38-9; **39**, 40954-39-0; **40**, 40954-40-3; **41**, 40954-41-4; **41** semicarbazone, 40954-42-5; **42**, 40954-43-6; **43**, 1121-65-9; **44**, 1901-34-4; **45**, 40954-46-9; **46**, 40954-47-0; **47**, 40954-48-1; **50**, 40954-49-2; **51**, 934-62-3; **52**, 16177-46-1; **53**, 40954-52-7; **54**, 40954-53-8; **55**, 40954-54-9; **56**, 40954-55-0; **57**, 40954-56-1; **58**, 40954-57-2; **59**, 40954-58-3; **60**, 40954-59-4; **61**, 40954-60-7; **61** 2,4-DNPH, 40954-61-8; **62**, 2826-65-5; **63**, 40954-63-0; **65**, 22118-00-9.

The Synthesis of an Analog of Camptothecin by a General Method

ROBERT E. LYLE,* JAMES A. BRISTOL,[1a,b] MICHAEL J. KANE,[1a] AND DAVID E. PORTLOCK

Department of Chemistry, Parsons Hall, University of New Hampshire, Durham, New Hampshire 03824

Received May 1, 1973

The introduction of the α-hydroxybutyrate chain on the 4 position of β-picoline *via* the 4-lithio derivative gave **7**. The oxidation of the 3-methyl substituent required for lactone formation between the substituents on the 3 and 4 positions of **7** to give **14** could only be accomplished after introducing a chloro group adjacent to the ring nitrogen. The quaternization of **2** and the hydrolysis of the aryl-α-chloro substituent completed the synthesis of the camptothecin analog **16**.

The discovery was made that the alkaloid camptothecin (**1**) possessed a high activity against several mouse lymphocytic leukemias[2] and inhibited the growth of solid tumors as well. The isolation of the 10-hydroxy- and 10-methoxycamptothecin as minor alkaloids from *Camptotheca acuminata* provided compounds with activity against leukemia, L1210.[3] The limited availability of the natural material provided an impetus for the synthesis of camptothecin and led to several successful preparations during a 1-year period.[4] The toxicity observed on continued administration of camptothecin led to an increased interest in the synthesis of close structural analogs as a possible means of obtaining compounds which retained the desirable anticancer effects but with reduced chronic toxicity. This article reports a general method for the synthesis of such compounds using an analog with the A and B rings carbocyclic and a seco ring C to illustrate the method.

The antineoplastic activity of camptothecin has been shown to be associated with the pyridone and lactone systems of the D and E rings.[2] Simple D and E ring analogs having methyl substituents on the pyridone ring at the 6 position[4c] or 1 position[4f,g] have been reported and the former was reported to have 0.01 times the activity of camptothecin as a cytotoxic agent. The synthetic methods used for these analogs were not readily applicable for the preparation of a variety of N-substituted derivatives which might be converted to pentacyclic analogs. The synthetic scheme utilized in this study provided a logical approach to any aromatic pentacyclic analog as well as natural camptothecin.

The crucial intermediate in this synthesis was the pyrido-δ-lactone **2**. β-Picoline *N*-oxide[5] was nitrated following the procedure of Taylor and Crovetti to give the 4-nitro derivative **3**, which was converted by acetyl bromide[6] or hydrobromic acid[7] to 84 or 81% of 4-bromo-β-picoline 1-oxide (**4**), respectively. Attempts to cause the displacement of the nitro group by bromine and reduction of the *N*-oxide in the same reaction with phosphorus tribromide[7] gave a mixture of **5** and 4-nitro-β-picoline (**6**). A more satisfactory route to **5** was by the two-step conversion from **3** using Raney nickel catalyst to remove the *N*-oxide function from **4** following a procedure described for a related reaction.[8] This reaction gave 83% yields of **5**, isolated as the hydrobromide, with no complication of nucleophilic displacement of the 4-bromo group as was observed when phosphorus trichloride was used for the reduction.

