Pyrimido[5,4-*d*][1,2,3]triazines

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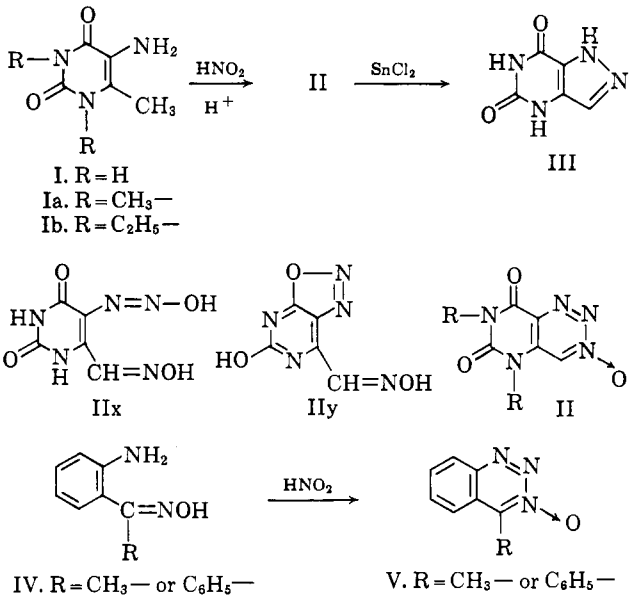
The products obtained from the reactions of 5-amino-6-methyluracils (I, Ia, and Ib) with nitrous acid are shown to be pyrimido[5,4-*d*][1,2,3]triazine 3-oxides (II, IIa, and IIb). Hydrolyses of the 4-chloropyrimidotriazines, VIa and b, yield 5-diazobarbituric acids, VIIa and b. A mechanism is postulated for this unusual hydrolysis.

Our interest in the possible physiological activity of derivatives of 1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-dione[2] (III), an isomer of xanthine, prompted us to reinvestigate the nature of the reactions and intermediates used for its synthesis. Compound III has been synthesized by the action of nitrous acid on 5-amino-6-methyluracil (I)[3] followed by the reduction, with stannous chloride, of the intermediate compound II so formed. The intermediate II has been formulated by Behrend as IIx and by Rose as diazouracil-6-aldoxime IIy. The evidence presented in this paper will establish the correct structure for the intermediate II to be pyrimido[5,4-*d*][1,2,3]triazine-6,8(5*H*,7*H*)-dione 3-oxide.

Since, for pharmacological reasons, we were largely interested in alkylated derivatives of the pyrimidines, we chose as our starting materials 1,3,6-trimethyluracil and 1,3-diethyl-6-methyluracil. The reactions in the two series closely paralleled each other. Only the reactions of the methyl derivatives will be discussed. Descriptions of the comparable ethyl derivatives are given in Experimental.

1,3,6-Trimethyl-5-aminouracil (Ia), prepared *via* nitration of 1,3,6-trimethyluracil and catalytic reduction of the 5-nitro compound so obtained, was treated with nitrous acid under conditions similar to those used by Behrend.[3a] The compound so formed, IIa, agreed with $C_7H_7N_5O_3$. The analysis was not consistent with a formula corresponding to Behrend's IIx (see also ref. 3b) and the compound could not be formulated by a structure analogous to Rose's IIy. The infrared spectrum of IIa showed no absorption in the 4-μ region as would be expected for a diazo ketone.[4] On the other hand, Meisenheimer[5] had shown that treatment of the *syn*-oximes of *o*-aminoacetophenone and *o*-aminobenzophenone (IV) with nitrous acid led to the formation of products best formulated as 4-substituted 1,2,3-benzotriazine 3-oxides (V). In a similar manner, compounds of structures IIx or IIy, if formed as intermediates, would be expected to give the pyrimido[5,4-*d*][1,2,3]-triazine 3-oxide (II).



