The aqueous acidic layer was neutralized with solid $NaHCO_3$ and extracted with three 50-ml portions of ether. After the combined organic layers were dried over anhydrous sodium sulfate, evaporation of the solvents afforded a residue of 637 mg whose NMR spectrum was very similar to that of starting **13.**

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Registry No.—**8,** 100-69-6; **10,** 1121-18-2; **11,** 538-49-8; **12,** 13694-36-5; **13,** 101-82-6; **14,** 4556-09-6.

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Purine *N*-Oxides. LXII. 2,4-Dioxopyrido[2,3-*d*]pyrimidine *N*-Oxides[1]

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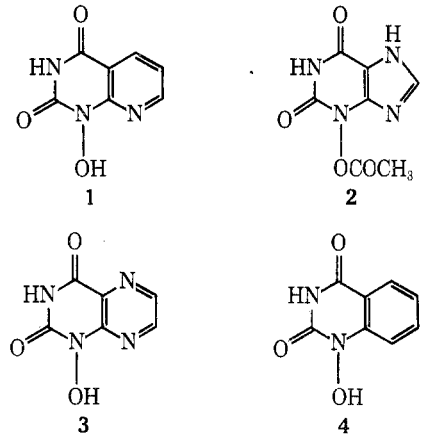
Our interest in analogs of the oncogenic 3-hydroxyxanthine,[2] the recent synthesis of 3-hydroxy-2,4-dioxopyrido[2,3-*d*]pyrimidine,[3] and the antitumor activity reported[4] for the parent compound 2,4-dioxopyrido[2,3-*d*]pyrimidine[5] against Walker muscle carcinosarcoma in rats, prompted us to synthesize the two other possible *N*-oxides, **1** and **15.**

Chemical[6-10] and biochemical[11,12] studies have shown that the oncogenicity of 3-hydroxyxanthine and some of its derivatives are paralleled by unique chemical reactivities of their esters.[2] Thus 3-acetoxyxanthine (**2**) (Chart I) undergoes, under mild conditions, an SN1′ reaction with nucleophiles to yield 8-substituted xanthines.[6-9] A series of ring analogs of 3-hydroxyxanthines are being investigated to determine the structural features of the ring system which permit the facile SN1′ reaction, and eventually the pertinence of that reactivity to oncogenicity. Our initial studies showed that the esters of ring systems with electron-rich π systems are more likely to undergo an elimination–substitution reaction similar to that of the esters of 3-hydroxyxanthine. Thus the esters of the pyrrolo[2,3-*d*]pyrimidine analog of 3-hydroxyxanthine,[13] a ring system with our electron-rich π system, undergo a reaction similar to that of the esters of 3-hydroxyxanthine, whereas esters of the electron-deficient pteridine analogs,[14] **3,** do not undergo a similar reaction, and the esters of quinazoline analogs,[15] **4,** undergo a similar reaction only under very vigorous conditions. The pyridopyrimidine analog is a slight modification of **3** or **4** and its reactivity is, as expected, intermediate between them.

