Table III—Absorption Rate Constants at pH 4.0 and Related Parameters for Penicillins

Number	Penicillin	Molecular Weight (MW)[a]	pKa[b]	log P_u^b	k_a, 10^3 min^{-1}
1	Penicillin V	350.4	2.79	1.95	5.22
2	Phenethicillin	364.4	2.80	2.20	7.08
3	Propicillin	378.4	2.76	2.70	12.48
4	Oxacillin	401.4	2.73	2.31	8.05
5	Cloxacillin	435.9	2.78	2.43	7.05
6	Floxacillin	453.9	2.76	2.61	10.15
7	Dicloxacillin	470.3	2.76	2.91	16.25

[a] As free acid. [b] P_u is the partition coefficient of the undissociated penicillins in the octanol–water system. All data were at 37° and taken from Ref. 14.

perimental values. This finding indicates that the absorption of monobasic penicillins, excluding amphoteric ones such as amoxicillin and cyclacillin (6, 7), follows the common mechanisms of: (*a*) the lipoidal membrane transport of the undissociated species permeating the aqueous diffusion layer barrier and (*b*) the apparent first-order transport of the ionized species permeating some forms of the barrier almost insensitive to antibiotic lipophilicity.

A previous study (1) revealed that, below pH 6, the intestinal absorption rate of propicillin is about 100 times faster than the gastric absorption rate. This significant difference is undoubtedly due to the relative surface area in the alimentary tract. Naturally, other monobasic β-lactam antibiotics can be expected to exhibit absorption behavior similar to propicillin. The present and previous results (1, 9) indicate that a small amount of these orally ingested antibiotics may be absorbed in the stomach while almost all absorption takes place in the duodenum, where the fluid pH is relatively lower, and that absorption occurs *via* passive diffusion of the undissociated species, largely dependent on their lipophilicity. A small amount may be also absorbed by ionic transport during the slow transit through the intestine. Poor absorbability (16) of orally ingested cephalosporins such as cefazolin, the P_u of which is about one-thirtieth lower than that of penicillin V (17), may be due to the considerable reduction of k_u values effective both in the stomach and upper duodenum.

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Pyridones as Potential Antitumor Agents

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Abstract □ Based on the finding that 3-acetoxy-2-pyridone had reproducible activity against murine P-388 lymphocytic leukemia, derivatives in this series were synthesized and evaluated to determine structural parameters important for activity. Of the 32 compounds tested, 10 were active. At least two oxygen-containing functional groups are required for P-388 activity, and the 2,3-isomeric arrangement provides the greatest activity. Carbamate or acyloxy groups in the 3-position produced the most active 2-pyridones.

Keyphrases □ Pyridone derivatives—antineoplastic activity, structure–activity relationships, mice □ Antineoplastic agents, potential—pyridone derivatives, structure–activity relationships, mice □ Structure–activity relationships—pyridone derivatives, antineoplastic activity, mice

During an investigation of hydroxypyridine derivatives, it was discovered that 3-acetoxy-2-pyridone (I) possessed reproducible activity against P-388 leukemia in mice. There are other scattered reports of pyridone antitumor activity. A nucleoside presently undergoing clinical evaluation, which can be classed as a pyridone, is 3-deazauridine (1, 2). Mimosine, a naturally occurring 4-pyridone, was reported as active against Walker 256 carcinosarcoma (3) and B16 melanotic melanoma (4). Other pyridones studied possess less antitumor activity (5–8). Based on the antitumor properties of I, a study was undertaken to determine the structural parameters important for activity.

RESULTS AND DISCUSSION

Compounds I–XXXII were evaluated. 3-Hydroxy-2-pyridone (II) was reacted with various acid chlorides, anhydrides, and isocyanates to produce 3-substituted and 1,3-disubstituted 2-pyridones. 2-Pyridone (VII) was oxidized to 5-hydroxy-2-pyridone (IV) by the Elbs persulfate reaction. UV and other spectral data were consistent with those expected for 2-pyridones (9, 10). The properties of these compounds are shown in Table I.

