Trimethyl Heptafluoroorthothiobutyrate.—Reaction involving 11.5 g. of ethyl heptafluorobutyrthioimidate with an excess of methyl mercaptan was carried out in accordance with the procedure described for the proceeding orthothioester. The yield of pure trimethyl heptafluoroorthothiobutyrate was 4 g. (27%), b.p. 111° at 0.7 mm.

Anal. Calcd. for $C_7H_9F_7S_3$: C, 26.06; H, 2.79; S, 29.81; F, 41.30. Found: C, 25.83; H, 3.05; S, 29.53; F, 41.17.

Trimethyl Pentafluoroorthothiopropionate.—Reaction of 6 g. of methyl pentafluoropropionthioimidate with methyl mercaptan under conditions described for the first compound of this series of orthothioesters gave 2 g. (25% yield) of pure trimethyl pentafluoroorthothiopropionate, b.p. 86° at 0.7 mm.

Anal. Calcd. for $C_6H_9F_5S_3$: C, 26.44; H, 3.30; S, 35.25; F, 34.92. Found: C, 26.69; H, 3.61; S, 35.44; F, 35.02.

Pyrido[2,3-*d*]pyrimidines from Malonaldehydes[1]

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The product from the condensation of 2,4-diamino-6-hydroxypyrimidine with nitromalonaldehyde has now been shown to be 2-amino-4-hydroxy-6-nitropyrido[2,3-*d*]pyrimidine (I). A number of analogs and derivatives have been prepared but various efforts to convert several of these to the folic acid analog failed.

Further investigation of the product formed readily by condensation of nitromalonaldehyde with 2,4-diamino-6-hydroxypyrimidine[2] has shown it to be 2-amino-4-hydroxy-6-nitropyrido[2,3-*d*]-pyrimidine (I). Evidence in support of this structure and the preparation and characterization of a number of related compounds is presented.

Experimental[3]

2-Amino-4-hydroxy-6-nitropyrido[2,3-*d*]pyrimidine (II).—A mixture of 12.6 g. of 2,4-diamino-6-hydroxypyrimidine (I)[4] and 15.7 g. of sodium nitromalonaldehyde monohydrate[5] in 100 ml. of 1% alkali was refluxed vigorously for 1 hr. On chilling to 5°, a voluminous mass of yellow needles separated, 18.4 g. (75%). Recrystallization from aqueous alkali gave samples of the sodium salt which tenaciously held from 0.5 to 2.5 moles of water.

Anal. Calcd. for $C_7H_4O_3N_5Na \cdot {}^1/_2H_2O$: C, 35.30; H, 2.12; N, 29.41. Found: C, 35.78; H, 2.69; N, 30.33.

A 5.9-g. sample of this material was dissolved in 800 ml. of boiling 20% hydrochloric acid and filtered hot through glass wool. On cooling, green-tan needles separated, 3.6 g. (73%).

Anal. Calcd. for $C_7H_5O_3N_5$: C, 40.58; H, 2.43; N, 33.81. Found: C, 40.32; H, 2.56; N, 34.11.

The acetyl derivative of II was prepared by refluxing 0.21 g. of II in 20 ml. of acetic anhydride for 2.5 hr. On cooling, 0.17 g. of white crystals separated, which were recrystallized from ethanol, m.p. 320° dec.

Anal. Calcd. for $C_9H_7O_4N_5$: C, 43.38; H, 2.83; N, 28.11. Found: C, 43.72; H, 2.90; N, 28.47.

2,6-Diamino-4-hydroxypyrido[2,3-*d*]pyrimidine (III).—A mixture of 3.6 g. of II and 7.9 g. of stannous chloride was refluxed vigorously in 40 ml. of 20% hydrochloric acid for 45 min. The dark solution was diluted to 650 ml. and, at 60°, gaseous hydrogen sulfide was passed in for 1.5 hr. After filtration the clear, green fluorescent filtrate was evaporated to 150 ml. and neutralized with excess solid sodium bicarbonate, precipitating 2.0 g. (65%) of orange-yellow solid, which was recrystallized from dilute sodium bicarbonate.