Alkylation of 4-nitro-β-picoline 1-oxide (**3**) or 4-bromo-β-picoline 1-oxide (**4**) by nucleophilic displacement of the 4 substituent by a carbanion proved unsuccessful. Thus the sodium salts of ethyl cyanoacetate and diethyl ethylmalonate in several solvents failed to give reaction. Spectroscopic evidence for a very small yield from the reaction of the sodium salt of diethyl malonate and 4-bromo-β-picoline 1-oxide (**4**) was obtained. The yield could not be improved by the application of more vigorous reaction conditions, so the introduction of the 4 side chain by this approach was abandoned.

(1) (a) This research was abstracted from the theses of J. A. B. and M. J. K. presented to the Graduate School of the University of New Hampshire in partial fulfillment of the requirements for the Ph.D. degree. (b) NDEA Fellow, 1969–1971; UNH Dissertation Year Fellow, 1971–1972.

(2) (a) M. E. Wall, Abstracts, 4th International Symposium on the Biochemistry and Physiology of Alkaloids, Halle, East Germany, Academic Press, Berlin, 1969, pp 77–87; (b) R. C. Gallo, J. Whang-Peng, and R. H. Adamson, *J. Nat. Cancer Inst.*, **46**, 789 (1971); (c) H. B. Bosmann, *Biochem. Biophys. Res. Commun.*, **41**, 1412 (1970); (d) R. S. Wu, A. Kuman, and J. R. Warner, *Proc. Nat. Acad. Sci. U. S.*, **68**, 3009 (1971); (e) D. Kessel, *Cancer Res.*, **31**, 1883 (1971); (f) J. A. Gottlieb, A. M. Guarino, J. B. Call, V. T. Oliverio, and J. B. Block, *Cancer Chemother. Rep. Part 1*, **54**, 461 (1970); (g) J. L. Hartwell and B. J. Abbott, *Advan. Pharmacol. Chemother.*, **7**, 137 (1969); (h) L. G. Hart, J. B. Call, and V. T. Oliverio, *Cancer Chemother. Rep.*, **58**, 211 (1969); (i) S. Danishefsky and J. Quick, *Tetrahedron Lett.*, (1973).

(3) (a) M. C. Wani and M. E. Wall, *J. Org. Chem.*, **34**, 1364 (1969); (b) M. Shamma, *Experientia*, **24**, 107 (1968).

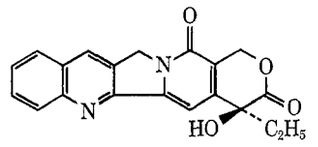
(4) (a) G. Stork and A. Schultz, *J. Amer. Chem. Soc.*, **93**, 4074 (1971); (b) R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *J. Amer. Chem. Soc.*, **93**, 5576 (1971); (c) M. C. Wani, H. F. Campbell, G. A. Brine, J. A. Kepler, M. E. Wall, and S. G. Levine, *ibid.*, **94**, 3631 (1972); M. E. Wall, H. F. Campbell, M. C. Wani and S. G. Levine, *ibid.*, **94**, 3632 (1972); (d) E. Winterfeldt, T. Korth, D. Pike, and M. Boch, *Angew. Chem., Int. Ed. Engl.*, **11**, 289 (1972); (e) M. Boch, T. Korth, J. M. Nelke, D. Pike, and E. Winterfeldt, *Chem. Ber.*, **105**, 2126 (1972); (f) C. Tang and H. Rapoport, *J. Amer. Chem. Soc.*, **94**, 8615 (1972); J. J. Plattner, R. D. Gless and H. Rapoport, *ibid.*, **94**, 8613 (1972); (g) T. Sugasawa, T. Toyoda, and K. Sasakura, *Tetrahedron Lett.*, 5109 (1972); (h) A. S. Kende, T. J. Bentley, R. W. Draper, J. K. Jenkins, M. Joyeux, and I. Kubo, *ibid.*, 1307 (1973); (i) A. I. Meyers, R. L. Nolen, E. W. Collington, T. A. Narwid, and R. Strickland, *J. Org. Chem.*, **38**, 1974 (1973); J. F. Hansen, K. Kamata, and A. I. Meyers, *J. Heterocycl. Chem.*, **10**, in press; (j) a summary of the research on camptothecin will appear by A. G. Schultz, *Chem. Rev.*, in press; (k) M. Shamma, D. S. Smithers, and V. St. Georgiev, *Tetrahedron*, **29**, 1949 (1973).