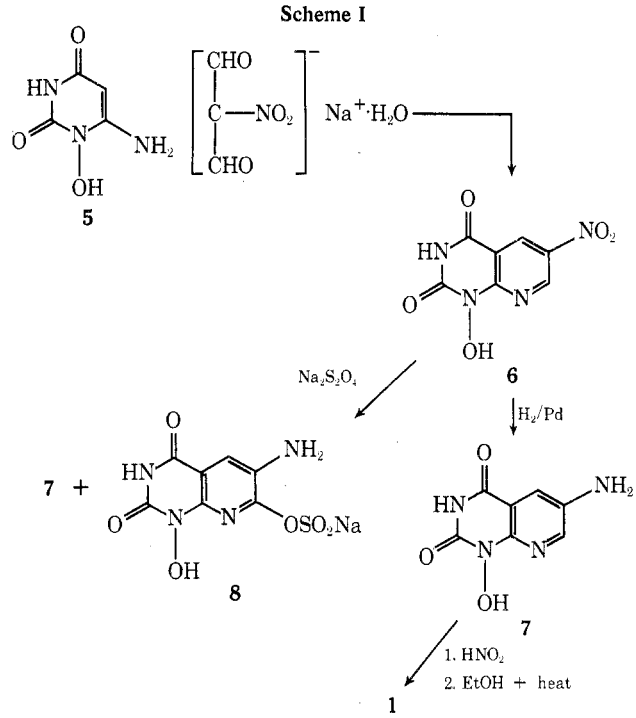
Chart I



1 **2** **3** **4**

The starting material for the synthesis of 1-hydroxy-2,4-dioxopyrido[2,3-*d*]pyrimidine (**1**) was 1-hydroxy-2,4-dioxo-6-aminopyrimidine[16] (**5**), which was condensed with nitromalonaldehyde[17,18] by heating under reflux with dilute sodium hydroxide to yield 1-hydroxy-6-nitropyrido[2,3-*d*]pyrimidine (**6**) in 73% yield (Scheme I). This method[16] was chosen because the mild conditions do not affect the sensitive N–OH bond. Hydrogenation of **6** in the presence of Pd/C gave **7** in 40% yield. Deamination of **7** was achieved by refluxing its diazonium salt in ethanol to give **1** in 89% yield. The structure of each compound (**6, 7, 1**) was confirmed by its NMR spectrum. When **6** was reduced with so-

Scheme I

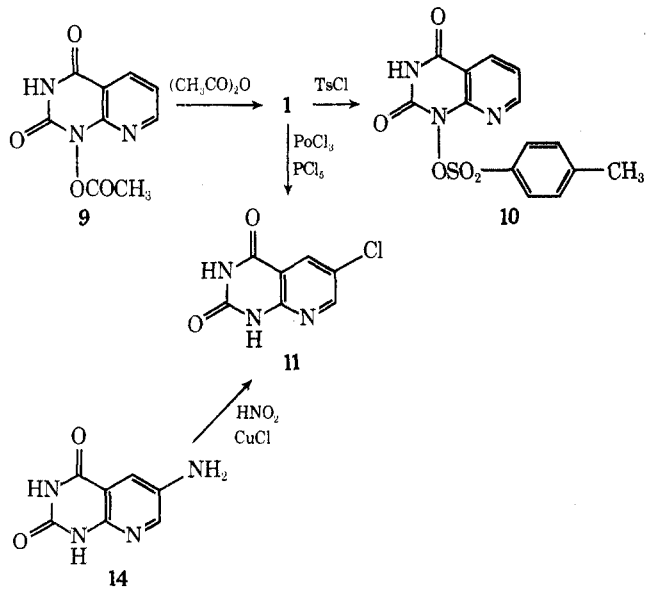


5 **6** **7** **8** **7** **1**

dium dithionite, two products were isolated, the expected amino compound 7 in 40% yield, and a second compound which analyzed as a hemihydrate of $C_7H_5N_4O_6SNa$. The structure was assigned as sodium 1-hydroxy-2,4-dioxo-6-aminopyrido[2,3-*d*]pyrimidine-7-sulfonate (8) based on the distinctive ir[19] and NMR spectra, its water solubility, and its strong $FeCl_3$ test. That structure was substantiated by hydrolysis and deamination to 2,4-dioxo-7-hydroxypyridopyrimidine, the structure of which was confirmed by NMR that give a pair of doublets in the aromatic proton region with a large 5–6 proton spin–spin coupling constant (9 Hz).[20] A similar observation was reported[21] in reduction of 2,4-dioxo-5-nitropyrimidine with sodium dithionite to give some 2,4-dioxo-5-aminopyrimidine-6-sulfonic acid. When 7 was treated with sodium bisulfite under conditions similar to those for the addition of sulfite to cytosine or uracil and its derivatives,[22,23] the starting material was recovered unchanged (Scheme I).

