colorless crystals, m.p. 169–171° dec. Elemental analyses corresponded to that of an alcoholate of the desired tosylate ester. An infrared absorption spectrum obtained in potassum bromide did not show a peak at 9.1 μ, the major absorption band of 4-cyanoformyl-1-methylpyridinium chloride oxime (V). This would eliminate the possibility that appreciable alcoholysis of *p*-toluenesulfonyl chloride occurred to give V as an impurity.

Anal. Calcd. for $C_{15}H_{14}ClN_3S\cdot 1.9CH_3OH$; C, 49.2; H, 5.2. Found: C, 49.2; H, 5.2.

O-Benzoyl-4-cyanoformyl-1-methylpyridinium Iodide Oxime XI.—To 1.0 g. (0.004 mole) of 4-pyridylglyoxylonitrile oxime benzoate[10] in 15 ml. of acetone was added 5 ml. of methyl iodide. The solution was allowed to stand for 2 days, then filtered to give 1.0 g. (63.6%) of orange-red needles, m.p. 137° dec.[1] An infrared absorption spectrum obtained in potassium bromide corresponded closely to that of IX.

Anal. Calcd. for $C_{15}H_{12}IN_3O_2$: C, 45.8; H, 3.1; I, 32.3. Found: C, 45.7; H, 3.2; I, 32.3.

Attempted Recrystallization of 4-Cyanoformyl-1-methylpyridinium Iodide Oxime from Benzene–Methanol and Toluene–Methanol.—To 1.0 g. of I dissolved in the minimum amount of hot methanol was added benzene dropwise until cloudiness was observed. The solution was kept hot during the addition. On allowing the solution to cool to room temperature an orange-brown solid precipitated, m.p. 184–189° dec.

Anal. Calcd. for $C_8H_8IN_3O\cdot C_6H_6$: I, 34.4; N, 11.4. Found: I, 34.4; N, 11.1.

The previous procedure was repeated using toluene to give XI, m.p. 193–196° dec. (an infrared absorption spectrum obtained in potassium bromide corresponded to this of an authentic sample of XI).

Anal. Calcd. for $C_{16}H_{15}I_3N_6O_2$: C, 27.3; H, 2.2; I, 54.1; N, 11.9. Found: C, 27.4; H, 2.4; I, 52.9; N, 11.9.

Synthesis of the benzene solvate was not reproducible and evidence for iodide oxidation also was obtained.

Acknowledgment.—Elemental analyses were performed by the Analytical Research Branch, U. S. Army Chemical Research and Development Laboratory.

(10) E. J. Poziomek, unpublished results.

Pyrano[2,3-*d*]- and Pyrido[2,3-*d*]pyrimidines

HOMER C. SCARBOROUGH

Department of Organic Chemistry, Mead Johnson Research Center, Evansville, Indiana

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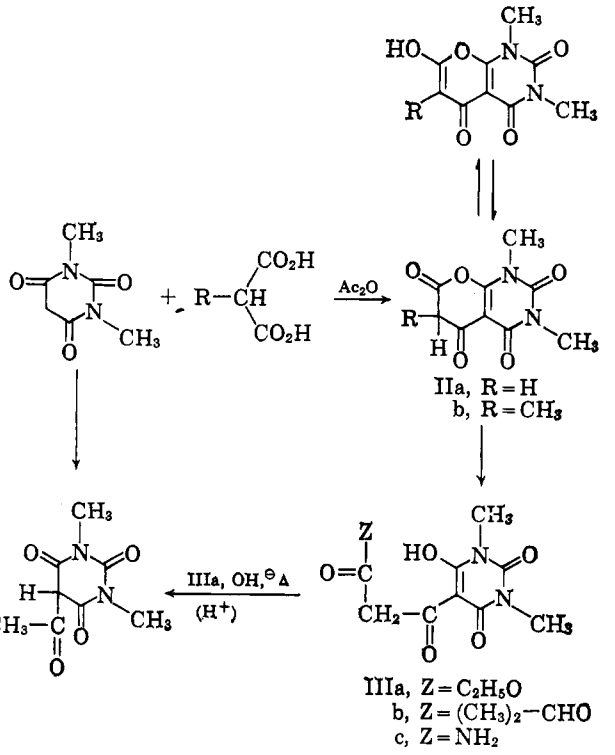
Pyrano[2,3-*d*]- and pyrido[2,3-*d*]pyrimidines in which the pyrano or pyrido ring incorporates an enolizable 1,3-dicarbonyl system have been investigated. These compounds were desired because of their acidic hydrogen which might be functionally analogous to that of the imidazole ring of xanthines.