(5) E. C. Taylor and H. J. Crovetti, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 654.

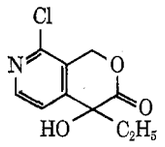
(6) S. Kajuhara, *Nippon Kagaku Zasshi*, **86**, 1060 (1965); *Chem. Abstr.*, **65**, 16936 (1966).

(7) R. A. Abramovitch and M. Saha, *Can. J. Chem.*, **44**, 1765 (1966).

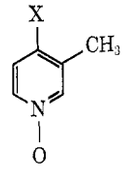
(8) E. Hayashi, H. Yamanaka, and K. Shimigu, *Chem. Pharm. Bull.*, **7**, 141 (1959).



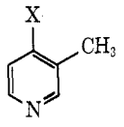
1



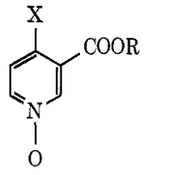
2



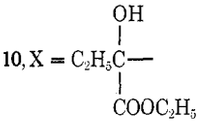
3, X = NO_2
4, X = Br



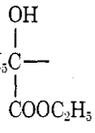
5, X = Br, HCl
6, X = NO_2



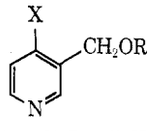
8a, X = NO_2; R = H
b, X = Br; R = H
c, X = CH_3O; R = CH_3
d, X = Cl; R = CH_3
e, X = Cl; R = H



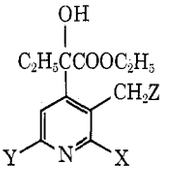
10, X = $C_2H_5C(OH)(COOC_2H_5)$—



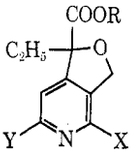
7, X = $C_2H_5C(OH)(COOC_2H_5)$—



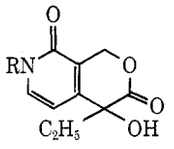
9a, X = Cl; R = H(HBr)
b, X = I; R = H(HBr)



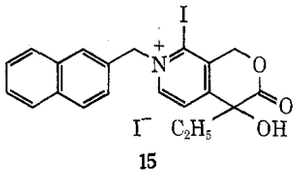
11a, X = Cl; Y = H; Z = Br
b, X = H; Y = Cl; Z = Br
13a, X = Cl; Y = H; Z = OAc
b, X = H; Y = Cl; Z = OAc



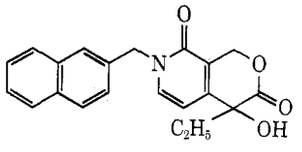
12a, X = Cl; Y = H; R = H
b, X = H; Y = Cl; R = H



14, R = H



15



16

The reported conversion of 4-bromopyridines to Grignard reagents was difficult;[9] however, the 4-lithio derivatives were reported to be formed by metal–halogen exchange and to undergo reaction with ketones successfully.[7,9] The reaction of 4-lithio-3-methylpyridine, from the reaction of **5** with *n*-butyllithium, with ethyl α-ketobutyrate gave a 52% yield of ethyl 2-hydroxy-2-(3′-methyl-4′-pyridyl)butyrate (**7**) which could be isolated in two crystalline forms, mp 72–73 and 108–110°. The solution spectra of the two forms were identical; however, the infrared spectra as mulls showed small but definite differences.

All attempts to brominate or oxidize the 3-methyl substituent of **7** to close the lactone ring failed.[10] The conversion of 4-nitronicotinic acid 1-oxide (**8a**) to 4-halo-3-hydroxymethylpyridines (**9**) could be accomplished; however, attempts to protect the hydroxyl group and form the 4-lithio derivative failed. Thus the introduction of the 4 side chain after the oxidation of the 3 substituent did not prove successful.

The discovery that the steric and electronic effects of a 2-chloro substituent permitted bromination of β-methyl quinolines and pyridines with *N*-bromosuccinimide[10] suggested a method of circumventing the difficulty in closing the lactone to form **2**. The conversion of **7** to the *N*-oxide **10** with *m*-chloroperoxybenzoic acid was easily accomplished and reaction of **10** with phosphorus oxychloride gave a mixture of 2- and 6-chloro derivatives which readily underwent benzylic bromination to form a mixture of **11a** and **11b** in 80% yield from **7**.