Antitumor activity was evaluated in the P-388 lymphocytic leukemia system using standard protocols (11) of the National Cancer Institute. Multiple biological tests were carried out with each compound using a dose response on the QD 1–9 treatment schedule. Physiological saline was the vehicle. Drugs were administered intraperitoneally to mice with

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Table I—Physical and Chemical Data

Compound	Melting Point	Yield, %	Formula	Analysis, %	
				Calc.	Found
V	166–168°	39	$C_7H_7NO_3$	C 54.88	54.85
				H 4.61	4.86
				N 9.18	9.21
XI	150–151°	74	$C_8H_9NO_3$	C 57.46	57.20
				H 5.42	5.11
				N 8.41	8.31
XII	84–88°	10	$C_8H_9NO_3$	C 57.46	57.19
				H 5.42	5.32
				N 8.41	8.20
XIII	196–198°	72	$C_9H_9NO_3$	C 60.31	60.36
				H 5.06	5.29
				N 7.85	8.05
XIV	128–129°	24	$C_{10}H_{13}NO_3$	C 61.51	61.40
				H 6.71	6.88
				N 7.20	7.05
XV	176–178°	62	$C_{16}H_{19}NO_3$	C 70.29	70.08
				H 7.01	6.95
				N 5.15	5.21
XVI	139–141°	37	$C_8H_9NO_4$	C 52.44	52.18
				H 4.95	5.17
				N 7.68	7.96
XVII	174–176°	59	$C_{12}H_9NO_3$	C 66.95	66.83
				H 4.21	4.41
				N 6.53	6.73
XVIII	200–202°	69	$C_{12}H_8FNO_3$	C 61.79	61.85
				H 3.46	3.66
				N 6.03	5.76
XIX	208°	35	$C_{12}H_8N_2O_5$	C 55.37	55.66
				H 3.09	3.42
				N 10.81	11.00
XX	269°	84	$C_{12}H_{17}N_3O_7$	C 47.20	46.90
				H 2.31	2.29
				N 13.82	13.81
XXI	190–192°	76	$C_{13}H_{11}NO_4$	C 63.66	63.52
				H 4.52	4.75
				N 5.73	5.74
XXII	164–165°	51	$C_7H_8N_2O_3$	C 49.97	49.87
				H 4.79	5.09
				N 16.72	16.49
XXIII	159–160°	50	$C_9H_{11}N_3O_4$	C 47.96	47.71
				H 4.92	5.17
				N 18.72	18.85
XXIV	138–139°	76	$C_8H_{10}N_2O_3$	C 52.71	52.74
				H 5.52	5.80
				N 15.43	15.18
XXV	178–179°	86	$C_{12}H_{16}N_2O_3$	C 60.97	61.14
				H 6.82	6.81
				N 11.90	11.71
XXVI	111–113°	18	$C_{11}H_{13}Cl_2N_3O_4$	C 40.81	40.94
				H 4.49	4.21
				N 13.03	12.84
XXVII	190–192°	33	$C_8H_{10}N_2O_3$	C 52.71	52.25
				H 5.53	5.44
				N 15.43	15.16
XXVIII	176–178°	81	$C_{12}H_{10}N_2O_3$	C 62.57	62.66
				H 4.38	4.40
				N 12.21	12.15
XXIX	197–199°	60	$C_{12}H_9FN_2O_3$	C 58.04	57.71
				H 3.65	3.84
				N 11.33	11.18
XXX	138–139°	53	$C_8H_9NO_4$	C 52.44	52.57
				H 4.95	4.89
				N 7.67	7.87
XXXI	182–184°	17	$C_6H_7NO_4S$	C 38.08	37.94
				H 3.73	3.70
				N 7.43	7.63
XXXII	172–173°	2	$C_7H_9NO_2S_2$	C 31.45	31.47
				H 3.39	3.44
				N 5.26	5.24

intraperitoneally implanted tumors. Active compounds are defined (11) as those that produce a T/C value[1] equal to or greater than 125%.

