droindan (1)[21] in 50 ml of methylene chloride was stirred rapidly at −70° while a stream of ozone from a Welsbach generator (200 W) was bubbled through the solution for 45 min. An aqueous solution of 5 g of potassium iodide was added and the reaction mixture was allowed to warm to room temperature The iodine color was discharged with an aqueous solution of sodium thiosulfate and the organic phase was separated, washed with water, and dried ($MgSO_4$). The methylene chloride was removed and ethanol was added to precipitate 2.34 g (17%) of a white solid (3), which was recrystallized from ethanol: mp 186–187°; ir ($CHCl_3$) 1700, 1470, 1450, 1075 cm^{-1}; NMR ($CDCl_3$) τ 7.3–7.6 (8 H, m), 7.8–8.5 (20 H, m); mass spectrum *m/e* (rel intensity) 154 (14), 126 (40), 112 (46), 98 (89), 55 (100); mol wt (osmometric) calcd 340, found 347.

Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.47; H, 8.48.

Thermolysis of 3. A sample of 0.30 g (0.88 mmol) of diperoxide 3 was added in portions to 3 ml of refluxing *n*-decane and the resultant solution was refluxed for 1.5 hr. The cooled reaction solution was chromatographed on silica gel (60–200 mesh) using pentane to elute the *n*-decane and 3% ethyl acetate–chloroform to elute the 0.22 g of thermolysis products. GC analysis (190–270°) of these products indicated 18% of **7**, 50% of diones 8 and **9**, 16% of macrolides **10**, and smaller amounts of several other components.

Identification of Thermolysis Products from 3. A. Product **7**, the first major GC peak, was collected and found to be identical with a sample of bicyclo[4.3.0]-1(6)-nonen-2-one prepared previously.[3]

B. Compounds 8 and **9** analyzed as two partially resolved GC peaks of equal area. The first peak was collected, recrystallized from petroleum ether (bp 60–80°), and shown to be 1,8-cyclohexadecanedione (8) on the basis of the following data and comparison of this data with that published previously:[11] mp 68–69°; ir (CCl_4) 2940, 2870, 1712, 1460, 1370, 1125 cm^{-1}; mass spectrum *m/e* (rel intensity) 252 (M^+, 14), 234 (13), 195 (21), 140 (17), 125 (18), 112 (37), 97 (41), 84 (74), 55 (100). Similarly, the second peak of the doublet was collected, recrystallized from petroleum ether, and shown to be 1,9-cyclohexadecanedione (**9**) by comparison of the following data with that published previously:[11] mp 80–81° (lit.[11] 78–79°); ir (CCl_4) 2940, 2870, 1719, 1465, 1370, 1115, 1025 cm^{-1}; mass spectrum *m/e* (rel intensity) 252 (M^+, 23), 195 (13), 169 (14), 126 (46), 111 (30), 98 (88), 83 (56), 55 (100).

C. The lactones **10** upon GC analysis (266°) showed three peaks in a ratio of 1:2:1. These peaks were collected by preparative GC and the following data were found for each peak (in order of GC elution). **5,14-Diketoheptadecanolide (10a):** mp 50.5–51.0° (recrystallized as plates from petroleum ether, bp 60–80°); ir (CCl_4) 2930, 2855, 1736, 1716, 1158, 1128 cm^{-1}; mass spectrum *m/e* (rel intensity) 296 (M^+, 14), 278 (19), 167 (56), 97 (100), 84 (86), 55 (62).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.73; H, 9.46.

Mixture of 5,13-Diketoheptadecanolide (10b) and 6,14-Diketoheptadecanolide (10c). This GC fraction was an oil: ir (CCl_4) 2930, 2860, 1734, 1714, 1160 cm^{-1}; mass spectrum *m/e* (rel intensity) 296 (M^+, 12), 278 (9), 167 (19), 153 (28), 111 (56), 98 (80), 97 (65), 84 (61), 55 (100). **6,13-Diketoheptadecanolide (10d).** This last GC peak was recrystallized from petroleum ether (bp 60–80°): mp 59.0–59.5°; ir (CCl_4) 2935, 2860, 1738, 1718, 1135 cm^{-1}; mass spectrum *m/e* (rel intensity) 296 (M^+, 7), 278 (8), 153 (33), 111 (70), 98 (100), 55 (90).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.85; H, 9.75.