The treatment of the mixture of **11a** and **11b** with base in water or DMSO gave a product which clearly was a carboxylic acid, based on its solubility in base and conversion to a methyl ester in methanolic hydrogen chloride. The spectral data suggested that intramolecular cyclization had occurred with ether formation to give **12**, followed by saponification of the ester. The proton magnetic resonance spectrum of the methyl ester of **12** showed it to be the 2-chloro derivative only, for the aromatic hydrogens gave an AB quartet and there was no evidence of a mixture from the other signals as well.

Since the cyclization to form the ether was so rapid with strong base, it was evident that displacement of the benzylic bromide by a weakly basic oxygen nucleophile would be required prior to saponification of the ester. The mixture of **11a** and **11b** was therefore treated with potassium acetate in acetic acid to form the mixture of acetates **13a** and **13b**. Hydrolysis of the acetate mixture of **13a** and **13b** in methanolic potassium hydroxide and acidification gave 7-chloropyrido[5,4-*c*]-2-oxo-3-ethyl-3-hydroxy-3,6-dihydropyran (**2**) in 23% yield from the *N*-oxide **10**. No product could be isolated which arose from the 6-chloro series (**11b** and **13b**). Possibly the less hindered 6-chloro substituent underwent nucleophilic displacement to give the pyridone which was lost in the isolation of **2**.

The 2-chloro group of **2** was inert to nucleophilic displacement in acidic or basic media. The pyridone **14** was formed by photochemical nucleophilic substitution.[11]

The formation of quaternary salts of **2** was very difficult. Heating **2** with methyl iodide, benzyl bromide, or 2-bromo-3-bromomethylquinoline failed to give any salt. The addition of sodium iodide to the reaction mixture of **2** and 2-bromomethylnaphthalene with no solvent gave a quantitative yield of the 2-napthylmethyl iodide salt of 7-iodopyrido-[5,4-*c*]-2-oxo-3-ethyl-3-hydroxy-3,6-dihydropyran (**15**). The salt **15** on standing in dimethyl sulfoxide[12,13] was cleanly converted to the pyridone **16** in quantitative yield.

The reactions provide a general procedure for the preparation of pyridone analogs of camptothecin. This route is currently being explored as a method of preparing other such compounds.

(9) I. P. Wibaut and L. G. Herringa, *Recl. Trav. Chim. Pays-Bas*, **74**, 1003 (1955).
(10) R. E. Lyle, D. E. Portlock, M. J. Kane, and J. A. Bristol, *J. Org. Chem.*, **37**, 3967 (1972).
(11) D. E. Portlock, M. J. Kane, J. A. Bristol, and R. E. Lyle, *J. Org. Chem.*, **38**, 2351 (1973).
(12) R. E. Lyle and M. J. Kane, *J. Org. Chem.*, in press.
(13) N. D. Harris, *Synthesis*, 625 (1972).

Experimental Section

Preparation of 4-Bromo-β-picoline Hydrochloride (5).—A solution of 4-bromo-β-picoline *N*-oxide[7] (4) (20.0 g, 0.106 mol) in 200 ml of methanol was reduced with hydrogen (1 atm over water) over about 3 g of W-2 Raney nickel[14] until hydrogen uptake ceased (about 3 hr). A total of 2.5 l. of hydrogen (about 93% of the theoretical amount) was absorbed. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to remove most of the methanol. The residual liquid was diluted with 600 ml of dry ether, and the mixture was filtered. The filtrate was treated with gaseous HCl, and the hydrochloride was collected by filtration, washed with several portions of ether, and then dried in a vacuum desiccator to give 18.4 g (83%) of 4-bromo-β-picoline hydrochloride (5), mp 177–179°. An analytical sample was prepared by two recrystallizations of the salt from acetonitrile–ether to give pure 5, mp 178–179°.

Anal. Calcd for C_6H_7BrClN: C, 34.53; H, 3.35; N, 6.71. Found: C, 34.38; H, 3.15; N, 6.59.