Further evidence that IIa was actually a triazine 3-oxide was obtained by the following series of reactions. Treatment of IIa with thionyl chloride at room temperature, followed by chromatography of the products so formed, yielded the pyrimidotriazinetrione VIIIa and 1,3-dimethyl-5-diazobarbituric acid (VIIa). Since it appeared very probable that both VIIa and VIIIa were products of hydrolysis of an initially formed 4-chloropyrimidotriazine VIa, an attempt was made to isolate this expectedly rather unstable compound.[6] By repeated and rapid crystallizations of the product from the reaction of IIa with thionyl chloride,[7] pure 4-chloro-5,7-dimethylpyrimido[5,4-*d*][1,2,3]triazine-6,8(5*H*,7*H*)-dione (VIa) was obtained in moderate yield. Hydrolysis of VIa with dilute hydrochloric acid produced both VIIa and VIIIa.

It was realized that VIIIa could be formulated as 5,7-dimethylpyrimido-[5,4-*d*][1,2,3]triazine-4,6,8-

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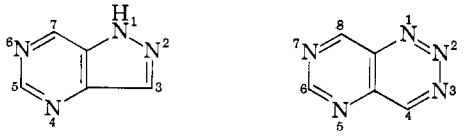
(2) The compounds in this paper are named as derivatives of 1*H*-pyrazolo-[4,3-*d*]pyrimidine and pyrimido[5,4-*d*][1,2,3]triazine. Throughout this



paper, with the exception of formulas IV and V, where the nature of R is clearly designated, Roman numerals without letters refer to compounds in which R = H; Roman numerals combined with "a" (*e.g.*, VIIIa) refer to compounds in which R = CH_3— and combined with "b" (*e.g.*, VIIIb) to compounds in which R = C_2H_5—. Combinations with x and y refer to alternate ways of formulating a given compound.

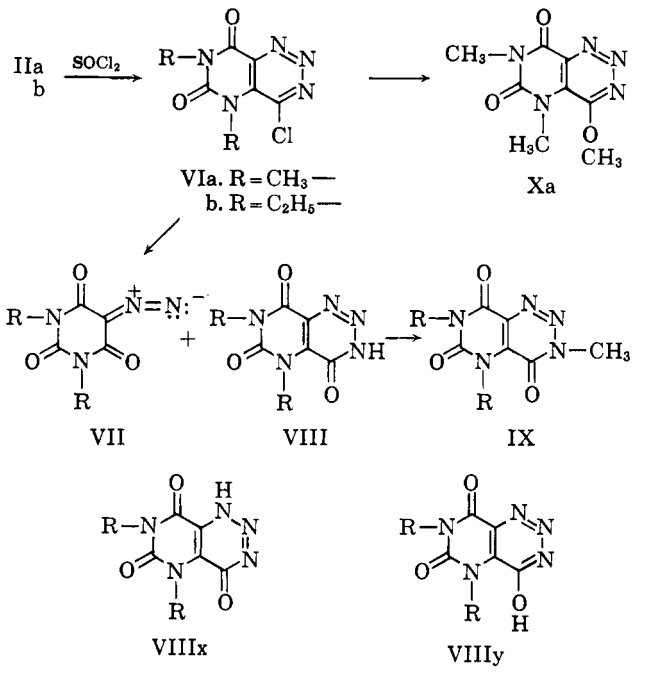
(3) (a) R. Behrend, *Ann.*, **245**, 213 (1888); (b) F. L. Rose, *J. Chem. Soc.*, 3448 (1952). The pyrazolopyrimidinedione (III) has also been prepared by R. K. Robins, F. W. Furcht, A. D. Grauer, and J. W. Jones [*J. Am. Chem. Soc.*, **78**, 2418 (1956)], by the fusion of 4-aminopyrazole-3-carboxamide with urea. The preparation and proof of structure of alkylated derivatives of III will be reported in the future.

(4) For a brief discussion of the structure and spectra of diazo phenols (diazo ketones, "1,2,3-oxadiazoles") see "Heterocyclic Compounds," R. C. Elderfield, ed., John Wiley and Sons, Inc., New York, N. Y.; J. H. Boyer, Vol. 7, 1961, p. 522. See also J. D. C. Anderson, R. J. W. LeFèvre, and I. R. Wilson, *J. Chem. Soc.*, 2082 (1949); R. J. W. LeFèvre, J. B. Sousa, and R. L. Werner, *ibid.*, 4686 (1954).

