6-phenylpteridine 5-oxide (XXVII). 4-Methylthio groups undergo displacement more readily than the 2-isomers; compound XXVII was converted into XXVIII with piperidine at reflux. When XXVII was boiled with sodium methoxide in methanol, displacement accompanied by N-oxide reduction occurred. Compound XXIX was produced. It was identical with the product of the reaction[12] of 2,4-diamino-6-methoxy-5-nitrosopyrimidine (XXX) with phenylacetonitrile. Methoxide in methanol is not a general reducing agent, for neither XVIIIa nor XXXII (*vide infra*) was altered under conditions which produced XXIX.

2,4,6-Triamino-5-nitrospyrimidine reacted with difficulty with XXIII just as it had with III, VIIa, and VIIb. Its blue diacetyl derivative reacted readily, however, and an acetylated pteridine was produced. This derivative underwent deacetylation upon treatment with alkali, or even upon brief boiling with methanol, to produce 2,4,7-triamino-6-phenylpteridine 5-oxide (XXXII). The very facile loss of the acetyl group suggests that the initial product had structure



XXXI and that the oxide function participated in the solvolysis.

The ultraviolet absorption maxima of selected pteridines prepared during the course of this work are listed in Table II.

Several of the compounds produced potent diuretic effects in experimental animals. The biological data will be reported elsewhere at a later date.

Experimental

The *ultraviolet spectra* of Table II at pH 1 were determined in 4.5% aqueous formic acid. The spectra at pH 13 were determined by taking a 5- to 10-ml. aliquot of compound in 4.5% formic acid and bringing the volume to 100 ml. with 1 *N* aqueous sodium hydroxide. In those cases where the compound crystallized from alkaline solution, no values at pH 13 are recorded.

For analyses, the pteridines were dried *in vacuo* at 150°.

Phenyl 4,7-Diamino-2-phenyl-6-pteridyl Ketone (Va).—To a mixture of 12.5 g. (0.058 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 12.5 g. (0.086 mole) of benzoylacetonitrile and 150 ml. of ethanol was added a solution of 9.0 g. of sodium cyanide in 50 ml. of water. The resulting mixture was heated under reflux with stirring for 1.5 hr. and then cooled. The yellow crystalline product (16.1 g.) was collected. Upon recrystallization from dimethylformamide and then from dioxane it melted at 327–328° dec.

Anal. Calcd. for $C_{19}H_{14}N_6O$: C, 66.66; H, 4.12; N, 24.54. Found: C, 66.63; H, 4.20; N, 24.84.

Va and 4-Amino-2,7-diphenyl-6-pteridinecarbonitrile (VIa).—To 1.4 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine (IVa) in in 15 ml. of ethanol was added 1.4 g. of phenacylpyridinium bromide in 15 ml. of 50% ethanol and 0.5 g. of sodium cyanide in 2 ml. of water. The mixture was boiled for 15 min., cooled, and filtered to yield 1.2 g. of Va, identical with the product of the reaction of III and IVa.

The aqueous alcoholic filtrate was concentrated by boiling on a steam bath for 30 min. On cooling there was obtained 0.3 g. of a second compound (VIa), identical with a sample[7] to be described in a subsequent publication.

Phenyl 4,7-Diamino-6-pteridyl Ketone (Vb).—To a mixture of 7.0 g. (0.05 mole) of 4,6-diamino-5-nitrosopyrimidine, 10.15 g.

(10) R. M. Dodson and H. W. Turner, *J. Am. Chem. Soc.*, **73**, 4517 (1951).

(11) I. J. Pachter and M. C. Kloetzel, *ibid.*, **74**, 971 (1952).

(12) This reaction was carried out by Dr. Blaine Sutton and Miss Alice Sheppard of these laboratories.