The pyranopyrimidines were prepared by the condensation of malonic acid or methylmalonic acid with 1,3-dimethylbarbituric acid in the presence of acetic anhydride. A related 1,3-diphenyl-2-thiopyrano[2,3-*d*]pyrimidine has been prepared by the condensation of malonyl dichloride with 1,3-diphenyl-2-thiobarbituric acid.[1]

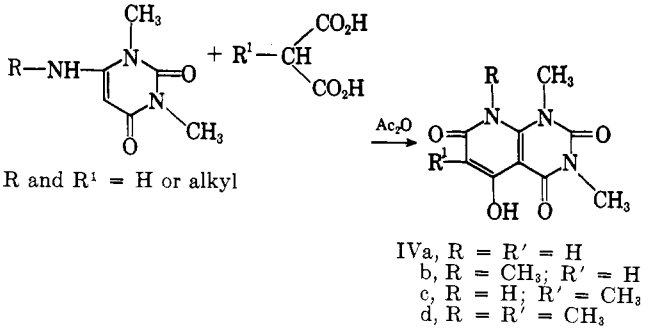
Earlier workers postulated the existence of compound IIa in rationalizing the isolation of IIIa accompanying the synthesis of 1,3-dimethylbarbituric acid.[1] We found that the lactone function of compound IIa was indeed chemically reactive although both IIa and IIb were hydrolytically stable during isolation.



Compound IIa reacted readily with ethanol to form IIIa and with isopropyl alcohol to form IIIb. The isopropyl ester IIIb also was obtained upon attempted recrystallization of IIa from isopropyl acetate. The reaction of IIa with aqueous ammonium hydroxide furnished the amide (IIIc). Compound IIa was precipitated unchanged after standing in 0.1 *N* aqueous sodium hydroxide at 25° for 0.5 hr. The compounds were insoluble in 10% aqueous sodium carbonate solution.

When the ester (IIIa) was heated with aqueous sodium hydroxide and the solution acidified, 5-acetyl-1,3-dimethylbarbituric acid was obtained in 90% yield. The latter was identical with the product obtained from the reaction of 1,3-dimethylbarbituric acid with acetic anhydride.

The pyridopyrimidines were obtained when 4-amino-1,3-dimethyluracils were acylated with malonic acid or alkyl malonic acids in the presence of acetic anhydride. These pyrido[2,3-*d*]pyrimidines (IV) are listed in Table I. Since this work was completed, compound IVa has been reported in 17% yield from a malonic acid preparation using phosphorus oxychloride as condensing agent.[3] No structural proof for IVa was presented.[3]



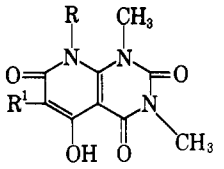
(1) H. Schulte, *Ber.*, **87**, 820 (1954).

(2) J. W. Clark-Lewis and M. J. Thompson, *J. Chem. Soc.*, 1628 (1959).

(3) E. Ziegler and E. Nolken, *Monatsh.*, **92**, 1184 (1961).

TABLE I

5-HYDROXYPYRIDO[2,3-*d*]PYRIMIDINE-2,4,7-1*H*,3*H*,8*H*-TRIONES

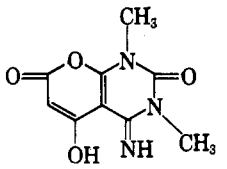


	R	R¹	M.p., °C.	Yield,[a] %	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IVa	H	H[b]	280–282.5[b]	45 (cd, e)	$C_9H_9N_3O_4$	48.43	4.06	18.83	48.48	4.11	18.91
IVb	CH_3	H	220.5–222	46.5 (b, c)	$C_{10}H_{11}N_3O_4$	50.63	4.67	17.72	50.64	4.66	17.68
IVc	H	CH_3	287.5–289.5	58 (d, b)	$C_{10}H_{11}N_3O_4$	50.63	4.67	17.72	50.91	4.76	17.82
IVd	CH_3	CH_3	259.5–260.5	48 (b)	$C_{11}H_{13}N_3O_4$	52.58	5.22	16.73	52.66	5.22	16.90
IVe	H	$CH_3(CH_2)_2CH_2$	195–196	24 (b)	$C_{13}H_{17}N_3O_4$	55.90	6.14	15.05	55.55	6.27	15.19
IVf	CH_3	$CH_3(CH_2)_2CH_2$	119–120	38 (f, ga)	$C_{14}H_{19}N_3O_4$	57.32	6.53	14.33	57.14	6.48	14.21

[a] Yields are of analytically pure material recrystallized from a, heptane; b, acetonitrile; c, butanone; d, dimethylformamide; e, acetic acid; f, methyl alcohol; g, benzene. [b] Reference 3 reports 270°.