(5) J. Meisenheimer, O. Senn, and P. Zimmermann, *Ber.*, **60**, 1736 (1927). For a discussion of the chemistry of 1,2,3-triazines see, "The Chemistry of Heterocyclic Compounds," A. Weissberger, consulting ed., Interscience Publishers, Inc., New York, N. Y., "The 1,2,3- and 1,2,4-Triazines, Tetrazines and Pentazines," J. G. Erickson, P. F. Wiley, and V. P. Wystrach, 1956, p. 1.

(6) For the synthesis and properties of 4,5,6-triphenyl-1,2,3-triazine, see E. A. Chandross and G. Smolinsky, *Tetrahedron Letters*, **13**, 19 (1960).

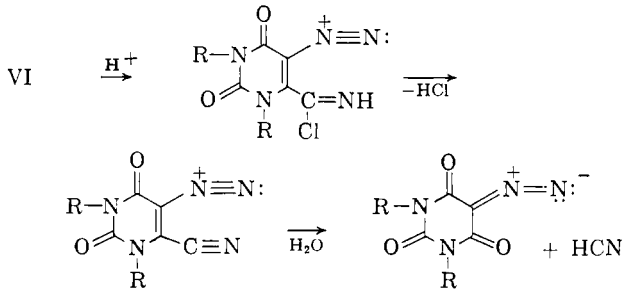
(7) For related reactions on pyridine 1-oxide using sulfuryl chloride, see B. Bobranski, L. Kochanska, and A. Kowalewska, *Ber.*, **71**, 2385 (1938).



(3*H*,5*H*,7*H*)-trione, as the corresponding 1*H*-trione VIIIax or as the 4-hydroxypyrimidotriazinedione VIIIay. To obtain further evidence for its structure, VIIIa was methylated with dimethyl sulfate to IXa. The 4-chlorotriazine VIa, in turn, was converted to the 4-methoxytriazine Xa with sodium methoxide in methanol. The ultraviolet spectra of VIa, VIIIa, IXa, and Xa fell into two groups: the spectra of VIa and Xa were very similar in form, and position and intensity of maxima; the spectra of VIIIa and IXa were also very similar in form, and position and intensity of maxima (see Experimental). On the other hand, there was little resemblance in form between the ultraviolet spectra of the two groups. From the structures of VIa and Xa and the comparison of spectra, VIIIay probably can be eliminated as an important tautomer for VIIIa. The structure IXa was assigned to the methylation product of VIIIa on the basis of analogous methylations in the benz[*d*][1,2,3]triazin-4-one series.[8] Because of the similarity of the ultraviolet spectra of VIIIa and IXa, formula VIIIa is considered to be the most important tautomer of that compound. However, it is realized that the position of methylation of VIIIa is not rigorously established.

To relate more clearly the structure of pyrimido[5,4-*d*][1,2,3]triazine-6,8(5*H*,7*H*)-dione 3-oxide (II) to that of its dimethylated and diethylated derivatives, IIa and IIb, a sample of II was prepared by the method described by Rose.[3b] The observation by Rose of the existence of a very stable hydrate of II was confirmed. Comparison of the ultraviolet spectra of II, IIa, and IIb showed a great similarity in form and intensity of maxima. The λ_{max} 256.5 mμ of II was at slightly lower wave length than that of IIa (λ_{max} 263 mμ) and IIb (λ_{max} 264 mμ).

5-Diazobarbituric Acid.—The formation of 1,3-dimethyl-5-diazobarbituric acid (VIIa) by the hydrolysis of 4-chloro-5,7-dimethylpyrimido[5,4-*d*][1,2,3]triazine-6,8(5*H*,7*H*)-dione (VIa) came as a surprise to us. The compound VIIa was identified by its analysis, by the presence of strong absorption at 4.62 μ in its infrared spectrum,[4] and by direction comparison of its infrared spectrum with that of authentic sample.[9] Its formation can be rationalized on the basis of the following equations. The liberation of HCN from the hydrolysis was detected by the use of picric acid test



paper.[10] The reactions postulated above resemble those that were recently described by M. S. Gibson[11] to explain the isomerization of substituted pyrazolo[2,3-*c*][1,2,3]benzotriazines to pyrazolo[4,3-*c*]cinnolines. They are also related to the conversion of 3,4-dihydro-4-oxobenzo-1,2,3-triazine to *o*-chlorobenzonitrile by reaction with a mixture of phosphorus pentachloride and phosphorus oxychloride.[12]