TABLE II

ULTRAVIOLET SPECTRA

Compound	λ_{max} mμ (log ε)	pH
Vb	280 (4.39), 386 (4.05)	1
	256 (s) (4.26), 280 (4.11), 358 (3.89), 389 (3.90)	13
Vd	279 (4.36), 384 (4.08)	1
	252 (s) (4.23), 283 (4.18), 393 (4.06)	13
Ve	287 (4.26), 394 (4.45)	1
Vf	280 (4.30), 386 (4.27)	1
	247 (4.48), 290 (4.19), 402 (4.39)	13
VIIIa	277 (4.53), 394 (4.22)	1
VIIIb	275 (4.46), 382 (4.07)	1
	248 (4.21), 272 (s) (4.05)	13
VIIIc	277 (4.46), 391 (4.33)	1
	250 (4.47), 382 (4.27), 397 (4.30)	13
VIIId	278 (4.24), 387 (4.45)	1
	247 (4.58), 292 (4.21), 409 (4.52)	13
XII	256 (4.22), 281 (s) (3.77), 345 (4.32)	1
	260 (4.20), 284 (s) (3.74), 356 (4.21)	13
XIIIa	258 (4.42), 354 (4.31)	1
	246 (4.54), 350 (4.23)	13
XIIIb	252 (4.18), 285 (3.60), 344 (4.16)	1
	240 (4.33), 262 (s) (4.04), 338 (4.05)	13
XIIIc	262 (4.18), 350 (4.37), 365 (s) (4.31)	1
	267 (4.34), 293 (s) (3.97), 371 (4.20)	13
XVIIIa	276 (4.41), 292 (s) (4.32), 330 (4.09), 368 (s) (4.21), 382 (4.27)	1
XVIIIb	282 (4.38), 313 (4.15), 342 (4.01), 358 (3.99)	1
XVIIIc	284 (3.81), 340 (3.95), 354 (3.97)	1
	254 (4.10), 285 (3.88), 354 (3.84)	13
XIXa	254 (4.33), 278 (s) (4.22), 312 (4.01), 361 (4.35), 373 (4.35)	1
XIXb	271 (4.25), 301 (4.15), 320 (4.15), 333 (4.16), 346 (s) (4.08)	1
	269 (4.41), 342 (3.97)	13
XXVa	258 (4.50), 366 (4.28)	1
XXVb	269 (4.40), 309 (3.76), 365 (4.27)	1
	245 (4.46), 277 (4.38), 370 (4.18)	13
XXVIII	252 (4.21), 380 (4.18)	1
	244 (s) (4.35), 277 (4.19), 391 (4.10)	13
XXIX	286 (3.85), 354 (4.40)	1
	274 (3.99), 362 (4.33)	13
XXXII	246 (4.42), 296 (3.70), 362 (4.25)	1
	240 (4.61), 267 (4.39), 374 (4.20)	13

(0.07 mole) of benzoylacetonitrile, and 250 ml. of ethanol was added a solution of 3.5 g. of sodium cyanide in 20 ml. of water. The resulting mixture was heated under reflux for 1 hr., concentrated, and cooled. There was obtained 7.90 g. of yellow plates. Upon recrystallization from ethanol the product melted at 291–293°.

Anal. Calcd. for $C_{13}H_{10}N_6O$: C, 58.64; H, 3.79; N, 31.56. Found: C, 58.66; H, 3.81; N, 31.53.

Phenyl 4,7-Diamino-2-methylthio-6-pteridyl Ketone (Vc).—To 5.49 g. of 4,6-diamino-2-methylthio-5-nitrosopyrimidine and 10.7 g. of phenacylpyridinium bromide in 100 ml. of 80% ethanol was added a solution of 5.0 g. of sodium cyanide in 20 ml. of water. The mixture was heated under reflux for 20 min., cooled, and filtered. The yellow product was washed copiously with water[13] and dried to give 7.9 g. of crude Vc. Upon two recrystallizations from dimethylformamide there was obtained 4.5 g. of Vc, m.p. 335° dec.

Anal. Calcd. for $C_{14}H_{12}N_6OS$: C, 53.83; H, 3.87; N, 26.91. Found: C, 53.54; H, 3.93; N, 27.40.

Phenyl 4,7-Diamino-2-methyl-6-pteridyl Ketone (Vd).—This compound was prepared from 4,6-diamino-2-methyl-5-nitrosopyrimidine (1.0 g.) and phenacylpyridinium bromide (2.0 g.) by a procedure similar to that used for the synthesis of Vc. There was obtained 1.1 g. of yellow product from dimethylformamide, m.p. 307° dec.

Anal. Calcd. for $C_{14}H_{12}N_6O$: C, 59.99; H, 4.32; N, 29.99. Found: C, 59.87; H, 4.24; N, 29.85.