Acknowledgment. The authors acknowledge the financial assistance of the National Research Council of Canada.

Registry No.—1, 695-90-9; 3, 56678-87-6; **7**, 22118-01-0; **8**, 17853-46-2; **9**, 31067-25-1; **10a**, 56678-88-7; **10b**, 56678-89-8; **10c**, 56678-90-1; **10d**, 56678-91-2; ozone, 10028-15-6.

References and Notes

(1) R. Criegee and H. Zogel, *Chem. Ber.*, **84**, 215 (1951). We thank Professor Criegee for bringing this paper to our attention.
(2) R. Criegee and G. Wenner, *Justus Liebigs Ann. Chem.*, **564**, 9 (1949); R. Criegee, *Rec. Chem. Prog.*, **18**, 111 (1957).
(3) G. L. Lange, T. W. Hall, and E. Neidert, *J. Org. Chem.*, **39**, 3819 (1974).
(4) T. Ledaal, *Tetrahedron Lett.*, 3661 (1969).
(5) K. H. Overton and P. Owen, *J. Chem. Soc., Perkin Trans. 1*, 226 (1973).
(6) P. R. Story, D. D. Denson, C. E. Bishop, B. C. Clark, Jr., and J.-C. Farine, *J. Am. Chem. Soc.*, **90**, 817 (1968).
(7) P. R. Story and P. Busch, *Adv. Org. Chem.*, **8**, 67–95 (1972).
(8) J. R. Sanderson and P. R. Story, *J. Org. Chem.*, **39**, 3183 (1974).
(9) J. R. Sanderson and P. R. Story, *J. Org. Chem.*, **39**, 3463 (1974).
(10) J. R. Sanderson, P. R. Story, and K. Paul, *J. Org. Chem.*, **40**, 691 (1975).
(11) L. G. Wideman, *J. Org. Chem.*, **33**, 4541 (1968).
(12) Q. N. Porter and J. Baldas, "Mass Spectrometry of Heterocyclic Compounds", Wiley, New York, N.Y., 1971, pp 208–212.
(13) K. L. Rinehart and G. VanLear in "Biochemical Applications of Mass Spectrometry", G. R. Walker, Ed., Wiley, New York, N.Y., 1972, Chapter 17.
(14) H. C. Hill, "Introduction to Mass Spectrometry", 2nd ed, Heyden and Son, New York, N.Y., 1972, p 54; S. R. Shrader, "Introductory Mass Spectrometry", Allyn and Bacon, Boston, Mass., 1971, p 79.
(15) W. H. McFadden, E. Day, and M. J. Diamond, *Anal. Chem.*, **37**, 89 (1965).
(16) W. Keller-Shierlein, *Fortschr. Chem. Org. Naturst.*, **30**, 313 (1973); A. Burger, "Medicinal Chemistry", 3rd ed, Wiley-Interscience, New York, N.Y., 1970, p 328.
(17) E. J. Corey, K. C. Nicolaou, and S. Melvin, Jr., *J. Am. Chem. Soc.*, **97**, 653, 654 (1975); J. D. White, S. N. Lodwig, G. L. Trammell, and M. P. Fleming, *Tetrahedron Lett.*, 3263 (1974); I. J. Borowitz, V. Bandurco, M. Heyman, R. D. G. Rigby, and S. Ueng, *J. Org. Chem.*, **38**, 1234 (1973), and earlier papers.
(18) For example: H. Ogura, K. Furuhata, H. Kuwano, and N. Harada, *J. Am. Chem. Soc.*, **97**, 1930 (1975); E. J. Corey and L. S. Melvin, Jr., *Tetrahedron Lett.*, **929** (1975).
(19) A substituted heptadecanolide, borrelidin, has been isolated from a species of streptomyces: K. Anderton and R. W. Rickads, *Nature (London)*, **206**, 269 (1965); W. Keller-Schierlein, *Helv. Chim. Acta*, **50**, 731 (1967).
(20) Melting points were determined on a Gallenkamp apparatus and are uncorrected. Infrared spectra were recorded on a Beckman Model IR 12 spectrophotometer, mass spectra on a Varian MAT CH7 spectrometer operating at 70 eV, and nuclear magnetic resonance spectra on a Varian A-60A spectrometer using the internal standard tetramethylsilane (τ 10.0). Gas chromatographic (GC) analyses and collections were carried out on an Aerograph Autoprep Model A-700 using a column with a 20% OV 210 liquid phase on HP Chromosorb W, 80–100 mesh, 6 ft × 0.25 in. Peak areas were determined by triangulation and were not corrected for differences in thermal response. Elemental analyses were performed by H. S. McKinnon, Chemistry Department, University of Guelph, or A. B. Gygli, Microanalysis Laboratory, Toronto, Canada.
(21) H. O. House and C. J. Blankley, *J. Org. Chem.*, **33**, 47 (1968); E. M. Kaiser and R. A. Benkesser, *Org. Synth.*, **50**, 88 (1970).