Experimental[13]

1,3,6-Trimethyl-5-nitrouracil.—To a solution of 1.5 ml. of fuming nitric acid (*d* 1.50) in 39 ml. of concentrated sulfuric acid cooled to 10° was added 12.7 g. of 1,3,6-trimethyluracil at such a rate that the temperature never exceeded 20°. When all of the 1,3,6-trimethyluracil had dissolved, an additional 5.23 ml. of fuming nitric acid was added at temperatures below 20°. The resulting solution was poured over ice, and the resulting precipitate (13.5 g., m.p. 146–148°) was separated by filtration and was washed thoroughly with ice–water. Crystallization of a portion of this material from dilute alcohol gave analytically pure 1,3,6-trimethyl-5-nitrouracil, m.p. 153–154°.

Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.21; H, 4.55; N, 21.10. Found: C, 42.12; H, 4.78; N, 20.85.

1,3-Diethyl-5-nitro-6-methyluracil, m.p. 85–86°, was prepared from 1,3-diethyl-6-methyluracil by a similar procedure.

Anal. Calcd. for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.59; H, 5.63; N, 18.83.

1,3,6-Trimethyl-5-aminouracil (Ia).—1,3,6-Trimethyl-5-nitrouracil (36 g.) in 1 l. of absolute alcohol was hydrogenated at 70–99° and 740–750 p.s.i. using 3.6 g. of a 5% palladium-on-carbon catalyst. After completion of the hydrogenation, the solution was filtered, then evaporated *in vacuo* to 125 ml. On being cooled this solution deposited 14 g. of 1,3,6-trimethyl-5-aminouracil (Ia), m.p. 169–171°. An additional 7.7 g. of the same product, m.p. 167–169°, was obtained by further evaporation of the mother liquors.

Anal. Calcd. for $C_7H_{11}N_3O_2$: C, 49.69; H, 6.55; N, 24.84. Found: C, 49.56; H, 6.74; N, 25.25.

1,3-Diethyl-5-amino-6-methyluracil (Ib), m.p. 96–99°, was prepared from the corresponding 5-nitro derivative by a similar method.

Anal. Calcd. for $C_9H_{15}N_3O_2$: C, 54.80; H, 7.67; N, 21.31. Found: C, 54.89; H, 7.57; N, 21.15.

(8) K. Kratz, *J. prakt. Chem.*, **53**, 210 (1896).

(9) E. Fahr, *Ann.*, **627**, 213 (1959); F. G. Fischer, W. P. Neumann, and J. Roch, *Chem. Ber.*, **85**, 752 (1952); F. J. DiCarlo, A. S. Schultz, and A. M. Kent, *J. Biol. Chem.*, **194**, 769 (1952). We are indebted to Dr. E. Fahr, University of Würzburg, Germany, for a copy of this infrared spectrum.

(10) Houben-Weyl, "Methoden der Organischen Chemie, Analytische Methoden," Georg Thieme Verlag, Stuttgart, 1953, p. 21.

(11) M. S. Gibson, *Chem. Ind.* (London), 698 (1962).

(12) D. Buckley and M. S. Gibson, *J. Chem. Soc.*, 3242 (1956).

(13) We are indebted to Drs. R. T. Dillon and W. H. Sause of the Analytical Division of G. D. Searle and Co. for the analytical and optical data reported, to Mr. W. M. Selby for help with catalytic reductions, to Dr. E. G. Daskalakis for help with chromatographic separations, and to Dr. W. M. Hoehn and the Special Synthesis Group for the preparation of larger quantities of some of these materials. All ultraviolet spectra were determined in methanol.