Methyl 4,7-Diamino-2-phenyl-6-pteridyl Ketone (VIIIa).—To 21.5 g. (0.1 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 20.6 g. (0.12 mole) of acetonylpyridinium chloride and 200 ml. of ethanol was added 7.5 g. (0.15 mole) of sodium cyanide in 50 ml. of water. The resulting mixture was heated under reflux with stirring until the green color of the nitrosopyrimidine was no longer apparent (80 min.). The mixture was cooled, filtered, and the product was washed thoroughly with hot water,[13] and dried. There was obtained 26.6 g. of yellow VIIIa.

For analysis, a sample was recrystallized from dimethylformamide and then from aqueous acetic acid. It then melted at 306–310° dec.

Anal. Calcd. for $C_{14}H_{12}N_6O$: C, 59.99; H, 4.32; N, 29.99. Found: C, 60.10; H, 4.23; N, 29.81.

Phenylhydrazone of VIIIa.—A solution of 0.7 g. of VIIIa, 1.0 g. of phenylhydrazine and 75 ml. of acetic acid was heated under reflux for 10 min. It was diluted with 50 ml. of water and cooled. The product was collected and washed with ethanol. The resulting 0.65 g. of yellow solid was recrystallized first from acetic acid and then from ethanol to give beautiful yellow needles, m.p. 306–308°.

Anal. Calcd. for $C_{20}H_{18}N_8$: C, 64.85; H, 4.90; N, 30.25. Found: C, 64.48; H, 4.73; N, 30.21.

Methyl 4,7-Diamino-6-pteridyl Ketone (VIIIb).—To a boiling mixture of 1.4 g. of 4,6-diamino-5-nitrosopyrimidine, 2.5 g. of acetonylpyridinium chloride and 100 ml. of ethanol was added a solution of 0.75 g. of sodium cyanide in 10 ml. of water. The mixture was stirred under reflux for 30 min., cooled, and filtered. The product (1.6 g.) was dissolved in water containing a few milliliters of acetic acid, treated with charcoal, and precipitated with ammonia. The 1.5 g. of long yellow needles thus obtained melted over 340°.

Anal. Calcd. for $C_8H_8N_6O$: C, 47.06; H, 3.95; H, 41.16. Found: C, 47.10; H, 4.09; N, 41.35.

Methyl 4,7-Diamino-2-methylthio-6-pteridyl Ketone (VIIIc).—A mixture of 6.0 g. of finely powdered 4,6-diamino-2-methylthio-5-nitrosopyrimidine, 5.0 g. of sodium cyanide, 7.5 g. of acetonylpyridinium chloride and 200 ml. of 80% ethanol was heated under reflux for 1.5 hr. The yellow product that formed was filtered, washed well with water,[13] and dried. It weighed 6.1 g. It became light orange in color upon recrystallization from dimethylformamide. It became black when heated over 280°.

Anal. Calcd. for $C_9H_{10}N_6OS$: C, 43.19; H, 4.03; N, 33.58. Found: C, 43.37; H, 4.03; N, 33.87.

Phenyl 4,7-Diamino-2-piperidino-6-pteridyl Ketone (Ve).—A mixture of 5.0 g. of phenyl 4,7-diamino-2-methylthio-6-pteridyl ketone (Vc) and 150 ml. of piperidine was heated under reflux for 26 hr. It was then evaporated to dryness under reduced pressure. The residue was washed with ethanol and dried to give 4.2 g. of yellow product. For analysis a sample was recrystallized from methanol. It melted at 300–301° dec.

Anal. Calcd. for $C_{18}H_{19}N_7O$: C, 61.88; H, 5.48; N, 28.06. Found: C, 61.91; H, 5.40; N, 28.31.

Methyl 4,7-Diamino-2-piperidino-6-pteridyl Ketone (VIIId).—A 1.0-g. sample of methyl 4,7-diamino-2-methylthio-6-pteridyl ketone (VIIIc) and 50 ml. of piperidine was heated under reflux for 24 hr. Excess piperidine was removed under reduced pressure and the product was recrystallized from ethanol with the aid of charcoal to obtain 0.76 g. of orange needles, m.p. 293–298° dec.

Anal. Calcd. for $C_{13}H_{17}N_7O$: C, 54.34; H, 5.96; N, 34.13. Found: C, 54.66; H, 6.07; N, 34.44.