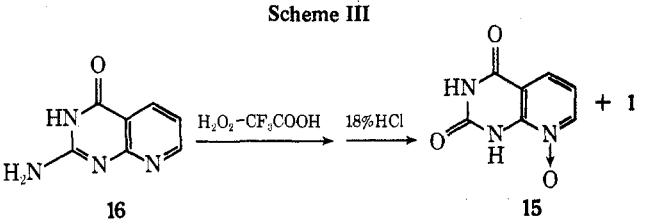
When 1 was refluxed in acetic anhydride only the acetoxy derivative 9 was obtained. Boiling in water hydrolyzed 9 to 1. No products comparable to those from 3-hydroxyxanthine results. Treatment of 1 with tosyl chloride in boiling pyridine resulted in a stable 1-sulfonyloxy derivative 10, in contrast to the substitution product, 8-sulfonyloxyquinazoline,[15] obtainable from 4. When 1 was refluxed with phosphorus oxychloride and phosphorus pentachloride, a substitution with elimination of the *N*-hydroxy group did occur, and 2,4-dioxo-6-chloropyrido[2,3-*d*]pyrimidine (11) was obtained. A similar result was obtained with the 1-hydroxyquinazoline 4 under the same conditions.[15] The mechanism of the reaction must be similar to that of the formation of 6-chloro-2,4-dioxoquinazoline from 4. The chlorine of 11 is assigned to the 6 position from the NMR spectrum. That structure was also established by unambiguous synthesis from 2,4-dioxo-6-aminopyrimidine (12) condensed with sodium nitromalonaldehyde to afford the nitro compound, 13. That was hydrogenated to the amino compound 14, and subsequent treatment of its diazonium salt with cuprous chloride yielded authentic 11 (Scheme II).

Scheme II



2,4-Dioxopyrido[2,3-*d*]pyrimidine 8-oxide (15), the third *N*-oxide isomer, was obtained in 42% yield by direct oxidation of 2-amino-4-oxopyrido[2,3-*d*]pyrimidine (16)[18] with 30% H_2O_2 in CF_3COOH, followed by refluxing with 18% HCl to deaminate the *N*-oxide of 16 to 15. Only a trace, 1.3%, of the 1 isomer, 1, was produced during the oxidation. Thus the nitrogen of the pyridine ring in 16 is more susceptible to N-oxidation than nitrogen 1 of pyrimidine ring despite the activation of the latter by an ortho amino substituent. The structure of 15 was established by comparison of its NMR spectrum with those of the two other isomers (Scheme III).

Scheme III



The 1-hydroxypyrido[2,3-*d*]pyrimidine (1) can undergo an elimination–substitution reaction to yield 11 only when it is treated with phosphorus oxychloride and phosphorus pentachloride. As expected an ester of 1 is found to be more reactive than the corresponding ester of the pteridine analog, 3,[13] and less than that of the quinazoline analog, 4.[14] In view of this relatively mild reactivity, it is improbable that 1 should be an oncogen. On the other hand, 1 might exhibit an antitumor activity such as that found for its parent compound.[4]

Experimental Section

1-Hydroxy-2,4-dioxo-6-nitropyrido[2,3-*d*]pyrimidine (6). A mixture of 1-hydroxy-2,4-dioxo-6-aminopyrimidine[16] (0.43 g, 0.003 mol) and sodium nitromalonaldehyde monohydrate (0.529 g, 0.0033 mol) in 15 ml of 1% NaOH was refluxed for 2.25 hr. The solution was cooled, acidified with glacial acetic acid to pH 5, and filtered to yield 0.49 g (73%) as a yellow solid, mp >300° dec. A $FeCl_3$ test was positive. An analytical sample was obtained by recrystallization from acetic acid: NMR (Me_2SO-d_6) δ 8.76 (d, H-5), 9.45 (d, H-7), 11.68 [broad singlet, OH + NH, exchangeable with D_2O ($J_{5,7}$ = 2.5 Hz)]; uv max (~pH) 318 nm (1), 318 (5), 280, 415 (12).

Anal. Calcd for $C_7H_4N_4O_5$: C, 37.51; H, 1.79; N, 24.99. Found: C, 37.42; H, 1.90; N, 24.81.

1-Hydroxy-2,4-dioxo-6-aminopyrido[2,3-*d*]pyrimidine (7). A. 6 (1.46 g, 0.0065 mol) was dissolved in H_2O (250 ml) by adding sufficient NH_4OH and 10% palladium on charcoal (0.4 g) was added. The theoretical amount of H_2 was absorbed during 1.5 hr. The reaction mixture was heated to 60° and filtered, and the filtrate was evaporated in vacuo nearly to dryness. The precipitate was collected to yield 0.5 g (40%), mp >300° dec. A $FeCl_3$ test was positive. An analytical sample was obtained by recrystallization from H_2O: NMR (Me_2SO-d_6) δ 5.50 (s, NH_2, exchangeable with D_2O), 7.55 (d, H-5), 8.20 (d, H-7) [two exchangeable protons (D_2O) in the offset: OH, NH] ($J_{5,7}$ = 3 Hz); uv max (~pH) 256 nm, 333 (1), 266, 362 (5), 281, 398 (12).