5,7-Dimethylpyrimido[5,4-*d*][1,2,3]triazine-6,8(5*H*,7*H*)-dione 3-Oxide (IIa).—A solution of 29.8 g. of 1,3,6-trimethyl-5-aminouracil (Ia) in 245 ml. of concentrated hydrochloric acid and 190 g. of ice was treated at 0–5° with 25 g. of sodium nitrite in 41.5 ml. of water. The sodium nitrite solution was added slowly with stirring under the surface of the amine hydrochloride solution. Toward the end of the reaction a precipitate formed. The mixture was stirred for an additional 1.5 hr. while the temperature was allowed to rise to room temperature. The resulting precipitate was separated by filtration, washed with water to remove the acid, then washed with alcohol, and dried. From the reaction 30 g. of the N-oxide IIa, m.p. 247–249° dec., was obtained. Crystallization of this material from acetic acid raised the m.p. to 249–250° dec.; λ_{max} 263 mμ (ε 35,000), $\lambda_{shoulder}$ 290 mμ (ε 10,480), $\lambda_{shoulder}$ 340 mμ (ε 2,050); λ_{max}^{KBr} 5.75, 5.91, 6.33, 6.89, 7.28, 7.51, and 7.71 μ.

Anal. Calcd. for $C_7H_7N_5O_3$: C, 40.19; H, 3.37; N, 33.48. Found: C, 40.04; H, 3.35; N, 33.54.

5,7-Diethylpyrimido[5,4-*d*][1,2,3]triazine-6,8(5*H*,7*H*)-dione 3-oxide (IIb), m.p. 244–245° dec., λ_{max} 264 mμ (ε 36,800), $\lambda_{shoulder}$ 290 mμ (ε 9,600); λ_{max} 340 mμ (ε 1,620); λ_{max}^{KBr} 5.78, 5.91, 6.31, 6.63, 6.95, 7.06, 7.22, 7.40, and 7.48 μ.

Anal. Calcd. for $C_9H_{11}N_5O_3$: C, 45.57; H, 4.67; N, 29.52. Found: C, 45.58; H, 4.59; N, 29.12.

1,3-Dimethyl-5-diazobarbituric Acid (VIIa) and 5,7-Dimethylpyrimido[5,4-*d*][1,2,3]triazine-4,6,8(3*H*,5*H*,7*H*)-trione (VIIIa).—5,7-Dimethylpyrimido[5,4-*d*][1,2,3]triazine-6,8(5*H*,7*H*)-dione 3-oxide (IIa) (15.0 g.) and 150 ml. of thionyl chloride were stirred at room temperature in a closed vessel for 18 hr. The excess thionyl chloride was removed *in vacuo* at a temperature of less than 35°. The residue was dissolved in 1800 ml. of benzene by prolonged stirring at room temperature and was then chromatographed on 800 g. of silica gel. The column was washed with benzene and then with a gradually increasing proportion of ethyl acetate in benzene.

Elution of the column with 15% ethyl acetate in benzene yielded 9.16 g. of 1,3-dimethyl-5-diazobarbituric acid. Repeated crystallizations of this material from methanol, after decolorization with carbon, gave 5.9 g. of 1,3-dimethyl-5-diazobarbituric acid (VIIa), m.p. 165–166° dec., λ_{max} 261 mμ (ε 13,800), λ_{max}^{KBr} 4.62, 5.81, 5.98, 6.75, 6.99, 7.21, 13.18, and 13.32 μ; (reported m.p. 165°).[9] The infrared spectrum of this material was identical with that of an authentic sample.[9]

Anal. Calcd. for $C_6H_6N_4O_3$: C, 39.57; H, 3.32; N, 30.77. Found: C, 39.90; H, 3.76; N, 30.68.

Elution of the column with a gradually increasing proportion of ethyl acetate in benzene was continued. Finally, elution with 75% ethyl acetate, 25% benzene gave 2.47 g. of the crude trione VIIIa, which after repeated crystallizations from ethyl acetate yielded pure 5,7-dimethylpyrimido[5,4-*d*][1,2,3]triazine-4,6,8-(3*H*,5*H*,7*H*)-trione, m.p. 202–203° dec.; λ_{max} 281 mμ (ε 8,350), 323 mμ (ε 7,350), $\lambda_{shoulder}$ 233 mμ (ε 4,820), 314 mμ (ε 7,080), λ_{min} 301 mμ (ε 6,150).