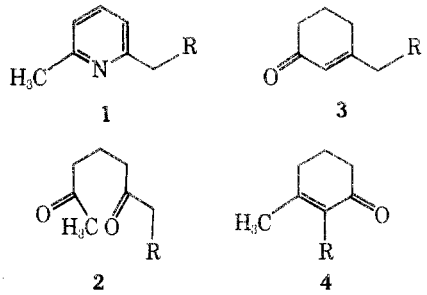
The Pyridine Route to α-Substituted Cyclohexenones

S. Danishefsky* and P. Cain

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received July 8, 1975

In the pyridine route to steroids,[1,2] it has been shown that 6-substituted α-picolines (1) may be converted to 3-substituted cyclohexenones of the type **3**. Fortunately, in the most relevant cases (i.e., where R represents a cycloalkanone ketal substituted at its α position), the 2,6-diketone intermediate **2** suffers aldolization to give **3** rather than its isomer, **4**. System **4** is, in fact, the predominant product

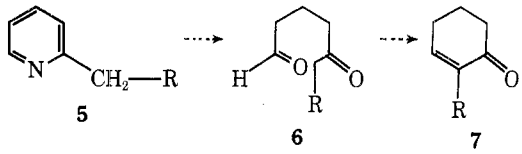


1 **3**

2 **4**

where R in diketone **2** represents a straight-chain alkyl group.[3,4] The structural factors which are decisive in promoting one mode of cyclization over the other are being investigated.[5] The issue of isomeric possibilities in the aldolization process does not arise for 4-acylbutyraldehydes (**6**). Such systems should be derived by reductive hydrolysis of 2-substituted pyridines (**5**). Below are described some ap-

plications of this concept to the synthesis of the α-substituted cyclohexenones (7). We believe that the pyridine



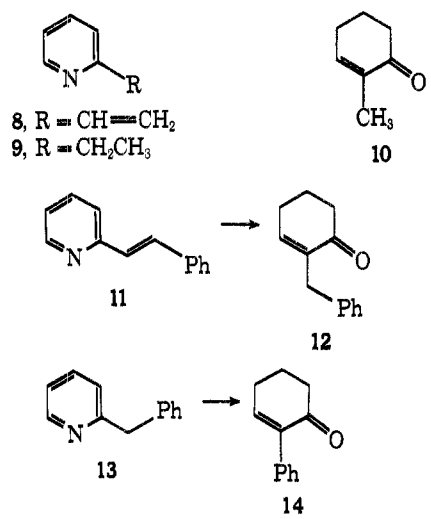
5 6 7

route to such systems offers advantages in terms of simplicity of operations and accessibility of starting materials.

Catalytic reduction of 2-vinylpyridine (8) affords 2-ethylpyridine (9). Compound 9 was treated with 1.1 equiv of sodium in ammonia containing 10 equiv of ethanol. The residue, upon evaporation of the ammonia, was treated with 2% aqueous ethanolic sodium hydroxide. A 57% yield of 2-methylcyclohexenone (10) was obtained. *Efforts to optimize the yield of this conversion were not persued when it was found that 2-vinylpyridine itself could be converted to 2-methylcyclohexenone in 56% yield.* For this purpose, a 6:1 molar ratio (i.e., 1.50 equiv) of sodium:2-vinylpyridine was employed. The yield for the direct conversion of 8 → 10 was increased to 63% by the use of lithium rather than sodium.