Diacetylated 2,4,6-Triamino-5-nitrosopyrimidine.—A mixture of 10 g. of 2,4,6-triamino-5-nitrosopyrimidine, 50 ml. of acetic anhydride and 100 ml. of acetic acid was heated on a hot plate slowly with stirring. The starting material dissolved, the solution turned blue, and the blue compound began to crystallize from solution. The mixture was then quickly cooled in an ice bath to prevent further acetylation. The product was filtered, washed with ethanol, and dried. It weighed 13 g. and melted at 199–200° dec.

Anal. Calcd. for $C_8H_{10}N_6O_3$: C, 40.33; H, 4.23; N, 35.28. Found: C, 40.59; H, 4.56; N, 35.38.

Triacetylated 2,4,6-Triamino-5-nitrosopyrimidine.—A mixture of 5.0 g. of 2,4,6-triamino-5-nitrosopyrimidine, 50 ml. of acetic anhydride and 150 ml. of acetic acid was boiled gently with stir-

(13) Failure to remove traces of sodium cyanide results in the formation of dark red impurities upon subsequent recrystallization from dimethylformamide.

ring for 10 min. until the color of the solution turned from blue to green. The solution was cooled to 0° and scratched. There was obtained 4.2 g. of light green crystals. Upon concentration of the filtrate under reduced pressure, an additional 2.2 g. of green product was obtained. The compound was recrystallized from ethanol to give green needles, m.p. 214° dec.

Anal. Calcd. for $C_{10}H_{12}N_6O_4$: C, 42.86; H, 4.32; N, 29.99. Found: C, 42.71; H, 4.46; N, 30.10.

Diacetylated 4,6-Diamino-5-nitroso-2-piperidinopyrimidine.—A 2.0-g. sample of 4,6-diamino-5-nitroso-2-piperidinopyrimidine was heated at 50° with a mixture of 8 ml. of acetic anhydride and 16 ml. of acetic acid for 15 min. Three milliliters of water was added. The mixture was cooled in an ice bath for 1 hr. and filtered to yield 2.55 g. of green needles, m.p. upon recrystallization from ethanol, 185–186°.

Anal. Calcd. for $C_{13}H_{18}N_6O_3$: C, 50.97; H, 5.92; N, 27.44. Found: C, 51.45; H, 5.99; N, 27.48.

Phenyl 2,4,7-Triamino-6-pteridyl Ketone (Vf).—A mixture of 20 g. of benzoylacetonitrile and 24 g. of diacetylated 2,4,6-triamino-5-nitrosopyrimidine in 350 ml. of absolute ethanol was brought to boiling and 14 g. of potassium acetate in 150 ml. of absolute ethanol was added. The mixture was stirred under reflux until no blue starting material was visible (30 min.). It was cooled and filtered. A small sample of the yellow product thus obtained was washed with water, recrystallized once from ethanol, and analyzed. The analytical results, although disagreeing by 0.7, 0.2 and 0.8% with the theoretical values for carbon, hydrogen and nitrogen, respectively, indicated that the product was predominantly a monoacetyl derivative. The remainder of the yellow granular compound was stirred at room temperature with 350 ml. of 1.5% sodium hydroxide for 2 hr., during which time it dissolved and a new product crystallized from solution. The new product (Vf) was dissolved in hot dilute acetic acid, treated with charcoal and then with excess ammonia. There was obtained 19.6 g. of Vf. For analysis, a sample was dissolved once again in dilute acetic acid and reprecipitated with ammonia. It melted at 338–339° dec.

Anal. Calcd. for $C_{13}H_{11}N_7O$: C, 55.51; H, 3.94; N, 34.86. Found: C, 55.75; H, 4.09; N, 34.95.

Phenyl 4,7-Diamino-2-piperidino-6-pteridyl Ketone (Ve) from Diacetylated 4,6-Diamino-5-nitroso-2-piperidinopyrimidine.—A mixture of 1.02 g. of diacetylated 4,6-diamino-5-nitroso-2-piperidinopyrimidine and 1.0 g. of benzoylacetonitrile was heated under reflux with 25 ml. of absolute ethanol for 5 min. It was then treated with 0.6 g. of potassium acetate in 5 ml. of absolute ethanol. Heating under reflux was continued (about 10 min.) until the color of the mixture turned from blue-green to bright yellow. The mixture was then cooled to 20° and a solution of 0.5 g. of sodium hydroxide in 5 ml. of water was added. The yellow compound dissolved and glittering yellow plates separated. The mixture was allowed to stand at room temperature for 30 min. and the product was collected, washed with water until the washings were neutral, and dried to yield 1.1 g. of Ve, m.p. 300–302° dec., identical with the product prepared from Vc and piperidine.