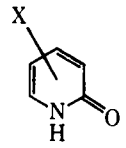
Antitumor data for the 10 reproducibly active compounds (*i.e.*, two or more T/C values ≥ 125%) are given in Table II. The compounds shown in Table I but not Table II were inactive in duplicate or two of three tests.

The initial part of this study involved a determination of whether both oxygen functions were necessary for activity and the importance of the isomeric relationship of these two groups.

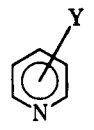
That none of the monooxygenated pyridine analogs (VII–X) related to I possessed P-388 antitumor activity was readily established.

Evaluation of the isomeric hydroxy-2-pyridones (III–VI) related to I showed that the 5-hydroxy (IV) but not the 4- or 6-hydroxy (III or VI) analogs were active. This finding is consistent with the chemical similarity of the 3- and 5-positions of the pyridine ring. The activity of the 5-acetoxy derivative (V) was variable (T/C 132, 121, and 119%). Neither 5-hydroxy analog was as active as the corresponding 3-substituted isomer. 4-Hy-

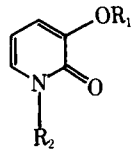
[1] T/C = (survival time of treated mice/survival time of control mice) × 100%.



I: X = 3-$OCOCH_3$
II: X = 3-OH
III: X = 4-OH
IV: X = 5-OH
V: X = 5-$OCOCH_3$
VI: X = 6-OH



VII: Y = 2-OH
VIII: Y = 3-OH
IX: Y = 3-$OCOCH_3$
X: Y = 4-OH



XI: R_1 = COC_2H_5, R_2 = H
XII: R_1 = $COCH_3$, R_2 = CH_3
XIII: R_1 = CO(cyclopropyl), R_2 = H
XIV: R_1 = CO(*tert*-butyl), R_2 = H
XV: R_1 = CO(1-adamantyl), R_2 = H
XVI: R_1 = $COCH_2OCH_3$, R_2 = H
XVII: R_1 = COC_6H_5, R_2 = H
XVIII: R_1 = COC_6H_4F(4-substituted); R_2 = H
XIX: R_1 = $COC_6H_4NO_2$(4-substituted), R_2 = H
XX: R_1 = $COC_6H_3(NO_2)_2$(2,4-disubstituted), R_2 = H
XXI: R_1 = $COC_6H_4OCH_3$(4-substituted), R_2 = H
XXII: R_1 = $CONHCH_3$, R_2 = H
XXIII: R_1 = R_2 = $CONHCH_3$
XXIV: R_1 = $CONHC_2H_5$, R_2 = H
XXV: R_1 = CONH(cyclohexyl), R_2 = H
XXVI: R_1 = R_2 = $CONHCH_2CH_2Cl$
XXVII: R_1 = $CON(CH_3)_2$, R_2 = H
XXVIII: R_1 = $CONHC_6H_5$, R_2 = H
XXIX: R_1 = $CONHC_6H_4F$(4-substituted), R_2 = H
XXX: R_1 = $COOC_2H_5$, R_2 = H
XXXI: R_1 = SO_2CH_3, R_2 = H
XXXII: R_1 = R_2 = SO_2CH_3

droxy-2-pyridone (III), the parent base for 3-deazauridine, had no P-388 activity, in contrast to the activity shown by both that nucleoside and II in this tumor system.

With the knowledge that at least two oxygen functions were required for antitumor activity and that 2,3-substitution was optimum, several derivatives of II were planned, prepared, and evaluated. Based on the observation that I was more active than II, several different types of derivatives were prepared at the 3-hydroxy position. Most of the derivatives were capable of hydrolysis since it was established early in the series that the ethers prepared in the 3-position were not active.

3-Acetoxy-2-pyridone (I) had good activity at high doses (Table II). The parent compound, 3-hydroxy-2-pyridone (II), also was active but somewhat less so than I. *N*-Methylation of I to give XII provided an active but toxic compound.