Anal. Calcd for $C_7H_6N_4O_3$: C, 43.30; H, 3.11; N, 28.85. Found: C, 43.15; H, 3.21; N, 28.60.

B. Sodium dithionite (0.79 g, 0.0045 mol) was added in small portions, at room temperature, to a stirred solution of 6 (0.29 g, 0.0013 mol) in H_2O (20 ml) and 1 *N* NaOH (5.5 ml). The color of the solution changed from red to yellow. After 2 hr the reaction mixture was acidified to pH 5 with glacial acetic acid and evaporated in vacuo to half of its original volume. The precipitate of 7 thus formed was collected, yield 0.1 g (40%). Concentration of the filtrate almost to dryness gave sodium 1-hydroxy-2,4-dioxo-6-aminopyrido[2,3-*d*]pyrimidine-7-sulfonate, 0.1 g, yellow solid. A $FeCl_3$ test was positive. An analytical sample was prepared by recrystallization from H_2O: NMR (Me_2SO-d_6) δ 5.92 (broad singlet, NH_2 exchangeable with D_2O), 7.70 (s, H-5); uv max (~pH) 227 nm, 269, 383 (2, 5), 229, 250 s, 289, 416 (12); ir showed characteristic sulfonic group absorptions,[19] 1240, 1198, 1055, and 731 cm^{-1}.

Anal. Calcd for $C_7H_5H_4O_6S_1Na_1 \cdot \frac{1}{2}H_2O$: C, 27.54; H, 1.97; N, 18.36; S, 10.49. Found: C, 27.41; H, 2.32; N, 18.08; S, 10.20.

1-Hydroxy-2,4-dioxopyrido[2,3-*d*]pyrimidine (1). Sodium nitrite solution (0.81 g, 0.012 mol, in 16 ml of H_2O) was added dropwise to a cooled (0–5°) and stirred solution of 7 (1.62 g, 0.0083 mol) in 18% HCl (35 ml). Stirring was continued for 15 min and H_2O was added (150 ml). The supernatant liquor was decanted, and the

ethanol (500 ml) was added to the residue. This mixture was then refluxed for 3 hr. Carbon black was added to the hot solution; filtration and evaporation in vacuo to 30 ml yielded, after filtration, 1 (1.33 g, 89%, mp 310–311° dec). An analytical sample was obtained by recrystallization from methanol: NMR (Me_2SO-d_6) δ 7.33 (dd, H-6), 8.35 (dd, H-5), 8.75 (dd, H-7), two exchangeable protons (D_2O) in the offset, OH, NH ($J_{5,6}$ = 8.0, $J_{6,7}$ = 5.0, $J_{5,7}$ = 1.8 Hz); uv max (~pH) 251 nm, 313 (1, 5), 259, 291, 368 (12).

Anal. Calcd for $C_7H_5N_3O_3$: C, 46.93; H, 2.81; N, 23.45. Found: C, 46.79; H, 2.71; N, 23.28.

1-Acetoxy-2,4-dioxopyrido[2,3-*d*]pyrimidine (9). 1 (0.09 g, 0.005 mol) was refluxed with acetic anhydride (3 ml) for 2.5 hr. After cooling, ether was added and the precipitate was collected and washed with ether to yield 9 (0.051 g, 46%). At room temperature 9 hydrolyzes in H_2O very slowly to 1. In boiling H_2O or in NaOH (pH 13) 9 is hydrolyzed very rapidly to 1: NMR (Me_2SO-d_6) δ 7.43 (dd, H-6), 8.41 (dd, H-5), 8.71 (dd, H-7), 12.2 (NH, exchangeable with D_2O).

Anal. Calcd for $C_9H_7N_3O_4$: C, 48.87; H, 3.19; N, 18.99. Found: C, 48.96; H, 3.28; N, 18.94.