Preparation of Ethyl 2-Hydroxy-2-(3′-methyl-4′-pyridyl)butyrate (7). A. From 4-Bromo-β-Picoline (5).—A solution of freshly distilled 4-bromo-β-picoline (16.2 g, 94.2 mmol), prepared from the hydrochloride 5 in 125 ml of dry ether was cooled to −50° in an addition funnel surrounded by Dry Ice. This solution was added dropwise over 0.5 hr to a stirred solution of 100 mmol of *n*-butyllithium in 66 ml of hexane and 100 ml of ether which was cooled in a Dry Ice–2-propanol bath. The reaction mixture was stirred for an additional 0.25 hr and then 14.0 g (108 mmol) of ethyl α-ketobutyrate[15] in 100 ml of ether was added over 10 min. The reaction mixture was stirred for an additional 0.3 hr and then allowed to warm to −30°. To this mixture was added dropwise 40 ml of 10% HCl. After warming to 0°, the layers were separated and the organic layer was extracted four times with 30-ml portions of 10% HCl. The combined acidic extracts were extracted with three 50-ml portions of ether, and the acidic solution was then basified with solid sodium carbonate. The basic solution was extracted with three 200-ml portions of ether, and the extract was dried (K_2CO_3) and concentrated under reduced pressure to give an orange oil which partially crystallized on standing for 18 hr in an ether–pentane solution in the refrigerator. The solid was separated by filtration and washed with cold pentane to give 6.5 g (31%) of crude 7, mp 70–73°. An analytical sample, mp 70–71°, was prepared by vacuum sublimation.

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.57; H, 7.62; N, 6.28. Found: C, 64.54; H, 7.79; N, 6.28.

B. From 4-Bromo-β-picoline Hydrochloride (5).—4-Bromo-β-picoline hydrochloride (5) (13.5 g, 64.5 mmol) was basified with a cold slurry of concentrated K_2CO_3 solution and the basic solution was extracted with 350 ml of ether in several portions. The extract was dried (K_2CO_3) and concentrated to a volume of 125 ml. Under a positive pressure of nitrogen, this ethereal solution was added over 0.5 hr to a vigorously stirred solution of 78 mmol of *n*-butyllithium in 50 ml of hexane and 80 ml of ether kept in a Dry Ice–2-propanol bath. The reaction mixture was stirred for an additional 0.25 hr and then 10.0 g (76.9 mmol) of ethyl α-ketobutyrate in 75 ml of ether was added over 5 min. The reaction was worked up as in A to give 7.5 g (52%) of the second allotropic form of 7, mp 102–104°, which gave pmr and ir spectra in solution identical with those of the form which melted at 70–71°.

Preparation of 4-Bromonicotinic Acid *N*-Oxide (8b).—4-Nitronicotinic acid *N*-oxide (8a)[16] (70.0 g, 0.381 mol) was added slowly to 285 ml of cold acetyl bromide. The mixture was then heated under reflux for 1 hr. The reaction mixture was cooled and the solid product was collected by filtration and washed with cold acetone and cold water. The solid was dried in a vacuum desiccator to give 62.7 g (76%) of 8b, mp 155° dec. An analytical sample was prepared by two recrystallizations of the solid from water to give 8b, mp 167° dec.

Anal. Calcd for $C_6H_4NBrO_3$: C, 33.02; H, 1.84; N, 6.42. Found: C, 32.86; H, 1.82; N, 6.35.

Preparation of Methyl 4-Methoxynicotinate *N*-Oxide (8c).—Following the method of Taylor and Crovetti,[17] a mixture of 6.00 g (32.6 mmol) of 4-nitronicotinic acid *N*-oxide (8a) and 120 ml of methanol was cooled to 0° and treated with gaseous HCl for 10 min. After 5 min, solution was achieved. The reaction was heated under reflux for 2 hr, and the solvent was removed by distillation under reduced pressure. Water was added to the residue and potassium carbonate was added. Extraction into chloroform, drying, and concentration gave an oil which crystallized with ether to give 3.4 g (57%) of 8c, mp 101–104°,[18] picrate mp 144–145.5° (lit.[17] mp 146–147°). The esterification of 8a with methanol using hydrogen bromide as catalyst also gave 8c, mp 118–121°.