4,7-Diamino-2-phenyl-6-pteridinecarboxamide (XV).—A mixture of 0.9 g. of the pyridinium salt of bromoacetamide, 0.3 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 0.1 g. of sodium cyanide dissolved in 4 ml. of water, and 12 ml. of ethanol was heated on a steam bath. Reaction proceeded to completion in less than a minute. There was obtained 0.35 g. of yellow crystals, identical with a sample of XV prepared from cyanoacetamide.[2]

α-Phenyl-2,4,7-triamino-6-pteridylcarbinol (XII).—A 9.0-g. sample of phenyl 2,4,7-triamino-6-pteridyl ketone (Vf) was boiled with 500 ml. of methanol for 10 min. and cooled to 50°. Over a 15-min. period, 6 g. of sodium borohydride in 100 ml. of methanol was added. The reaction temperature was kept between 50 and 55°. The mixture was filtered to remove 0.8 g. of insoluble material, neutralized with acetic acid, and evaporated to dryness under reduced pressure. The residue was thoroughly washed with water and dried to give 7 g. of crude product. A test showed that a small quantity of phenolic pteridine was present. The product was dissolved in dilute acetic acid and then made quickly alkaline with 5% sodium hydroxide. The finely divided precipitate that separated was stirred for 30 min. at room temperature with two 100-ml. portions of 1% sodium hydroxide. It was then recrystallized from dimethylformamide and finally dissolved in hot dilute acetic acid and reprecipitated from the hot solution with ammonia. There was obtained 3.1 g. of yellow prisms which turn black at about 275°.

Anal. Calcd. for $C_{13}H_{13}N_7O$: C, 55.12; H, 4.63; N, 34.61. Found: C, 55.16; H, 4.75; N, 34.75.

1-(4,7-Diamino-2-phenyl-6-pteridyl)ethanol (XIIIa).—A mixture of 5.0 g. of methyl 4,7-diamino-2-phenyl-6-pteridyl ketone (VIIIa) and 150 ml. of methanol was treated with a solution of 5.0 g. of sodium borohydride in 50 ml. of methanol at such a rate that the reaction temperature did not exceed 50°. After 25 min., the solution was clarified by filtration, neutralized with acetic acid, and evaporated to dryness under reduced pressure. The residue was thoroughly washed with water and dried to give 4.5 g. of pale yellow plates. After recrystallization from methanol, the m.p. was 274–276° dec.

Anal. Calcd. for $C_{14}H_{14}N_6O$: C, 59.56; H, 5.00; N, 29.77. Found: C, 59.58; H, 4.92; N, 29.69.

1-(4,7-Diamino-6-pteridyl)ethanol (XIIIb).—By a procedure similar to that used for the preparation of XIIIa, 1.0 g. of methyl 4,7-diamino-6-pteridyl ketone (VIIIb) was converted into 0.8 g. of XIIIb. The product formed off-white needles from methanol, m.p. 248–250° dec.

Anal. Calcd. for $C_8H_{10}N_6O$: C, 46.60; H, 4.89; N, 40.76. Found: C, 46.67; H, 5.20; N, 40.74.

1-(4,7-Diamino-2-piperidino-6-pteridyl)ethanol (XIIIc).—By a procedure similar to that used for the preparation of XIIIa, 4.0 g. of methyl 4,7-diamino-2-piperidino-6-pteridyl ketone (VIIId) was converted into 3.5 g. of XIIIc. The yellow product, m.p. 226–227°, was recrystallized for analysis from methanol.

Anal. Calcd. for $C_{13}H_{19}N_7O$: C, 53.96; H, 6.62; N, 33.89. Found: C, 53.99; H, 6.81; N, 33.54.

4-Amino-2,7-diphenylpteridine 5-Oxide (XVIIIa).—To a hot solution of 2.15 g. (0.01 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine and 1.96 g. (0.02 mole) of potassium acetate in 250 ml. of ethanol was added 3.98 g. (0.014 mole) of phenacylpyridinium bromide in 20 ml. of water. The resulting mixture was boiled for 1 hr., cooled, and filtered. The yellow product was recrystallized from dimethylformamide to give 2.3 g. of needles, m.p. 258–260°.

Anal. Calcd. for $C_{18}H_{13}N_5O$: C, 68.56; H, 4.16; N, 22.11. Found: C, 68.45; H, 4.22; N, 22.13.