Variations in the alkyl portion of the acyl group in the 3-position produced both active and inactive materials. An ethyl group (XI) provided reproducible activity, while the cyclopropyl (VIII), methoxymethyl (XVI), *tert*-butyl (XIV), and adamantyl (XV) compounds were inactive. The aryl substitution (XVII–XXI), which was chosen to affect the ester hydrolysis rate, produced no activity differences and uniformly abolished activity.

The reaction of II with isocyanates to provide alkyl- or arylaminocarbonyl analogs (carbamates) produced several active compounds (XXII–XXIV, XXVIII, and XXIX). In some instances (XXIII and XXVI), *N*- as well as *O*-substitution occurred. The methylamino and ethylamino compounds (XXII and XXIV) were active, but the cyclohexylamino (XXV) and dimethylamino (XXVII) analogs were not. Although 2-chloroethylisocyanate formed a diadduct (XXVI), which was inactive, the methylisocyanate diadduct (XXIII) was one of the most active derivatives prepared. Neither the monoadduct (XXXI) nor the diadduct (XXXII) from methanesulfonyl chloride was active. While the ethylcarbamate (XXIV) was active, the corresponding carbonate (XXX) was not.

This investigation indicates that derivatives of 3-hydroxy-2-pyridone can provide moderate activity against P-388 leukemia. At least two oxygen functions are required, with the 2,3-isomer being the most active.

Table II—2-Pyridones Reproducibly Active against P-388 Lymphocytic Leukemia [a]

Compound	Optimum Dose[b], mg/kg/day	T/C[c]	T − C[d]
I	600	163	−2.8
II	400	138	−2.4
IV	200	128	+0.8
XI	400	143	−0.8
XII	600	144	−5.0
XXII	400	153	−4.6
XXIII	150	161	−3.3
XXIV	200	129	−1.7
XXVIII	100	132	−4.6
XXIX	25	134	−2.0

[a] With 10^6 cells implanted intraperitoneally in CDF_1 mice. [b] Dose giving the maximum T/C value on the intraperitoneal QD 1–9 treatment schedule. [c] At least one other active test (T/C ≥ 125%) was obtained in a separate, duplicate experiment. [d] Weight difference between treated and control animals 5 days after tumor implant.

Bioisosteres, 4-pyridones, and pyridone nucleosides are being studied currently. Also under investigation is the possibility that biological oxidation of the hydroxypyridones to quinoid forms may be involved in antitumor activity.

EXPERIMENTAL[2]

5-Hydroxy-2(1*H*)-pyridone (IV)—This compound was prepared in a 20% yield from 0.4 mole of VII using the Elbs peroxydisulfate oxidation procedure of Behrman and Pitt (12), mp 245–250° dec. [lit. (12) mp 250–260° dec.].

5-Acetoxy-2(1*H*)-pyridone (V)—To a stirred dry mixture of IV (1.67 g, 0.015 mole) and pyridine (1.30 ml, 0.016 mole) in dry benzene (10 ml) was added acetic anhydride (1.5 ml, 0.016 mole) by syringe through a septum. The mixture was refluxed for 26 hr. After the solvent was removed *in vacuo*, ethyl acetate was added to the dark-brown semisolid. Cooling at 3° gave a gray precipitate, which was decolorized with charcoal in a small volume of ethyl acetate–ethanol to give 0.91 g (39%) of a white solid, mp 166–168°; NMR: δ 2.27 (s, 3H, CH_3), 6.33 (m, 1H, CH), 6.97 (m, 2H, CH), and 11.48 (broad, 1H, NH) ppm; UV: 306 (log ε 3.83) and 231 (4.05) nm; IR: 1740, 1665, and 1625 cm^{-1}.