Anal. Calcd. for $C_7H_7N_5O_3$: C, 40.19; H, 3.37; N, 33.48. Found: C, 40.21; H, 3.23; N, 33.81.

1,3-Diethyl-5-diazobarbituric Acid (VIIb) and 5,7-Diethylpyrimido[5,4-*d*][1,2,3]triazine-4,6,8(3*H*,5*H*,7*H*)-trione (VIIIb).—5,7-Diethylpyrimido[5,4-*d*][1,2,3]triazine-6,8(5*H*,7*H*)-dione 3-oxide (IIb) (10.0 g.) and 100 ml. of thionyl chloride were stirred overnight at room temperature. The resulting solution was evaporated *in vacuo* and the residue chromatographed as described above. Elution of the column with 5% ethyl acetate in benzene yielded 6.25 g. of 1,3-diethyl-5-diazobarbituric acid (VIIb), which, after crystallization from petroleum ether (b.p. 28–38°), gave 5.3 g. of pure material, m.p. 54–55°; λ_{max} 261.5 mμ (ε 13,600); $\lambda_{max}^{CHCl_3}$ 4.59 and 4.64 μ.

Anal. Calcd. for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.80; N, 26.66. Found: C, 46.02; H, 4.99; N, 27.02.

Elution of the column with 25% ethyl acetate in benzene gave 1.032 g. of the triazinetrione VIIIb, m.p. 179–180° dec. Crystallization of this material from water raised its m.p. to 193–194° dec.; λ_{max} 282 mμ (ε 8,540), 323 mμ (ε 7,650), $\lambda_{shoulder}$ 315 mμ (ε 7,350).

Anal. Calcd. for $C_9H_{11}N_5O_3$: C, 45.57; H, 4.67; N, 29.53. Found: C, 45.71; H, 4.87; N, 29.13.

4-Chloro-5,7-dimethylpyrimido[5,4-*d*][1,2,3]triazine-6,8-(5*H*,7*H*)-dione (VIa).—A suspension of 70 g. of the triazine N-oxide IIa in 1400 ml. of thionyl chloride was stirred overnight. The resulting solution was evaporated *in vacuo* at a temperature not exceeding 35°. The residue (72 g.) consisted largely of the 4-chlorotriazine VIa contaminated with a small quantity of the diazobarbituric acid VIIa (infrared spectrum). Repeated crystallization of this material from benzene–ethyl acetate failed to raise the melting point above 154° (39 g.). Crystallization of a 10-g. portion of this product from 300 ml. of methanol made weakly basic with a few drops of 10% sodium hydroxide yielded 7.0 g. of 4-chloro-5,7-dimethylpyrimido[5,4-*d*][1,2,3]triazine-6,8(5*H*,7*H*)-dione (VIa), m.p. 161–162° dec. The analytical sample, m.p. 165–166° dec., λ_{max} 275 mμ (ε 9,780), $\lambda_{shoulder}$ 310 mμ (ε 4,380), was obtained by chromatography of 3.0 g. of this material on silica gel. A small quantity of the triazinetrione VIIIa was also eluted from the column.

Anal. Calcd. for $C_7H_5ClN_5O_2$: C, 36.93; H, 2.66; Cl, 15.58; N, 30.78. Found: C, 36.91; H, 2.84; Cl, 15.31, N, 30.61.

Hydrolysis of an analytically pure sample of 4-chloro-5,7-dimethylpyrimido[5,4-*d*][1,2,3]triazine-6,8(5*H*,7*H*)-dione (VIa) with boiling 5% hydrochloric acid for 1 min. produced a mixture of 1,3-dimethyl-5-diazobarbituric acid (VIIa) and 5,7-dimethylpyrimido[5,4-*d*][1,2,3]triazine-4,6,8(3*H*,5*H*,7*H*)-trione (VIIIa) (*ca.* 1 part VIIa:3 parts VIIIa). The products were identified by isolation of the pure materials and comparison (m.p., m.m.p., infrared spectra) with those produced above. Hydrocyanic acid was evolved from the hydrolysis (picric acid test).