That the pyrido[2,3-*d*]pyrimidines had the tautomeric structure IV was shown by examination of the n.m.r. spectra of IVa, b, c, and d in dimethyl sulfoxide. Compounds IVa and IVb exhibit singlets comprising one olefinic proton (358 and 338 c.p.s.)[4] while the 6-methyl groupings of IVc and IVd absorbed as singlets contiguous with a double bond (115 and 113 c.p.s.). All spectra exhibited one hydroxyl proton (745 c.p.s.) that was intramolecularly bonded as shown by the low value for the chemical shift which was unchanged on dilution. The structure represented by IV is the only tautomer capable of intramolecular hydrogen bonding.

An isomeric structure represented by V can be eliminated with consideration of the previously reported N,5-diacetylation of 1,3-dimethyl-4-methylaminouracil.[5]



V

In addition, the chemical shift in dimethyl sulfoxide to 720 c.p.s. establishes the presence of an amide hydrogen for IVa and IVc. The amide hydrogen of these compounds exchanged with trifluoroacetic acid.

Experimental[6]

1,3-Dimethyl-6*H*-pyrano[2,3-*d*]pyrimidine-2,4,5,7-1*H*,3*H*,6*H*-tetrone (Ia).—A mixture of 7.8 g. (0.05 mole) of 1,3-dimethylbarbituric acid,[2] 6.3 g. (0.06 mole) of malonic acid, 11.3 ml. (0.12 mole) of acetic anhydride, and 5 ml. of acetic acid was heated at 80° for 3 hr. to furnish a dark reddish brown solution. The solution was cooled and diluted to 100 ml. with water. The orange solid which separated upon storage at 0° was collected, dried, and recrystallized two times from butanone. There was obtained 4 g. (33%) of lustrous white plates, m.p. 192–194°.

Anal. Calcd. for $C_9H_8N_2O_5$: C, 48.22; H, 3.60; N, 12.50. Found: C, 48.08; H, 3.90; N, 12.89.

1,3,6-Trimethyl-6*H*-pyrano[2,3-*d*]pyrimidine-2,4,5,7-1*H*,3*H*,-6*H*-tetrone (Ib).—A mixture of 7.8 g. (0.05 mole) of 1,3-dimethylbarbituric acid, 7.1 g. (0.06 mole) of methylmalonic acid,[7] 11.3 ml. of acetic anhydride, and 5 ml. of acetic acid was warmed to give a solution which was allowed to stand at 25° for 16 hr. The solution was then heated on the steam bath for 7 hr., a crystalline solid separating from the reaction solution after 3 hr. The solid product collected after cooling the reaction mixture was recrystallized from butanone and from acetonitrile to furnish 5.1 g. (43%) of material, m.p. 236–237.5°. In the 5–7- and 8–9-μ region, absorption peaks were observed at 5.67, 5.80, 5.95, 6.30, 6.60, 6.85 (weak), 8.05 (shoulder), 8.15, and 8.35 μ (0.5% in KBr).

Anal. Calcd. for $C_{10}H_{10}N_2O_5$: C, 50.52; H, 4.23; N, 11.76. Found: C, 50.52; H, 4.34; N, 11.84.

1,3-Dimethyl-5-ethoxycarbonylacetylbarbituric Acid (IIIa).—A solution of 2.24 (0.01 mole) of compound Ia in 75 ml. of absolute ethyl alcohol was concentrated on a hot plate to half volume and then chilled. The product was collected and recrystallized from absolute ethyl alcohol to furnish 2.6 g. (96%) of a white crystalline solid, m.p. 110.5–111°, lit.[2] m.p. 112°.

Anal. Calcd. for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.22; N, 10.37. Found: C, 48.83; H, 5.23; N, 10.38.

1,3-Dimethyl-5-isopropoxycarbonylacetylbarbituric Acid (IIIb).—A solution of 1.12 g. (0.005 mole) of compound Ia in 15 ml. of isopropyl alcohol was heated to boiling. The solution was cooled and diluted with heptane. The solid which separated upon cooling was collected and recrystallized from cyclohexane to furnish 1.3 g. (92%) of a white crystalline solid, m.p. 73–74.5°. The same material separated when compound Ia was dissolved in hot isopropyl acetate.

Anal. Calcd. for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.86. Found: C, 50.83; H, 5.60; N, 9.66.