Reduction of 4-Amino-2,7-diphenylpteridine 5-Oxide (XVIIIa). Synthesis of XIXa.—A mixture of 1.0 g. of XVIIIa, 200 ml. of ethanol, and a half teaspoonful of Raney nickel was shaken with hydrogen at 50 p.s.i. for 10 hr. The nickel was removed and the solution concentrated to give 0.8 g. of needles of XIXa, m.p., 252–253°, identical with a sample prepared from phenylglyoxal and 4,5,6-triamino-2-phenylpyrimidine.

Anal. Calcd. for $C_{18}H_{13}N_5$: C, 72.22; H, 4.38; N, 23.40. Found: C, 71.94; H, 4.66; N, 23.86.

4-Amino-2,7-diphenylpteridine (XIXa).—To 6.0 g. (0.03 mole) of 4,5,6-triamino-2-phenylpyrimidine in 100 ml. of ethanol was added 6.16 g. (0.04 mole) of phenylgyoxal hydrate in 20 ml. of ethanol, and 3.92 g. (0.04 mole) of potassium acetate and 4.6 ml. (0.08 mole) of acetic acid in 10 ml. of water. The mixture was heated on a steam bath for 30 min., cooled, and filtered. The yellow product thus obtained weighed 8.6 g. It was recrystallized from dimethylformamide to give 7.1 g. of prisms, m.p. 252–253°.

4-Amino-7-methyl-2-phenylpteridine 5-Oxide (XVIIIb).—To a boiling mixture of 21.5 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 20.0 g. of potassium acetate and 1 l. of ethanol was added a solution of 25.6 g. of acetonylpyridinium chloride in 100 ml. of water. The resulting mixture was boiled for 1 hr. during which time the green nitroso compound disappeared and a golden yellow product (22.7 g.) separated. It was recrystallized from dimethylformamide to give 19.0 g. of well formed crystals, m.p. 287° dec.

Anal. Calcd. for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.65. Found: C, 61.43; H, 4.72; N, 27.61.

Reduction of 4-Amino-7-methyl-2-phenylpteridine 5-Oxide (XVIIIb). Synthesis of XIXb and XXIb.—A mixture of 2.0 g. of 4-amino-7-methyl-2-phenylpteridine 5-oxide (XVIIIb), one-half teaspoonful of Raney nickel, and 200 ml. of ethanol was shaken under 50 p.s.i. of hydrogen for 30 min. The nickel was removed and the solution was evaporated to dryness. Upon treatment of the residue with dilute acetic acid, all but 150 mg. of yellow needles dissolved. The needles, upon recrystallization from ethanol, melted at 269–270° and proved to be identical with a sample of XIXb prepared from methylglyoxal and 4,5,6-triamino-2-phenylpyrimidine.

The yellow acetic acid solution was made basic with ammonia and a colorless solid (1.4 g.) separated. Upon recrystallization from methanol, colorless prisms of XXIb, m.p. 174–176°, were obtained.

When 1.8 g. of XVIIIb was similarly hydrogenated for 1.5 hr., 1.6 g. of XXIb was obtained as the only product.

Anal. Calcd. for $C_{13}H_{15}N_5$: C, 64.71; H, 6.27; N, 29.03. Found: C, 64.77; H, 6.33; N, 29.28.

4-Amino-7-methyl-2-phenylpteridine (XIXb).—To a solution of 30.2 g. of 4,5,6-triamino-2-phenylpyrimidine, 72 g. of 30% methylglyoxal in water and 500 ml. of ethanol was added a solution of 29.4 g. of potassium acetate and 34 ml. of acetic acid in 100 ml. of water. Upon heating on a steam bath, yellow crystals rapidly formed. After 30 min. the mixture was cooled and filtered to yield 31.7 g. of XIXb. The product was dissolved in dilute hydrochloric acid, treated with charcoal, and then precipitated with 10% sodium hydroxide. Upon recrystallization from dimethylformamide there was obtained 18.7 g. of pale yellow needles, m.p. 269–271 dec.

Anal. Calcd. for $C_{13}H_{11}N_5$: C, 65.81; H, 4.67; N, 29.52. Found: C, 66.04; H, 4.81; N, 29.67.

Reduction of XIXb.—Hydrogenation of 18.6 g. of XIXb with Raney nickel in 500 ml. of ethanol under 50-p.s.i. pressure yielded 16.7 g. of crude XXIb which, upon recrystallization from methanol, gave 13.0 g. of prisms, m.p. 174–176°.