The feasibility of consolidating the reduction of a conjugated double bond with the reduction of a pyridine to the dihydro level was demonstrated with the readily available *trans*-2-stilbazole (11) (prepared by condensation of α-picoline with benzaldehyde).[6] Compound 11 was converted to 2-benzylcyclohexenone (12) in 52% yield. The feasibility of reducing the pyridine ring in the presence of the benzene ring is thus also established.

In the light of the *trans*-2-stilbazole result, it was not surprising to find that 2-benzylpyridine (13) could be converted in good yield to 2-phenylcyclohexenone (14) by reductive hydrolytic cyclization.



8, R = CH=CH$_2$
9, R = CH$_2$CH$_3$
10
11
12
13
14

Previous methodology for obtaining compound 10 involves (1) selective functionalization of 2-methylcyclohexanone[7] or (2) manipulations which start with 2-methylcyclohexane-1,3-dione.[8] Similarly, compound 12 has been prepared[9] from the relatively inaccessible 2-phenylcyclohexanone,[9] 2-phenylcyclohexane-1,3-dione,[10] and 1-phenylcyclohexene.[11] Compound 14 has been obtained by equilibration of 2-benzylidenecyclohexanone[12] or through oxidative manipulations starting with 1-benzylcyclohexene.[13,14] The pyridine route, which produces such systems in one step from readily available starting materials, is the most convenient and efficient.

The inability to achieve higher yields was apparently due to different factors in the various cases. In the reduction of 9 and 11, substantial amounts of basic material were recovered. NMR analysis of this material indicated the absence of pyridine absorption. In the case of 13, the basic extract, ca. 40%, was largely starting material.

It was surprising to find, even after many attempts, that 2,5-lutidine did not produce any recognizable amounts of 4-methylcyclohexenone. The bulk (87%) of the material was obtained as a basic fraction which was largely starting material. Mass spectral analysis of some minor products, partially purified by preparative GLC, indicated the presence of reductively dimerized materials (*m/e* 216 and 218) in the reaction mixture.

Similarly, attempted conversion of 3-methyl-2-stilbazole[15] to 2-benzyl-6-methylcyclohexenone was not successful. The reasons for the nonextendability of this reduction method to systems with substitution in the 3 or the 5 positions are not clear, particularly in the light of the applicability of the reaction to 4-substituted systems.[16a,b]

Experimental Section[17]

Conversion of 2-Vinylpyridine (8) to 2-Methylcyclohexenone (10). To a solution prepared from the dissolution of lithium metal (3.45 g, 0.496 mol) in 1000 ml of dry NH_3 was quickly added a solution containing 2-vinylpyridine (10.5 g, 0.1 mol) and absolute ethanol (36.8 g, 0.8 mol) in 300 ml of anhydrous ether. After the disappearance of the blue color, the ammonia was evaporated in a stream of nitrogen, and the residue was dissolved in 480 ml of ethanol. A solution of sodium hydroxide (12.0 g, 0.3 mol) in 240 ml of H_2O was then added, and the resulting system was stirred at room temperature under an atmosphere of nitrogen for 2.5 hr. The solution was acidified by the addition of 10% HCl. The resulting solution was extracted four times with 200-ml portions of ether. The combined ether layers were washed twice with saturated $NaHCO_3$ and then once with saturated brine. The organic solution was dried over anhydrous sodium sulfate. Evaporation of the solvents followed by distillation of the residue afforded 6.97 g (63%) of **10**: bp 61–62° (10 mm); $\bar{\nu}$ ($CHCl_3$) 2920, 1667 cm^{-1}; δ ($CDCl_3$) 1.73 (m, 3 H), 1.9–2.6 (m, 6 H), 6.65 (m, 1 H); λ_{max} (95% ethanol) 236 nm (ε 9600); *m/e* 110; 2,4-DNP mp 207.5–209° (lit.[7] 207–208°).

Neutralization of the aqueous acidic layer with $NaHCO_3$ followed by extraction with three 150-ml portions of ether afforded a residue of 3.01 g whose NMR spectrum showed essentially no absorption in the region of δ 6–9 ppm.