5-Aminocarbonylacetyl-1,3-dimethylbarbituric Acid (IIIc).—To 4.5 g. (0.02 mole) of compound Ia was added 50 ml. of concentrated ammonium hydroxide. A bulky white solid was obtained in a few minutes. The solid was collected, rinsed with acetone, and recrystallized from acetic acid and from butanone. There was obtained 3.5 g. (73%) of a white crystalline solid, m.p. 176–178° dec. (gas).

Anal. Calcd. for $C_9H_{11}N_3O_5$: C, 44.81; H, 4.60; N, 17.42. Found: C, 44.73; H, 4.55; N, 17.65.

5-Acetyl-1,3-dimethylbarbituric Acid.—A solution of 1 g. of compound Ia in 20 ml. of 10% aqueous sodium hydroxide was boiled for 10 min. The white solid which precipitated upon acidification of the cooled solution was collected, dried, and recrystallized from cyclohexane to furnish 0.8 g. (90%) of white product, m.p. 96.5–98.5°. A mixture melting point of this product with that prepared by the reaction of 1,3-dimethylbarbituric acid with acetic anhydride showed no depression.

5-Hydroxy-1,3,6,8-tetramethylpyrido[2,3-*d*]pyrimidine-2,4,7-1*H*,3*H*,8*H*-trione (IVd).—A mixture of 8.45 g. (0.05 mole) of 1,3-dimethyl-4-methylaminouracil,[8] 7.1 g. of methylmalonic acid,[7] 11.3 ml. of acetic anhydride, and 10 ml. of acetic acid was heated on the steam bath for 2 hr. During this time the suspended material dissolved and the solution boiled gently. The solution was then cooled in an ice bath and the crystallized product collected

(4) The absorption frequencies were observed at 60 Mc. with respect to internal tetramethylsilane.

(5) W. Pfleiderer and G. Strauss, *Ann.*, **612**, 173 (1958).

(6) Microanalyses were performed by Mr. Clarence Kennedy, Mead Johnson Research Center.

(7) J. N. Norris and H. F. Tucker, *J. Am. Chem. Soc.*, **55**, 4697 (1933).

(8) W. Pfleiderer and K. H. Schundehutte, *Ann.*, **612**, 158 (1958).

by filtration. The method of purification and physical data are listed in Table I.

The other pyridopyrimidines were prepared in a similar manner and are listed in Table I. The compounds are precipitated unchanged by the addition of acid to solutions in 5% aqueous sodium hydroxide. They are insoluble in 10% aqueous sodium carbonate solution.

Attempted Preparation of 6,6-Disubstituted Products.—5-Acetyl-1,3-dimethylbarbituric acid was obtained in 95% yield when diethylmalonic acid and acetic anhydride were heated with 1,3-dimethylbarbituric acid. No discrete products could be isolated from the reaction of diethylmalonic acid and acetic anhydride with 4-amino-1,3-dimethyluracil. The reaction of diethylmalonyl dichloride with 4-amino-1,3-dimethyluracil in dimethylformamide furnished 4-amino-1,3-dimethyl-5-formyluracil. The latter also has been prepared by the reaction of formic acetic anhydride with 4-amino-1,3-dimethyluracil.[5]

Acknowledgment.—The author is indebted to Mr. Charles Combs of the Mead Johnson Research Center for the n.m.r. data. Certain of the intermediates were prepared by Dr. T. A. Martin and Mr. D. H. Causey.

Decomposition of Dimethyl Sulfoxide Aided by Ethylene Glycol, Acetamide, and Related Compounds[1]

VINCENT J. TRAYNELIS AND WILLIAM L. HERGENROTHER[2]

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana

Received July 26, 1963

Dimethyl sulfoxide appears to be thermally quite stable but upon prolonged reflux it does decompose slightly to methyl mercaptan and bismethylthiomethane.[3] This decomposition is aided by acids and retarded by many bases. Nace and Monagle[4] reported the appearance of dimethyl sulfide, methyl mercaptan, and dimethyl disulfide during the reaction of primary halides with dimethyl sulfoxide and, if precautions were not taken to remove the acid produced in this reaction, large amounts of formaldehyde also were formed. The acid-catalyzed cleavage of sulfoxides recently was discussed by Kenney, Walsh, and Davenport[5] and generally results in the reduction of sulfur to a mercaptan and the oxidation of the α-carbon to a carbonyl group. Subsequent reactions of these initial products may result. An alternate path for the decomposition of dimethyl sulfoxide involves disproportionation to dimethyl sulfone and dimethyl sulfide which requires osmium tetroxide as a catalyst.[6]

In our investigations of the dehydration of alcohols in dimethyl sulfoxide,[7] which required elevated temperatures for substantial periods of time, we have noted a number of dimethyl sulfoxide decomposition products. This report summarizes our observations on the thermal decomposition of dimethyl sulfoxide and the effect of certain glycols and amides on this cleavage.