Anal. Calcd. for $C_7H_7ON_5$: C, 47.45; H, 3.69; N, 39.53. Found: C, 47.25; H. 4.15; N, 39.23.

The *diacetyl* derivative was prepared by refluxing 0.19 g. of III in 15 ml. of acetic anhydride for 20 hr. The resulting white solid was recrystallized from a large volume of water.

Anal. Calcd. for $C_{11}H_{13}O_3N_5$: C, 50.18; H, 4.98; N, 26.61. Found: C, 50.03; H, 4.58; N, 27.15.

The *6-N-formyl* derivative was prepared by boiling 1.0 g. of III in 20 ml. of 98% formic acid until it was concentrated to 5 ml. On dilution with 20 ml. of water, a pale yellow solid precipitated. It was purified by reprecipitation from formic acid solution.

Anal. Calcd. for $C_8H_7O_2N_5 \cdot {}^1/_2H_2O$: C, 44.86; H, 3.77; N, 33.46. Found: C, 44.81; H, 4.03; N, 33.29, 32.68.

2-Amino-4-hydroxy-6-(*p*-dimethylaminophenylazo)pyrido-[2,3-*d*]pyrimidine (IV).—A suspension of 0.48 g. of III in 15 ml. of 20% hydrochloric acid was prepared by chilling a hot solution to 3–5°. On adding 0.17 mg. of sodium nitrite in 5 ml. of water dropwise with cooling, the amine first dissolved and then the diazonium salt precipitated. A solution of 0.30 g. of dimethylaniline in 10 ml. of 1.5% hydrochloric acid and 25 ml. of 36% aqueous sodium acetate were added simultaneously to the diazonium salt suspension. After standing overnight, the deep red crystalline solid (0.48 g., 57%) was collected and recrystallized from dimethylformamide.

Anal. Calcd. for $C_{15}H_{15}ON_7$: C, 58.24; H, 4.89; N, 31.70. Found: C, 57.94; H, 5.23; N, 31.62.

2-Amino-4-hydroxypyrido[2,3-*d*]pyrimidine (V). A. By Deamination of III.—A diazonium salt suspension was prepared as above from 1.2 g. of III and 3.5 g. of sodium hypophosphite monohydrate in 30 ml. of cold water was added. The mixture was stirred for 1 hr. at 5° and 1 hr. at 25°. After filtration, the solution was diluted with 2 volumes of water and neutralized with excess sodium bicarbonate precipitating 0.91 g. (83%) of dark solid. It was purified by recrystallization from dilute aqueous sodium bicarbonate; the solutions fluoresced sky blue under ultraviolet light.

Anal. Calcd. for $C_7H_6ON_4 \cdot H_2O$: D, 46.67; H. 4.48; N, 31.10. Found: C, 47.38; H, 4.16; N, 31.70.

The water was not lost even on prolonged exposure at 110° (0.1 mm.). The same product was obtained from the diazonium salt in ethanol, although in poorer yield.

The *acetate* was prepared by refluxing 0.27 g. of V in 20 ml.

(1) Abstracted largely from the Ph.D. dissertation of Raffaele Bernetti (1959).

(2) T. L. V. Ulbricht and C. C. Price, *J. Org. Chem.*, **22**, 235 (1957).

(3) Melting points are uncorrected; if none is given the compound did not melt below 300°. Analyses by Midwest Microlab and Galbraith.

(4) B. Roth, M. R. Hultquist, and J. M. Smith, *J. Am. Chem. Soc.*, **72**, 1915 (1950).

(5) P. E. Fanta, *Org. Syn.*, **32**, 95 (1952).

of acetic anhydride for 3.5 hr. The solution was filtered hot and, on cooling, yielded white crystalline solid, which was recrystallized from ethoxyethanol.

Anal. Calcd. for $C_9H_8O_2N_4$: C, 52.94; H, 4.14; N, 28.08. Found: C, 52.68; H, 4.17; N, 27.77.