Conversion of *trans*-2-Stilbazole (11) to 2-Benzylcyclohexenone (12). To a solution prepared from the dissolution of sodium metal (3.8 g, 0.165 mol) in 500 ml of ammonia (freshly distilled from sodium) was quickly added a solution comprised of *trans*-2-stilbazole (5.0 g, 0.0276 mol) and absolute ethanol (10.5 g, 0.229 mol) in 200 ml of absolute ether. After disappearance of the blue color, the ammonia was evaporated under a stream of nitrogen. The residue was dissolved in 120 ml of ethanol and the resulting solution was worked up as before to give 3.17 g of crude neutral material which was chromatographed on 60 g of silica gel. Elution with benzene afforded 2.61 g (52%) of 2-benzylcyclohexenone (**12**): $\bar{\nu}$ ($CHCl_3$) 2899, 1667, 1600, 1488 cm^{-1}; NMR ($CDCl_3$) δ 1.8–2.6 (m, 6 H), 3.43 (d, J = 1 Hz, 2 H), 6.63 (t, 1 H), 7.06 (s, 5 H); *m/e* 186; 2,4-DNP mp 152–153.5° (lit.[14] 153°).

The acidic aqueous layer was neutralized with solid $NaHCO_3$ and extracted with three 25-ml portions of ether. After the combined organic layers were dried over anhydrous sodium sulfate, removal of the solvents afforded a residue of 1.87 g. The NMR of this material contains essentially no absorption in the region δ 6–9 ppm.

Conversion of 2-Benzylpyridine (13) to 2-Phenylcyclohexenone (14). To a solution prepared by the dissolution of lithium (621 mg, 0.09 mol) in 300 ml of ammonia (freshly distilled from sodium) was quickly added a solution of 2-benzylpyridine (2.53 g, 0.015 0.015 mol) and absolute ethanol (6.9 g, 0.150 mol) in 100 ml of anhydrous ether. After the disappearance of the blue color, the ammonia was evaporated under a stream of nitrogen. The residue was dissolved in 60 ml of ethanol and the resulting solution was worked up in the manner described above to give 1.81 g of crude, crystalline 2-phenylcyclohexenone (14). Recrystallization from hexane–ethyl acetate gave pure **14**: mp 93–94° (lit.[11] 96–97°); $\bar{\nu}$ ($CHCl_3$) 2976, 1680 cm^{-1}; δ ($CDCl_3$) 1.9–2.8 (m, 6 H), 6.93 (t, 1 H), 7.32 (s, 5 H); *m/e* 172.

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.**

Acknowledgments. This research was supported by PHS Grant CA-12107-05-11. NMR spectra were obtained on facilities supported by PHS Grant RR-00292-05.

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.