3-Propionyloxy-2(1*H*)-pyridone (XI)—A mixture of II (27.75 g, 0.25 mole), propionic anhydride (80 ml), and dry pyridine (50 ml) was refluxed for 89 hr, and the solvent was evaporated *in vacuo* to yield a crude solid product, which was washed with ethyl acetate. Recrystallization from anhydrous ethanol gave white crystals (30.90 g, 74%), mp 150–151°; NMR: δ 1.08 (t, 3H, CH_3), 2.48 (m, 2H, CH_2), 6.15 (t, 1H, CH), 7.28 (d, 2H, CH), and 11.98 (broad, 1H, NH) ppm; UV: 226 (log ε 3.79) and 297 (3.81) nm; IR: 1760 and 1655 cm^{-1}.

1-Methyl-3-acetyloxy-2(1*H*)-pyridone (XII)—To a cold, stirred solution of I (12.25 g, 0.08 mole) in dry dimethylformamide (50 ml) was slowly added (35 min) sodium hydride (50% mineral oil suspension, 3.86 g, 0.16 mole) under nitrogen. As the mixture became harder to stir, additional dry dimethylformamide (30 ml) was added. The mixture was stirred in an ice water bath for 3 hr, at which time methyl iodide (5.05 ml, 11.51 g, 0.081 mole) was added by syringe over 15 min. Sodium iodide separated during the addition. The mixture was stirred for 2.5 hr at room temperature. Acetic acid (7 ml), followed by portions of methylene chloride, was added.

The combined methylene chloride extracts were quickly washed with water and dried (sodium sulfate). After solvent evaporation *in vacuo*, the resulting red oil was distilled (ambient to 150° at 0.1 torr) to give a yellow oil, which was triturated with petroleum ether to remove mineral oil. Upon cooling, a solid precipitated. This solid was dissolved in methylene chloride and reprecipitated by addition to petroleum ether. The resulting solid was a light-sensitive, white, crystalline material (1.48 g, 10%), mp

[2] All melting points were recorded on a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were performed by the National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Md. Compounds I–III, VI, and VII–X were obtained commercially. When several compounds were prepared by comparable procedures, only one representative example is included in this section. Reference should be made to Table I for supplementary information.

New compounds were identified by NMR, UV, and IR spectra. These spectra were determined in dimethyl sulfoxide-d_6, 95% ethanol, and Nujol, respectively, unless otherwise indicated. NMR data are relative to tetramethylsilane.

84–88° [lit. (13) mp 99–101°]; NMR (deuterochloroform): δ 2.30 (s, 3H, NCH_3), 3.53 (s, 3H, CH_3), 6.05, and 7.11 (m, 3H, aromatic) ppm; UV: 236.5 (log ε 3.65) and 298 (3.94) nm; IR (chloroform): 1775 and 1665 cm^{-1}.

1,2-Dihydro-2-oxo-cyclopropanecarboxylic Acid-3-pyridinyl Ester (XIII) (General Procedure for XV, XVI, XVIII–XXI, XXVII, XXX, and XXXI)—A mixture of II (5.56 g, 0.05 mole), cyclopropanecarboxylic acid chloride (4.63 ml, 0.05 mole), dry pyridine (4.04 ml, 0.05 mole), and dry tetrahydrofuran (50 ml) was refluxed for 24 hr under nitrogen. Addition of methylene chloride to the ambient solution produced a solid, which was a mixture of XIII and pyridine hydrochloride. Recrystallization from absolute ethanol with charcoal gave 6.42 g (72%) of XIII as white crystals, mp 196–198°; NMR: 0.97 (m, 4H, CH_2), 1.80 (m, 1H, CH), 6.12 (t, 1H, CH), 7.25 (d, 2H, CH), and 11.88 (broad, 1H, NH) ppm; UV: 226.5 (log ε 3.79) and 297.5 (3.81) nm; IR: 1750 and 1650 cm^{-1}.

3-Benzoyloxy-2(1*H*)-pyridone (XVII) (General Procedure for XIV and XXXII)—A mixture of II (2.22 g, 0.02 mole), benzoyl chloride (2.44 ml, 0.021 mole), anhydrous potassium carbonate (2.90 g, 0.021 mole), and dry acetone (15 ml) was refluxed for 28 hr. Methylene chloride (20 ml) was added, followed by water (5 ml). Additional methylene chloride was added, and the mixture was thoroughly stirred. The layers were separated, the suspended solid was discarded, and the aqueous phase was extracted with two 20-ml portions of methylene chloride.