When dimethyl sulfoxide was refluxed for 3 days, 3.7% of volatile material was collected and consisted of paraformaldehyde (1.9%), dimethyl sulfide, dimethyl disulfide, bismethylthiomethane, and water. The dimethyl sulfoxide residue contained a small amount of dimethyl sulfone. These results can be rationalized by the following series of equations.

$$(CH_3)_2SO \longrightarrow CH_3SH + CH_2O \longrightarrow \text{paraformaldehyde}$$

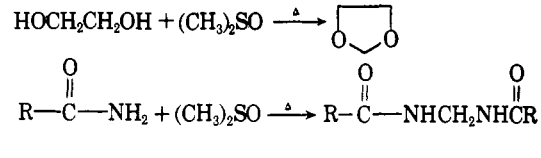
$$2CH_3SH + CH_2O \longrightarrow (CH_3S)_2CH_2 + H_2O$$

$$2CH_3SH + (CH_3)_2SO \longrightarrow CH_3SSCH_3 + CH_3SCH_3 + H_2O$$

$$2(CH_3)_2SO \longrightarrow CH_3SO_2CH_3 + CH_3SCH_3$$

The nature of the initial cleavage reaction is not clear at this time.

A variety of diols when heated in dimethyl sulfoxide undergo dehydration[7b]; however, purified ethylene glycol, heated in refluxing dimethyl sulfoxide for 3 days, promoted the previous cleavage reaction and gave dimethyl sulfide (16% isolated), dimethyl disulfide (19% isolated), and some bismethylthiomethane. The formaldehyde generated reacted with ethylene glycol to produce 1,3-dioxolane (54%). In a similar manner 1,2-propanediol and 1,3-propanediol promoted the cleavage reaction and were converted to 4-methyl-1,3-dioxolane (71% purified) and 1,3-dioxane (64% purified), respectively.



An increase in decomposition products also was observed when acetamide or benzamide was heated in dimethyl sulfoxide at 190° for 36 hr. The formaldehyde liberated combined with these amides to produce methylenebisacetamide (55%) and methylenebisbenzamide (60%). When acetanilide was subjected to the prior reaction conditions, only 7% of volatile materials was collected and 89% unchanged acetanilide was recovered.

The methylenebisamides and the dioxa heterocycles are usually prepared by an acid-catalyzed reaction of formaldehyde with nitriles[8] or amides[9] and with the appropriate diol.[10] The results in this work suggest the possible use of dimethyl sulfoxide in promoting these condensation reactions of formaldehyde and possibly other carbonyl compounds. One experiment in support of this was the reaction of benzamide and paraformaldehyde in dimethyl sulfoxide to form methylenebisbenzamide (63%) in 9 hr.

Although it appeared, in the previous reactions, that dimethyl sulfoxide decomposed into methyl mercaptan and formaldehyde which then reacted with the glycols or amides, we have not excluded the possibility of some interaction of the diols or amides directly with dimethyl

(1) Acknowledgment is made to the donors of the Petroleum Research Fund administered by the American Chemical Society for support of this research.

(2) Abstracted from part of the Ph.D. dissertation of W. L. H., July, 1963.

(3) "Dimethyl Sulfoxide Technical Bulletin," issued by Crown Zellerbach-Corp., Camas, Wash.

(4) H. R. Nace and J. J. Monagle, *J. Org. Chem.*, **24**, 1792 (1959).

(5) W. J. Kenney, J. A. Walsh, and D. A. Davenport, *J. Am. Chem. Soc.*, **83**, 4019 (1961). This paper reviews the literature of this cleavage.

(6) H. R. Davis, Jr., and D. P. Sorensen, U. S. Patent 2,870,215 (January 20, 1959); *Chem. Abstr.*, **53**, 11416*i* (1959).

(7) (a) V. J. Traynelis, W. L. Hergenrother, J. R. Livingston, and J. A. Valicenti, *J. Org. Chem.*, **27**, 2377 (1962); (b) V. J. Traynelis, W. L. Hergenrother, and in part H. T. Hanson and T. A. Valicenti, *ibid.*, **29**, 123 (1964).

(8) E. E. Magat, B. F. Faris, J. E. Reith, and L. F. Salisbury, *J. Am. Chem. Soc.*, **73**, 1028 (1951). Other references cited in this report.

(9) G. Pulvermacher, *Ber.*, **25**, 310 (1892).

(10) H. T. Clarke, *J. Chem. Soc.*, **101**, 1804 (1912).