4-Chloro-5,7-diethylpyrimido[5,4-*d*][1,2,3]triazine-6,8(5*H*,7*H*)-dione (VIb), m.p. 137–138° dec., λ_{max} 275 (ε 9,720), $\lambda_{shoulder}$ 310 (ε 4,390), was prepared by a similar process. The product was purified by crystallizations from ethyl acetate–ether.

Anal. Calcd. for $C_9H_{10}ClN_5O_2$: C, 42.28; H, 3.94; Cl, 13.87; N, 27.40. Found: C, 42.40; H, 4.09; Cl, 14.04; N, 27.25.

4-Methoxy-5,7-dimethylpyrimido[5,4-*d*][1,2,3]triazine-6,8-(5*H*,7*H*)-dione (Xa).—To a suspension of 1.1 g. of the 4-chloropyrimidotriazinedione VIa, m.p. 161–162° dec., in 50 ml. of methanol, cooled in an ice bath, was added a solution of 0.25 g. of sodium methoxide in 3 ml. of methanol. The reaction mixture was stirred for 15 min., the precipitate was separated by filtration, then crystallized from water. In this manner, 0.65 g. of the 4-methoxypyrimidotriazinedione Xa was obtained; m.p. 192–194° dec.; λ_{max} 274 mμ (ε 10,250), $\lambda_{shoulder}$ *ca.* 305 mμ (ε 5,580).

Anal. Calcd. for $C_8H_9N_5O_3$: C, 43.05; H, 4.06; N, 31.38. Found: C, 42.68; H, 3.76; N, 31.49.

3,5,7-Trimethylpyrimido[5,4,*d*][1,2,3]triazine-4,6,8(3*H*,5*H*,-7*H*)-trione (IXa).—To a suspension of 1.6 g. of 5,7-dimethylpyrimido[5,4-*d*][1,2,3]triazine-4,6,8-(3*H*,5*H*,7*H*)-trione (VIIIa) and 0.8 ml. of dimethyl sulfate in 20 ml. of methanol and 8 ml. of water was added, slowly and with stirring, 3.0 ml. of a 10% solution of sodium hydroxide in water. The clear solution that resulted was evaporated to a small volume, cooled, and the precipitate that resulted was separated by filtration. After two crystallizations from water, there was obtained 430 mg. of 3,5,7-trimethylpyrimido[5,4-*d*][1,2,3]triazine-4,6,8(3*H*,5*H*,7*H*)-trione (IXa), m.p. 174° dec.; λ_{max} 241 mμ (ε 6,430), 283.5 mμ (ε 7,510), 323 mμ (ε 7,940), $\lambda_{shoulder}$ 314 mμ (ε 7,140), λ_{min} 301 mμ (ε 5,900).

Anal. Calcd. for $C_8H_9N_5O_3$: C, 43.05; H, 4.06; N, 31.38. Found: C, 43.08; H, 4.02; N, 31.21.

Pyrimido[5,4-*d*][1,2,3]triazine-6,8(5*H*,7*H*)-dione 3-oxide (II), m.p. 232° dec. (reported m.p. 239° dec., 245° dec.),[3b] λ_{max} 256.5 mμ (ε 31,900), $\lambda_{inflection}$ *ca.* 280 mμ (ε 14,700), $\lambda_{shoulder}$ 330 mμ (ε 2,540), was prepared by the method described by Rose.[3b]

Anal. Calcd. for $C_5H_3N_5O_3 \cdot H_2O$: C, 30.16; H, 2.53; N, 35.17. Found: C, 30.15; H, 2.57; N, 35.33.

The anhydrous material was also prepared by the method described by Rose.[3b]

Anal. Calcd. for $C_5H_3N_5O_3$: C, 33.16; H, 1.67; N, 38.67. Found: C, 33.00; H, 1.46; N, 38.61.