1-Tosyloxy-2,4-dioxopyrido[2,3-*d*]pyrimidine (10). To a stirred solution of 1 (0.090 g, 0.0005 mol) in dry pyridine (10 ml), tosyl chloride (0.105 g, 0.00055 mol) was added in small portion at room temperature. The solution was heated at 90° for 2.5 hr. Most of the pyridine was evaporated in vacuo, H_2O was added, and the precipitate was collected and recrystallized from methanol to yield 10 (0.069, 36%): colorless needles; mp 221–222° dec; NMR (Me_2SO-d_6) δ 2.45 (s, CH_3), 8.50 (m, H-6, H′-3, H′-5), 7.93 (d, H′-2 + H′-6), 8.36 (dd, H-5), 8.50 (dd, H-7), 12.08 (s, NH) ($J_{5,6}$ = 8.0, $J_{6,7}$ = 5.0, $J_{5,7}$ = 2 Hz); uv max (~pH) 303 nm (1), 306 (12).

Anal. Calcd for $C_{14}H_{11}N_3O_5S_1$: C, 50.44; H, 3.32; N, 12.60; S, 9.62. Found: C, 50.34; H, 3.26; N, 12.54; S, 9.78.

2,4-Dioxo-6-chloropyrido[2,3-*d*]pyrimidine (11). A. A solution of 1 (0.09 g, 0.005 mol) and phosphorus pentachloride (0.329 g) in phosphorus oxychloride (5 ml) was refluxed for 3.5 hr. The cooled solution was poured into ice water $NaHCO_3$ was added to pH 5, the solution was extracted with ether (3 × 100 ml), and the ether was dried over Na_2SO_4 and evaporated to dryness. Concentrated HCl (4 ml) was added to the residue and the solution was heated under reflux for 3 hr. After evaporation of the solution to dryness, H_2O was added to the residue (3 ml). The 11 was precipitated by adjusting the acidity of the solution to pH 5 with $NaHCO_3$ to yield 14 mg (14%): mp 307° dec; NMR (Me_2SO-d_6) δ 8.20 (d, H-5), 8.61 (d, H-7), 11.56 (s, NH, exchangeable with D_2O), 11.80 (s, NH, exchangeable with D_2O) ($J_{5,7}$ = 2.5 Hz); uv max (~pH) 248 nm, 321 (1), 247, 319 (5), 240 (s), 271, 333, 364 (s) (12).

Anal. Calcd for $C_7H_4N_3O_2Cl\cdot\frac{1}{2}H_2O$: C, 40.66; H, 2.42; N, 20.33; Cl, 17.18. Found: C, 40.74; H, 2.45; N, 20.33; Cl, 17.10.

B. To a stirred solution of 14 (0.4 g, 0.0022 mol) in 18% HCl (10 ml) at 0° was added dropwise a solution of sodium nitrite (0.225 g, 0.0032 mol) in water (5 ml). After 10 min the cold diazonium chloride solution was slowly poured with stirring into a cold cuprous chloride solution in concentrated HCl (25 ml) prepared from 0.78 g of $CuSO_4\cdot5H_2O$. The thick mixture was allowed to warm at room temperature, then warmed at 60° for 1 hr. The reaction mixture was cooled, $NaHCO_3$ was added to ~pH 6, and the precipitate was collected to yield 11, 0.360 g (83%), mp 307° dec. Recrystallization from 50% CH_3COOH gave light yellow needles: uv max (~pH) 249 nm, 323 (1, 5), 240 (s), 272, 335, 364 (s) (12).

Anal. Calcd for $C_7H_4N_3O_2Cl$: C, 42.55; H, 2.04; N, 21.26; Cl, 17.94. Found: C, 42.67; H, 1.96; N, 21.40; Cl, 17.89.

2,4-Dioxo-6-nitropyrido[2,3-*d*]pyrimidine (13). A mixture of 2,4-dioxo-6-aminopyrimidine (12, 3.81 g, 0.03 mol) and sodium nitromalonaldehyde monohydrate (5.18 g, 0.033 mol) in 50 ml of 1% NaOH was refluxed for 5 hr. A precipitate started to form in a few minutes after refluxing. After cooling the precipitate was filtered to yield 13 (4.6 g, 73.7%) as light yellow crystals, mp 346° dec.

The analytical sample was prepared by recrystallization from 50% acetic acid: NMR (Me_2SO-d_6) δ 8.76 (d, H-5), 9.38 (d, H-7), 10.53 (s, broad, N^1H, N^3H, exchangeable with D_2O) ($J_{5,7}$ = 2.8 Hz); uv max (~pH) 292 nm (s), 313 (1, 5), 370 (12).