Preparation of Methyl 4-Chloronicotinate *N*-Oxide (8d). A. From 4-Bromonicotinic Acid *N*-Oxide (8b).—A mixture of 29.0 g (0.133 mol) of 4-bromonicotinic acid *N*-oxide (8b) and 150 ml of purified thionyl chloride was heated under reflux for 0.75 hr. Excess thionyl chloride was removed by distillation under reduced pressure, the residue was dissolved in 150 ml of cold methanol, and after 1 hr at room temperature the excess was removed by evaporation. The residue was dissolved in 100 ml of chloroform, and the solution was added dropwise to a slurry of saturated K_2CO_3 solution (100 ml) and chloroform (100 ml) at −5°. The layers were separated and the aqueous layer was filtered. The filter cake was washed with three 100-ml portions of chloroform which were then used to extract the aqueous solution. The combined extracts were dried (K_2CO_3) and concentrated under reduced pressure to give a light yellow solid which was triturated thoroughly with pentane and then dried in a vacuum desiccator to give 15.5 g (62%) of the methyl ester 8d, mp 105–106°.[19] An analytical sample, mp 105.5–106.5°, was prepared by two recrystallizations from benzene.

Anal. Calcd for $C_7H_6NClO_3$: C, 44.80; H, 3.20; N, 7.46. Found: C, 44.64; H, 2.97; N, 7.60.

Preparation of Methyl 4-Chloronicotinate *N*-Oxide (8d). B. From 4-Chloronicotinic Acid *N*-Oxide (8e).—4-Chloronicotinic acid *N*-oxide (8e) (40.0 g, 0.231 mol) was added to 200 ml of thionyl chloride and the mixture was heated under reflux for 0.5 hr. The excess thionyl chloride was removed by evaporation under reduced pressure and residual solid was dissolved in 150 ml of cold methanol and stirred in an ice bath for 0.25 hr. Ether (300 ml) was added, and the white solid which precipitated was collected by filtration. A solution of the solid in water was neutralized with potassium carbonate and worked up as in A to give 36.0 g (83%) of 8d, mp 116–117° dec, picrate mp 118–119° (methanol).

Preparation of Methyl 4-Chloronicotinate Hydrobromide.—A stirred solution of methyl 4-chloronicotinate *N*-oxide (8d) (20.0 g, 0.107 mol) in 200 ml of methanol was reduced with hydrogen (1 atm) over W-2 Raney nickel (21 g added in approximately three equal portions over 2.75 hr). The total uptake of hydrogen during this period was about 2 l. (90% of the theoretical amount). The product was isolated as in the preparation of 5 to give 24.1 g (89%) of the ester hydrobromide, mp 144–145° dec. An analytical sample, mp 138.5–140° dec, was prepared by recrystallization from acetone.

Anal. Calcd for $C_7H_7NBrClO_2$: C, 33.27; H, 2.77; N, 5.54. Found: C, 32.74; H, 2.70; N, 5.24.

Preparation of 4-Chloro-3-hydroxymethylpyridine Hydrobromide (9a).—Methyl 4-chloronicotinate hydrobromide (11.5 g, 45.7 mmol) was converted to the base with cold K_2CO_3 solution. To a solution in 75 ml of dry ether was added 38.8 mmol of $LiAlH_4$ in 65 ml of ether over 0.3 hr while cooling. Stirring was continued for 1 hr and then the reaction mixture was hydrolyzed by the successive dropwise addition of 1.5 ml of water, 1.5 ml of 15% NaOH, and then 4.5 ml of water and filtered. The filter cake was washed with ether, and the combined ether washings were dried and concentrated to give a light yellow solid which was taken up in ether and treated with anhydrous hydrogen bromide. The white product was collected by filtration, washed with ether, and dried in a vacuum desiccator to give 7.60 g (74%) of 9a, mp 160.5–161°.

Anal. Calcd for $C_6H_7BrClNO$: C, 32.07; H, 3.11; N, 6.23. Found: C, 32.16; H, 2.88; N, 5.94.

Preparation of 4-Iodo-3-hydroxymethylpyridine Hydrobromide (9b).—A mixture of 4-chloro-3-hydroxymethylpyridine hydrobromide (9a) (3.00 g, 13.4 mmol), sodium iodide (18 g), and methyl ethyl ketone (150 ml) was heated under reflux in an oil

(14) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965, p 147.