References and Notes

(1) (a) S. Danishefsky and A. Nagel, *J. Chem. Soc., Chem. Commun.*, 373 (1972); (b) S. Danishefsky, P. Cain, and A. Nagel, *J. Am. Chem. Soc.*, **97,** 380 (1975).
(2) S. Danishefsky and P. Cain, *J. Am. Chem. Soc.*, in press.
(3) S. Danishefsky, A. Nagel, and D. Peterson, *J. Chem. Soc., Chem. Commun.*, 374 (1972).
(4) G. Stork and R. Borch, *J. Am. Chem. Soc.*, **86,** 935 (1964).
(5) For a recent result which bears on this subject see C. Alexandre and F. Ronessac, *J. Chem. Soc., Chem. Commun.*, 275 (1975).
(6) J. L. R. Williams, R. E. Adel, J. M. Carlson, G. A. Reynolds, and J. A. Ford, *J. Org. Chem.*, **28,** 387 (1963).
(7) (a) E. W. Warnhoff and W. S. Johnson, *J. Am. Chem. Soc.*, **75,** 494 (1953); (b) E. W. Warnhoff, D. G. Martin, and W. S. Johnson, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 162; (c) C. L. Liotta and H. P. Harris, *J. Am. Chem. Soc.*, **96,** 2250 (1974); (d) G. Sturtz and A. Raphalen, *Tetrahedron Lett.*, 1529 (1970); (e) B. Bierling, K. Kirschke, H. Oberender, and M. Schulz, *J. Prakt. Chem.*, **314,** 170 (1972).
(8) G. H. Hiegel and P. Burk, *J. Org. Chem.*, **38,** 3637 (1973); (b) R. D. Clark and C. H. Heathcock, *ibid.*, **38,** 3658 (1973).
(9) (a) D. Elad and D. Ginsburg, *J. Chem. Soc.*, 2664 (1953); (b) B. Miller and H. Wang, *Tetrahedron*, **28,** 2369 (1972).
(10) H. Born, R. Pappo, and J. Szmuszkovicz, *J. Chem. Soc.*, 1779 (1953).
(11) D. Ginsburg and R. Pappo, *J. Chem. Soc.*, 516 (1951).
(12) J. M. Conia and P. Amice, *Bull. Soc. Chim. Fr.*, 2972 (1970).
(13) K. von Auwers and W. Treppmann, *Chem. Ber.*, **48,** 1207 (1915).
(14) A. I. Chirko, A. F. Mafishev, and A. N. Kurgifskaya, *Zh. Org. Khim.*, **30,** 28 (1967).
(15) A. Mustafa and M. K. Hilmy, *J. Chem. Soc.*, 1698 (1974).
(16) (a) A. J. Birch, *J. Chem. Soc.*, 1270 (1947); (b) A. J. Birch and E. A. Karakhanov, *J. Chem. Soc., Chem. Commun.*, 480 (1975).
(17) Infrared spectra were measured on a Perkin-Elmer 137 infrared spectrophotometer. NMR spectra were measured on a Varian Associates A-60D spectrometer with an internal tetramethylsilane standard. Chemical shifts are reported in parts per million (δ) from Me_4Si. Mass spectra were measured on an LKB 9000 by direct insertion. Melting and boiling points are uncorrected.

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

Tzoong-Chyh Lee* and Gad Salemnick

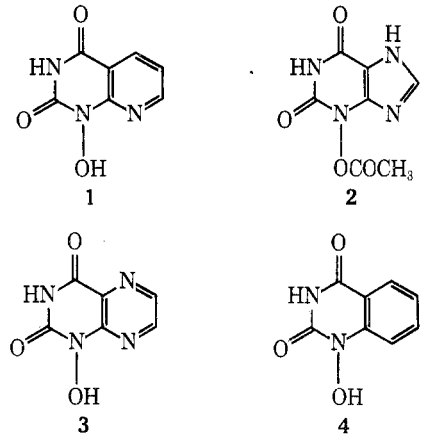
Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Received June 23, 1975

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.

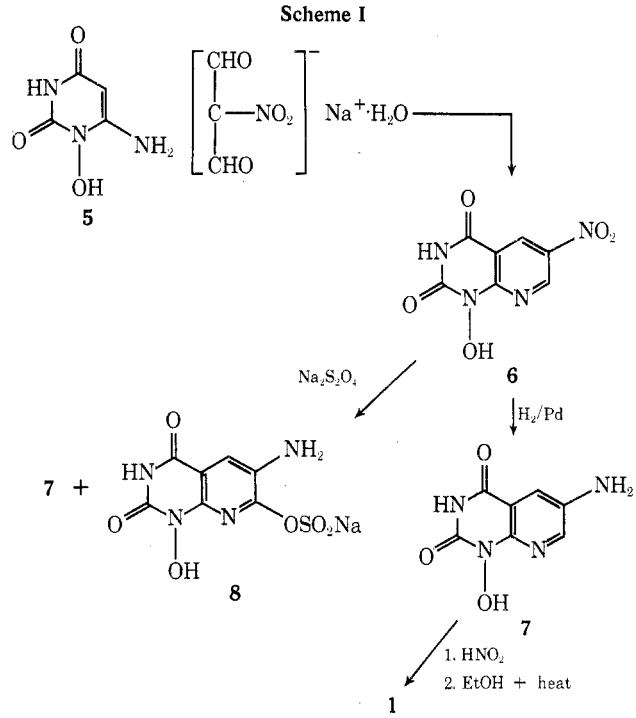
Chart I



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**