Anal. Calcd for $C_7H_4N_4O_4$: C, 40.39; H, 1.93; N, 26.92. Found: C, 40.57; H, 1.90; N, 26.83.

2,4-Dioxo-6-aminopyrido[2,3-*d*]pyrimidiee (14). To 13 (1.0 g, 0.0048 mol) in H_2O (200 ml) NH_4OH was added until it all dissolved. This was hydrogenated with 10% palladium on charcoal (0.25 g) until 360 ml of H_2 was absorbed. The palladium on charcoal was removed by filtering the boiling hot reaction mixture. Concentration of the filtrate in vacuo to ~50 ml yielded 14 (0.480 g, 56%), mp >360°. The analytical sample was obtained by recrystallization from H_2O: uv max (~pH) 243 nm, 312 (1), 260, 354 (5), 266, 360 (12).

Anal. Calcd for $C_7H_6N_4O_2$: C, 47.19; H, 3.39; N, 31.44. Found: C, 46.33; H, 31.5; N, 30.43.

1,7-Dihydroxy-2,4-dioxopyrido[2,4-*d*]pyrimidine. The above sodium sulfonate compound, 8 (41.57 mg) was dissolved in 0.1 *N* NaOH (7 ml) and stirred on a steam bath for 3 hr. The solution was acidified to pH 5.5 with acetic acid, and the solution was vaporized to dryness in vacuo. The residue was diazotized with 2 ml of 4 *N* HCl and sodium nitrite (50 ml) at 0°. After stirring at the same temperature for 15 min the mixture was added with water (25 ml). The precipitate thus formed was collected by centrifuging and was then heated under reflux for 4 hr in ethanol (25 ml). The resulting product was absorbed on a Dowex-50 [H^+] column. Elution with water gave the title compound (16 mg) in a first fraction, mp 225° dec. Further elution with water gave some 1: NMR (Me_2SO-d_6) δ 7.70, 6.17 ppm ($J_{5,6}$ = 9 Hz).

Anal. Calcd for $C_7H_5N_3O_4\cdot H_2O$: C, 39.45; H, 3.31; N, 19.71. Found: C, 39.35; H, 3.40; N, 19.61.

2,4-Dioxopyrido[2,3-*d*]pyrimidine 8-Oxide (15). To a stirred solution of 2-amino-4-oxopyrido[2,3-*d*]pyrimidine (16, 2.1 g, 0.013 mol) in CF_3COOH (32 ml) was added 30% H_2O_2 (1.6 ml). After 4 days at room temperature the solution was evaporated to dryness in vacuo, and 18% HCl (140 ml) was added to the residue which was refluxed for 15 hr. The solution was evaporated in vacuo, and H_2O (50 ml) and a few drops of NH_3 were added to the residue, which was heated to boiling, and chromatographed on a Dowex-50 [H^+] (200–400 mesh) column (2.5 × 25 cm) that was eluted with hot H_2O. Fraction 1 (1–253 ml) contained decomposition products. Fraction 2 (299–828 ml) was evaporated to yield 15 (0.97 g, 42%), mp 338° dec. Fraction 3 (897–1265 ml) was evaporated to yield 1 (0.031 g, 1.3%), mp 310–311° dec. 15 was recrystallized from H_2O for analysis: NMR (CF_3COOH) δ 7.71 (dd, H-6), 8.88 (2 superimposed dd, H-5, H-7) ($J_{5,6}$ = 8.0, $J_{6,7}$ = 7.0, $J_{5,7}$ = 1 Hz); uv max (~pH) 266 nm s, 338 (1, 5), 280, 372 (12).

Anal. Calcd for $C_7H_5N_3O_3$: C, 46.93; H, 2.81; N, 23.45. Found: C, 47.07; H, 2.80; N, 23.12.

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Registry No.—1, 56783-76-7; 5, 56783-77-8; 6, 56783-78-9; 7, 56783-79-0; 8, 56783-80-3; 9, 56783-81-4; 10, 56783-82-5; 11, 56783-83-6; 12, 873-83-6; 13, 56783-84-7; 14, 56783-85-8; 15, 56783-86-9; 16, 7255-87-0; sodium nitromalonaldehyde, 34461-00-2; tosyl chloride, 98-59-9; 1,7-dihydroxy-2,4-dioxopyrido[2,3-*d*]pyrimidine, 56783-87-0.

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