(15) E. Vogel and H. Sching, *Helv. Chim. Acta*, **33**, 116 (1950).

(16) G. M. Badger and R. P. Rao, *Aust. J. Chem.*, **17**, 1399 (1964).

(17) E. C. Taylor and A. J. Crovetti, *J. Amer. Chem. Soc.*, **78**, 214 (1956).

(18) The melting point of this compound was erroneously reported as 141–143° in ref 17.

(19) The melting point was reported to be 84° in ref 17.

bath for 23 hr. Treatment with water, base, and 40% sodium bisulfite solution gave the base of **9b** which was taken up in acetone and saturated with HBr. Ether (50 ml) was added to the mixture, and the salt was collected and washed with several portions of ether to give 2.79 g (66%) of **9b**, mp 161–162°.

Anal. Calcd for C_6H_7BrINO: C, 22.78; H, 2.21; N, 4.43. Found: C, 23.56; H, 2.14; N, 4.32.

Preparation of Ethyl 2-Hydroxy-2-(3′-methyl-4′pyridyl)butyrate *N*-Oxide (10).—A solution of ethyl 2-hydroxy-2-(3′-methyl-4′-pyridyl)butyrate (**7**) (1.00 g, 4.48 mmol) and 85% *m*-chloroperbenzoic acid (1.36 g, 6.72 mmol) in 40 ml of chloroform was allowed to stand at room temperature for 3 hr. The solution was poured into water and made basic with solid potassium carbonate. This solution was extracted with four 40-ml portions of chloroform, and the extract was dried (K_2CO_3) and concentrated under reduced pressure to give 940 mg (88%) of **10**, mp 172–173°. An analytical sample, mp 175.5–176°, was prepared from two recrystallizations from acetone.

Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.30; H, 7.12; N, 5.86. Found: C, 60.58; H, 7.19; N, 5.99.

Preparation of Ethyl 2-Hydroxy-2-[2′(6′)-chloro-3′-bromomethyl-4′-pyridyl]butyrate (11a and 11b).—A solution of *N*-oxide **10** (860 mg, 3.50 mmol) in 10 ml of $POCl_3$ was heated under reflux in an oil bath for 0.5 hr. After cooling the solution was poured over crushed ice and neutralized with solid K_2CO_3. The basic solution was extracted with four 50-ml portions of ether, and the extract was dried (K_2CO_3) and concentrated under reduced pressure to give 880 mg (95%) of the α-chloro derivative which was brominated without further purification.

A mixture of the chloropyridines (770 mg, 2.95 mmol), NBS (670 mg, 3.76 mmol), a catalytic amount of dibenzoyl peroxide, and 15 ml of carbon tetrachloride (stored over 4-A molecular sieves) was heated under reflux by means of a 100-W bulb for 3.5 hr. An additional 350 mg (1.97 mmol) of NBS was added and the heating was continued for 2.5 hr. The mixture was cooled and filtered. The filter cake was washed with several portions of CCl_4, and the filtrate was concentrated under reduced pressure to give 920 mg (92%) of **11a** and **11b** which was used directly.

Hydrolysis of 11a and 11b with Potassium Hydroxide in Aqueous DMSO.—To the bromomethylpyridines **11** (1.25 g, 3.70 mmol) from above was added a 2 *N* solution of KOH in 1:1 DMSO–H_2O and the solution was allowed to stand at ambient temperature for 3 hr. Water and hydrochloric acid were added and the solution was extracted with several portions of chloroform. The extract was dried (Na_2SO_4) and concentrated under reduced pressure to give 500 mg (59%) of **12** as a yellow oil: ir (neat) 3500–2500 and 1720 cm^{-1}; pmr ($CDCl_3$) δ 0.92 (t), 1.20 (m), 2.15 (m), 5.27 (s), 7.53 (d, 4.5 Hz), 8.49 (d, 4.5 Hz), and 11.6 (s).