4-Amino-7-methylpteridine 5-Oxide (XVIIIc).—A mixture of 1.39 g. (0.01 mole) of 4,6-diamino-5-nitrosopyrimidine, 1.96 g. (0.02 mole) of potassium acetate, and 250 ml. of ethanol was heated to boiling and diluted with 2.56 g. (0.015 mole) of acetonylpyridinium chloride in 20 ml. of water. The resulting mixture was boiled for 1.5 hr. Upon concentration and cooling there was obtained 2.0 g. of crude product which, upon recrystallization from ethanol with the aid of charcoal, yielded 1.0 g. of yellow prisms, m.p. 250–251.

Anal. Calcd. for $C_7H_7N_5O$: C, 47.45; H, 3.98; N, 39.53. Found: C, 47.72; H, 4.25; N, 39.86.

Reduction of 4-Amino-7-methylpteridine 5-Oxide (XVIIIc). Synthesis of XXIc.—A 3.4-g. sample of XVIIIc was hydrogenated in 200 ml. of ethanol at 50 p.s.i. for 8 hr. with 1 teaspoonful of Raney nickel as catalyst. Removal of the catalyst and evaporation of the solvent left a noncrystalline residue which was converted to a solid hydrochloride with ethereal hydrogen chloride. Recrystallization of the product from methanol gave 1.5 g. of pale yellow prisms of the dihydrochloride of XXIc, m.p. 243–245° dec.

Anal. Calcd. for $C_7H_{13}Cl_2N_5$: C, 35.31; H, 5.50; N, 29.41. Found: C, 35.85; H, 5.63; N, 29.00.

4,7-Diamino-2,6-diphenylpteridine 5-oxide (XXVa).—To 4.3 g. (0.02 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine in 250 ml. of acetone was added a solution of 7.4 g. (0.027 mole) of α-cyanobenzyl benzenesulfonate, 8 ml. of pyridine and 15 ml. of acetone which had been boiled previously for 5 min. To the resulting green solution was added 2.0 g. (0.04 mole) of sodium cyanide in 20 ml. of water. A deep red color developed instantly. The solution was heated to 40° for 5 min. and then allowed to stand at room temperature for 1 hr. The solid was collected, washed with water and ethanol and dried to give 6.5 g. of crude product. Recrystallization from dimethylformamide yielded 5.6 g. of fine pale yellow needles, m.p. over 350°.

Anal. Calcd. for $C_{18}H_{14}N_6O$: C, 65.44; H, 4.27; N, 25.44. Found: C, 65.21; H, 4.28; N, 25.73.

4,7-Diamino-2-methylthio-6-phenylpteridine 5-Oxide (XXVb).—A 3.7-g. (0.02 mole) sample of finely powdered 4,6-diamino-2-methylthio-5-nitrosopyrimidine was converted into XXVb by a procedure similar to that used for the preparation of XXVa. There was obtained 4.6 g. of product which was recrystallized from dimethylformamide to give 3.8 g. of pale yellow needles, m.p. 351° dec.

Anal. Calcd. for $C_{13}H_{12}N_6OS$: C, 51.99; H, 4.03; N, 27.98. Found: C, 51.91; H, 4.03; N, 28.26.

2,7-Diamino-4-methylthio-6-phenylpteridine 5-Oxide (XXVII).—The procedure used for the preparation of XXVa was modified to accommodate the lack of solubility of 2,6-diamino-4-methylthio-5-nitrosopyrimidine in pure acetone. A 3.7-g. (0.02 mole) sample of the nitrosopyrimidine was dissolved in 40 ml. of dimethyl sulfoxide. The resulting blue solution was diluted in rapid succession with 250 ml. of boiling acetone, with a solution of 8.0 g. of α-cyanobenzyl benzenesulfonate, 8 ml. of pyridine, and 15 ml. of acetone which had been boiled previously for 5 min., and finally with a solution of 2.0 g. of sodium cyanide in 20 ml. of water. Yellow prisms soon separated from the intensely colored solution. After 2 hr. the product was collected, washed with water and ethanol, and dried. The 3.5 g. of yellow compound thus obtained was dissolved in 50 ml. of dimethylformamide. Upon dilution with an equal volume of methanol, the solution deposited 2.8 g. of analytically pure prisms of XXVII, m.p. 306–308° dec.