The combined organic extracts were washed with water (3 × 20 ml), dried over sodium sulfate, and evaporated *in vacuo*. Trituration of the resulting solid with toluene gave a white solid, which was recrystallized from ethyl acetate to give white crystals (2.51 g, 59%), mp 174–176°; NMR (deuterochloroform): 6.18 (t, 1H, CH), 7.40 (m, 5H, CH), 8.17 (m, 2H, CH), and 13.32 (broad, 1H, NH) ppm; UV: 228 (log ε 4.26) and 297 (3.92) nm; IR (chloroform): 1735, 1655, and 1615 cm^{-1}.

3-[[(Methylamino)carbonyl]oxy]-2(1*H*)-pyridone (XXII) (General Procedure for XXIV, XXV, XXVIII, and XXIX)—A mixture of II (5.51 g, 0.05 mole), methyl isocyanate (3.1 ml, 0.052 mole), dry triethylamine (8 drops), and dry dimethylformamide (35 ml) was stirred at room temperature for 44 hr. Solvent evaporation gave a red-brown material, which was stirred with hot ethyl acetate to remove 0.39 g of the disubstituted product, XXIII, mp 159–160°. The material insoluble in ethyl acetate was dissolved in warm ethanol. Scratching the cold filtrate produced XXII (4.28 g, 51%), mp 164–165°; NMR: 2.63 (d, 3H, CH_3), 6.08 (t, 1H, CH), 7.17 (d, 2H, CH), 7.45 (broad, 1H, NH), and 11.67 (broad, 1H, NH) ppm; UV: 227 (log ε 3.77) and 297 (3.81) nm; IR: 1725 and 1665 cm^{-1}.

***N*-Methyl-3-[[(methylamino)carbonyl]oxy]-2-oxo-1(2*H*)-pyridinecarboxamide (XXIII)**—Compound XXIII, mp 161–162°, was prepared in a 49% yield using a 1:2 molar ratio of II to methylisocyanate and the procedure described for XXII; NMR (deuterochloroform): 2.75 (d, 3H, CH_3), 2.87 (d, 3H, CH_3), 5.15 (broad, 1H, NH), 6.17 (t, 1H, CH), 7.15 (m, 1H, CH), 8.18 (m, 1H, CH), and 10.08 (broad, 1H, NH) ppm; UV: 220 (shoulder) and 306 (log ε 3.70) nm; IR (chloroform): 3430, 3160, 1745, and 1655 cm^{-1}.

***N*-(2-Chloroethyl)-3-[[(2-chloroethylamino)carbonyl]oxy]-1(2*H*)-pyridinecarboxamide (XXVI)**—A mixture of II (5.56 g, 0.05 mole), 2-chloroethylisocyanate (5.38 g, 0.051 mole), dry triethylamine (8 drops), and dry dimethylformamide (30 ml) was stirred at room temperature for 19 hr with occasional warming to 40° to dissolve suspended solids. The solvents were removed *in vacuo*, ethyl acetate (50 ml) was added to the residue, and the mixture was cooled to 0° overnight. The resulting solid (II, 2.4 g) was removed, the ethyl acetate was evaporated, and chloroform was added. This solution was extracted with three 30-ml portions of water, dried with sodium sulfate, and evaporated *in vacuo* to give a gray solid. Dissolution in ethyl acetate, followed by the addition of petroleum ether, yielded a gray-white solid (4.97 g, 55%), mp 111–113°; NMR (deuterochloroform): 3.52 (m, 8H, CH_2), 5.83 (broad, 1H, NH), 7.28 (m, 1H, CH), 8.25 (m, 1H, CH), and 10.72 (broad, 1H, NH) ppm; UV: 226 (shoulder) and 305 (log ε 3.83) nm; IR: 3410, 3120, 1730, and 1655 cm^{-1}.

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