Preparation of 7-Chloropyrido[5,4-*c*]-2-oxo-3-ethyl-3-hydroxy-3,6-dihydropyran (2).—A solution of crude brominated pyridines **11** (920 mg, 2.85 mmol) from above and 1.40 g of potassium acetate in 10 ml of acetic acid was heated at 110° in an oil bath for 10 hr. The mixture was then poured into ice water and basified with solid $NaHCO_3$. The solution was extracted with three 50-ml portions of chloroform and the extract was dried (K_2CO_3) and concentrated under reduced pressure to give 660 mg (73%) of the acetate **13** as a brown oil. The oil was dissolved in a 1 *N* solution of KOH in 5 ml of methanol and 5 ml of water, and the solution was heated under reflux for 2.5 hr. The solution was then poured into 40 ml of water and chilled in an ice bath. Concentrated HCl was added until the solution was acidic; and after stirring for 0.25 hr, solid $NaHCO_3$ was added until the solution had been neutralized. Extraction with three portions of chloroform gave, after drying (K_2CO_3) and concentration under reduced pressure, an oil which solidified to give 94.3 mg (20%) of **2**, mp 95–105°. In another set of experiments, **2** was isolated in about 35% yield from **13** and in 23% yield from the *N*-oxide **10**. An analytical sample of **2**, mp 116–119°, was prepared by three vacuum sublimations.

Anal. Calcd for $C_{10}H_{10}ClNO_3$: C, 52.74; H, 4.39; N, 6.15. Found: C, 52.53; H, 4.52; N, 6.36.

Photolysis of 7-Chloropyrido[5,4-*c*]-2-oxo-3-ethyl-3-hydroxy-3,6-dihydropyran (2).—A dilute solution of **2** in concentrated hydrochloric acid was irradiated for 16 min with a 450-W Hanovia lamp using a Vycor filter. The ultraviolet absorption of **2** at the start showed absorption at 263 nm with a shoulder at 270 nm. After the irradiation the solution gave maximum absorption at 295, 264 (sh), and 255 nm, corresponding to the absorption of the pyridone **14**.

Preparation of the 2-Naphthylmethyl Quaternary Salt of 2.—To 200 mg (0.88 mmol) of 7-chloropyrido[5,4-*c*]-2-oxo-3-ethyl-3-hydroxy-3,6-dihydropyran (**2**) and 200 mg (0.88 mmol) of 2-bromomethylnaphthalene was added 256 mg (1.7 mmol) of sodium iodide. The mixture was heated under nitrogen in an oil bath. When the oil bath reached 125° a solid had formed and heating was discontinued. Ethyl acetate was added and the insoluble solid was separated by filtration and washed with water and ether. After drying the solid a quantitative yield of the quaternary salt **15**, mp 182.5–184°, was obtained.

Anal. Calcd for $C_{21}H_{19}I_2NO_3$: C, 42.95; H, 3.26; N, 2.38. Found: C, 42.54; H, 3.25; N, 2.48.

Preparation of the Pyridone 16 from the Salt 15.—A solution of the quaternary salt **15** in dimethyl sulfoxide was allowed to stand for 2 weeks at room temperature. The solution was poured into water and ether was added. The solid which precipitated was removed by filtration and washed with water and ether. After drying, the solid represented a quantitative yield of the pyridone **16**, mp 187–189°.

Anal. Calcd for $C_{21}H_{19}NO_4 \cdot H_2O$: C, 68.65; H, 5.22; N, 3.81. Found: C, 68.73; H, 5.29; N, 4.11.

Acknowledgment.—The authors wish to express appreciation to the National Cancer Institute of the National Institutes of Health for partial support of this research by grant CA-12149-01 and -02. The *n*-butyllithium used in this research was generously suppled by Foote Mineral Co. by Dr. O. F. Beumel.

Registry No.—**2**, 40899-34-1; **4**, 10168-58-8; **5**, 10168-00-0; **5** hydrochloride, 40899-37-4; **7**, 40899-38-5; **8a**, 1078-05-3; **8b**, 40899-40-9; **8c**, 40899-41-0; **8c** picrate, 40899-42-1; **8d**, 40899-43-2; **8d** picrate, 40899-44-3; **8e**, 1074-93-7; **9a**, 40899-46-5; **9b**, 40899-47-6; **10**, 40899-48-7; **11a**, 40899-49-8; **11b**, 40899-50-1; **12a**, 40899-51-2; **15**, 40899-52-3; **16**, 40899-53-4; methyl 4-chloronicotinate hydrobromide, 40899-54-5.