B. From Methyl 2-Aminonicotinate and Guanidine.—To a solution of 1 g. of sodium in absolute ethanol, 1.5 g. of guanidine hydrochloride was added and the precipitated sodium chloride was removed by filtration. Then, 2.1 g. of methyl 2-aminonicotinate[6] was added and the mixture was refluxed for 7 hr. After cooling, the supernatant alcohol was decanted from a white precipitate, which was then dissolved in 50 ml. of water. Addition of acetic acid gave 0.94 g. (42%) of gelatinous precipitate which was recrystallized from dilute aqueous sodium bicarbonate.

Anal. Found: C, 47.75, 48.09; H, 4.14, 4.31; N, 32.10, 32.24.

The *O-acetate* was recrystallized from ethoxyethanol.

Anal. Found: C, 52.71; H, 4.18; N, 27.87.

C. From I and Malonaldehyde Tetramethyl Acetal.—A hot filtered solution of 5.6 g. of I in 200 ml. of water and 0.5 ml. of acetic acid was treated with 3.8 g. of malonaldehyde tetramethyl acetal and 50 ml. of water. The solution was heated at 95° for 3 hr. Colorless needles began to separate in 30 min. and were collected from the chilled reaction mixture, 5.5 g. (86%). This *dianil* was recrystallized twice from 10% aqueous sodium bicarbonate.

Anal. Calcd. for $C_{11}H_{12}O_2N_8 \cdot H_2O$: C, 43.13; H, 4.61; N, 36.59. Found: C, 43.05; H, 4.49; N, 36.64.

The dianil (1.0 g.) dissolved rapidly in 10 ml. of concentrated sulfuric acid. The brown solution was heated to 160° for 2 hr., cooled, poured onto crushed ice, and diluted to 150 ml. The solution was gradually neutralized with sodium bicarbonate. A dark precipitate which separated at pH 3 was discarded. Further addition of bicarbonate precipitated a white solid, 0.42 g. (73%), identical in infrared spectra to the two samples of V described above. The *acetate* was also identical in infrared spectrum.

The three samples of V also had identical X-ray patterns with the following spacings (in Å., ±0.02 Å.): 9.40(w), 6.65(s), 5.91(m), 4.87(w), 4.67(m), 3.91(vw), 3.64(m), 3.47(vw), 3.36(vw), 3.26(vs), 2.32(s), 1.84(vw).

2-Amino-4-hydroxy-6-iodopyrido[2,3-*d*]pyrimidine (VI).—To a suspension of diazonium salt from 1.0 g. of III, 1.16 g. of potassium iodide in 10 ml. of water was added. After stirring for 20 min., the iodine was destroyed by saturated sodium bisulfite. The light brown solid was collected (1.3 g., 80%) and recrystallized from 5% aqueous sodium bicarbonate.

Anal. Calcd. for $C_7H_5ON_4I$: C, 29.18; H, 1.74; N, 19.45; I, 44.07. Found: C, 29.32; H, 2.52, N, 20.38; I, 42.95.

2-Amino-4-hydroxy-6-carbethoxypyrido[2,3-*d*]pyrimidine (VII).—A mixture of 1.8 g. of I and 2.0 g. of carbethoxymalonaldehyde[7] in 15 ml. of 2% alkali was heated at 130° for 1.5 hr. After standing overnight, the yellow solid (1.95 g., 62%) was collected and recrystallized from glacial acetic acid to give a white powder, m.p. 328–331°.

Anal. Calcd. for $C_{10}H_{10}O_3N_4$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.16; H, 4.34; N, 24.04.

2-Amino-4-hydroxy-6-carboxypyrido[2,3-*d*]pyrimidine (VIII).—The same reactants heated in 25 ml. of 6% alkali gave a clear red solution which, on acidification with glacial acetic acid, gave an amorphous solid, 1.2 g. (45%). The *hydrochloride* was prepared by dissolving in dilute hydrochloric acid and then saturating with hydrogen chloride gas to precipitate yellow crystals.

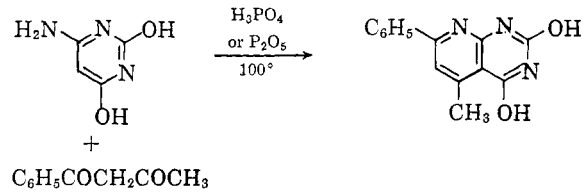
Anal. Calcd. for $C_8H_7O_3N_4Cl \cdot {}^1/_2H_2O$: C, 38.20; H, 3.10; N, 22.27; Cl, 14.10. Found: C, 38.37; H, 3.21; N, 22.13; Cl, 13.80.