Anal. Calcd. for $C_{13}H_{12}N_6OS$: C, 51.99; H, 4.03; N, 27.98. Found: C, 52.06; H, 4.24; N, 27.97.

2,7-Diamino-6-phenyl-4-piperidinopteridine 5-Oxide (XXVIII).—A 2.45 g. sample of 2,7-diamino-4-methylthio-6-phenylpteridine 5-oxide (XXVII) was heated under reflux for 16 hr. with 100 ml. of piperidine. Removal of excess piperidine and recrystallization of the residual product from ethanol gave 1.8 g. of yellow needles of XXVIII, m.p. 265° dec.

Anal. Calcd. for $C_{17}H_{19}N_7O$: C, 60.52; H, 5.68; N, 29.06. Found: C, 60.69; H, 5.56; N, 29.09.

Reaction of XXVII with Methanolic Sodium Methoxide. Synthesis of XXIX.—A 1.0-g. sample of XXVII was heated under reflux for 7.5 hr. with 1.0 g. of sodium methoxide in 150 ml. of methanol. The resulting clear solution was allowed to stand at room temperature for 16 hr. Yellow plates (0.6 g.) of XXIX, m.p., 256° dec., separated. Elemental analysis showed that the N-oxide function was no longer present. The product was found to be identical with a sample of XXIX prepared from 2,4-diamino-6-methoxy-5-nitrosopyrimidine and phenylacetonitrile.

2,7-Diamino-4-methoxy-6-phenylpteridine (XXIX).[12]—To a solution of 11 g. of 2,4-diamino-6-methoxy-5-nitrosopyrimidine in a mixture of 750 ml. of dry dimethylformamide and 250 ml. of methanol was added with stirring 3.2 g. of sodium methoxide and 7.6 g. of phenylacetonitrile. The reaction mixture was heated under reflux for 1.5 hr. The solvent was removed under reduced pressure and the residue was stirred with water, collected, and slurried twice with 5% hydrochloric acid. The crude hydrochloride was dissolved in water, treated with charcoal, filtered, and made basic with sodium hydroxide. The product was collected and recrystallized first from butanol and then from methanol to give 1.6 g. of yellow needles of XXIX, m.p. 258° dec.

Anal. Calcd. for $C_{13}H_{12}N_6O$: C, 58.20; H, 4.51; N, 31.33. Found: C, 58.14; H, 4.52; N, 31.22.

2,4,7-Triamino-6-phenylpteridine 5-Oxide (XXXII).—A 10.0-g. sample of diacetylated 2,4,6-triamino-5-nitrosopyridine was dissolved in 120 ml. of dimethyl sulfoxide. The resulting solution was diluted in rapid succession with 400 ml. of boiling acetone, with a solution of 16.6 g. of α-cyanobenzyl benzenesulfonate, 16.6 ml. of pyridine, and 50 ml. of acetone which had been boiled previously for 5 min., and finally with a solution of 4.1 g. of sodium cyanide in 40 ml. of water. Yellow crystals soon separated from the intensely colored solution. The product was filtered, washed with water and ethanol and dried to give 6.8 g. of bright yellow solid (XXXI).

A 5.0-g. sample of the yellow acetylated derivative was suspended in 100 ml. of boiling stirred methanol. A solution of 5 g. of sodium methoxide in 75 ml. of methanol was added and the resulting mixture was boiled with stirring for 5 min. The mixture was then diluted with an equal volume of water and cooled. The product (XXXII) was collected, slurried with 15 ml. of acetic acid, and heated with 200 ml. of water until solution was achieved. The yellow solution was clarified by filtration and, while still hot, diluted with excess concentrated aqueous ammonia. Beautiful yellow plates (3.55 g.) crystallized, m.p. 340° dec.

It was subsequently found that XXXII could be obtained from XXXI upon boiling with methanol alone.

Anal. Calcd. for $C_{12}H_{11}N_7O$: C, 53.53; H, 4.12; N, 36.41. Found: C, 53.77; H, 4.39; N, 36.33.

Acknowledgment.—The authors wish to thank Drs. Joseph Weinstock and James W. Wilson for their interest and for valuable suggestions offered during the course of this work. They are also grateful to Mrs. Doris Rolston of these laboratories for the analytical data and to Dr. Walter E. Thompson and Mr. Richard J. Warren for the spectral data.