(6) L. Klisiecki and E. Sucharda, *Roczniki Chem.*, **3**, 251 (1923); *Chem. Abstr.*, **19**, 72 (1925).

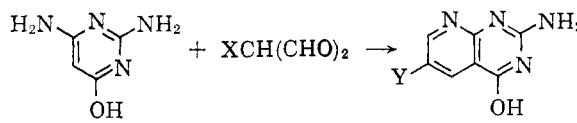
(7) L. Panizzi, *Gazz. chim. ital.*, **76**, 56 (1946).

Discussion

It was proposed by Ridi and Checchi[8] and confirmed by Robins and Hitchings[9] that 2,4 - dihydroxy-6-aminopyrimidine condenses with 1,3-dicarbonyl compounds to produce pyrido[2,3-*d*]-pyrimidine derivatives.



The presence of such a ring system in the condensation product of I with nitromalonaldehyde was indicated by the presence of a nitro group (infrared spectra) in II, by its reduction to generate a diazotizable aromatic amine (III), and by the replacement of this amine by hydrogen to produce V. Evidently the nitro group in the dialdehyde facilitates the condensation so that it occurs under



X = NO_2, H, CO_2Et

II. Y = NO_2
III. Y = NH_2
IV. Y = $N{=}NC_6H_4NMe_2$
V. Y = H
VI. Y = I
VII. Y = CO_2Et
VIII. Y = CO_2H

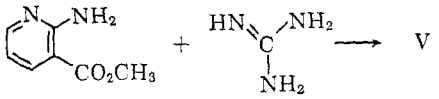
TABLE I

ULTRAVIOLET ABSORPTION SPECTRA DATA

Compound	in 0.1 *N*	λ_{max}	log ε	λ_{min}	log ε
II	NaOH	363	4.17	299	3.65
		263	3.89	244	3.80
		224	4.10		
III	NaOH	361	3.75	300	2.98
		271	3.88	261	3.97
		234	4.26		
	HCl	360	3.30	328	3.12
		279	3.84	260	3.74
		239(sh)	3.96		
III(Ac)$_2$	HCl	359	3.89	321	3.62
		287	4.22	245	3.75
V	NaOH	329	3.80	286	3.28
		264	3.87	255	3.83
		239	4.26		
	HCl	343	3.80	287	3.24
		272	3.98	253	3.70
		236	3.79		
V(Ac)	HCl	305	4.00	244	3.34
VI	NaOH	342.6	3.68	300	3.05
		283	3.94	264.5	3.88
		246	4.13		
VII	NaOH	330.7	3.88	306.1	3.69
		287	4.02	267	3.77
		246	4.17		
VIII	NaOH	330.7	3.85	307	3.69
		283.7	3.99	267.3	3.77
		243	4.10		

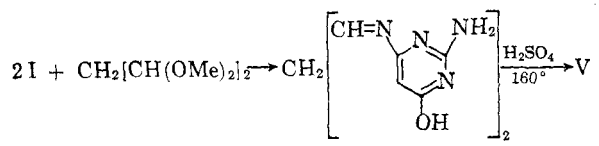
far milder conditions than those reported earlier for other 1,3-dicarbonyl compounds.[8,9]

The structure of V was confirmed by its synthesis from guanidine and methyl 2-aminonicotinate



The formation of V from both a pyridine and a pyrimidine can leave little doubt as to the structure assigned to V.

V was also synthesized from I and malonaldehyde (X = H, as its tetramethyl acetal). In this case, the primary product appeared to be the dianil,[10] which was converted to V by hot concentrated sulfuric acid.



Incidentally, the stability of V in concentrated sulfuric acid is quite remarkable; 50% of it is recovered unchanged after 20 minutes at 260°. This indicates a considerably greater stability than for the pteridine ring system.[11]

While the 6-amino group of III was successfully diazotized and replaced by hydrogen or iodine, numerous efforts to obtain the 6-cyano compound were unsuccessful. Either the compound was not formed or was so intractable as to defy our efforts to isolate and characterize it.

Our efforts to introduce a carbon function at the 6-position which might be used for the synthesis of the folic acid analog then turned to the malonaldehyde with X = CO_2Et. Condensation with I appeared to proceed normally to give products with ultraviolet spectra in accord with the assignment of a pyrido[2,3-*d*]pyrimidine structure (see Table I). All of our efforts to convert either the 6-carbethoxy (VII) or 6-carboxy (VIII) compounds to amide or hydroxymethyl analogs failed.

(8) S. Checchi and M. Ridi, *Ann. chim.*, **45**, 439 (1955); **46**, 428 (1956); **47**, 728 (1957).

(9) R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.*, **80**, 3449 (1958).

(10) Robins and Hitchings[9] have proposed on good grounds that the first condensation of dicarbonyl compounds occurs at the 5-position rather than the amino group. Since acetals condense particularly readily with amines to form anils, we suggest the alternate course here.

(11) "Chemistry and Biology of Pteridines," G. E. W. Wolstenholme and M. P. Cameron, Little, Brown & Co., Boston, 1954, p. 26.

Photochemical Preparation, Rearrangement, and Dehydration of Symmetrical Methyl and Phenyl Pyridyl Glycols

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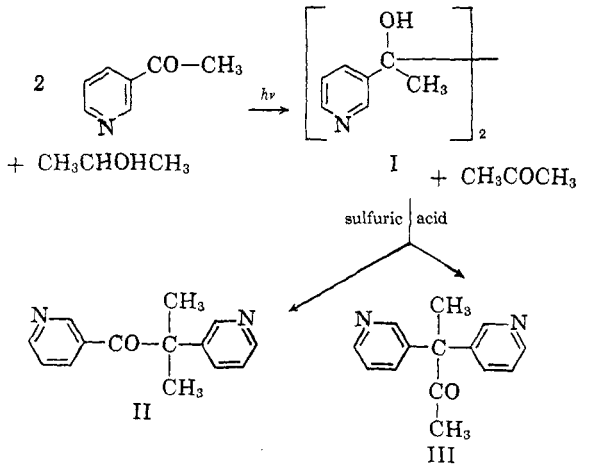
The effect of the 2-, 3-, and 4-pyridyl residues upon light-induced bimolecular reduction of the three isomeric pairs of methyl and phenyl pyridyl ketones and on the rearrangement and dehydration of the resulting pyridyl glycols has been discussed. Several compounds in this series possessed a valuable and specific adrenal cortical inhibitory activity.

Pinacol–pinacolone type rearrangement of the symmetrical ditertiary glycol (I), which in turn was obtained by a bimolecular reduction of methyl 3-pyridyl ketone, yielded two isomeric ketones (II and III).[1] One of the two ketones, 2-methyl-1,2-di-3-pyridyl-1-propanone (II), Mepyrapone,[2] was found to act as a specific 11-β-hydroxylase inhibitor in the biosynthesis of corticoid hormones in animals[3] as well as in man.[4] It has been advocated that this compound may serve as a valuable tool in the diagnosis of certain pathological derangements of the pituitary adrenal system.[5]

The present report deals with the photochemical



(1) W. L. Bencze and M. J. Allen, *J. Am. Chem. Soc.*, **81**, 4015 (1959).

(2) Trade name Metopirone™ formerly designated as Su-4885.

(3) J. J. Chart, H. Sheppard, M. J. Allen, W. L. Bencze, and R. Gaunt, *Experientia*, **14**, 151 (1958).

(4) J. S. Jenkins, L. Polthier, W. J. Reddy, D. Nelson, and G. W. Thorn, *Brit. Med. J.*, **1959**, I (398) [*Chem. Abstr.*, **53**, 15334 (1959)].

(5) G. W. Liddle, H. L. Estep, J. W. Kendall, Jr., W. Carter Williams, Jr., and A. W. Townes, *J. Clin. Endocrinol. and Metab.*, **19**, 875 (1959) [*Chem. Abstr.*, **53**, 22444 (1959)].