Table VII—Comparative Analysis of Commercial Liquid Formulations

Drug and Dosage Strength	Percent of Label Claim		
	Differential	Automated	Modified Official
Chlorpromazine hydrochloride concentrate, 100 mg/ml	99.0 (8)[a]	99.6 (2)	101.6 (1)
Trifluoperazine hydrochloride concentrate, 10 mg/ml	97.8 (5)	101.2 (2)	98.8 (2)
Prochlorperazine maleate concentrate, 10 mg/ml	96.1 (2)	97.5 (2)	100.2 (1)
Thioridazine hydrochloride concentrate, 100 mg/ml	97.9 (2)	99.3 (2)	99.7 (1)

[a] Number of determinations.

sufficiently stable for measurement in ~3 min after oxidation. This rise apparently is due to the expulsion of air bubbles formed as a result of mixing acetic acid and dilute hydrochloric acid.

Differential UV assays results were unaffected by 18 commonly used excipients. However, the differential fluorescence method was affected by one excipient, dibasic calcium phosphate. This problem was corrected by changing the fluorescence assay solvent from 0.1 *N* HCl to pH 2.2 buffer containing ~30% alcohol. Comparative assay results for the three methods are summarized in Tables VI and VII.

CONCLUSIONS

Previously published work on the phenothiazine differential oxidation method suggested its general applicability (3). The inclusion of a siliceous earth filtration step and the introduction of a fluorometric procedure for lower formulation strengths make the method facile and accurate. The method was shown to be reproducible to concentrations as low as 1 μg/ml. The procedure was applied to tablets, sustained-release preparations, concentrates, and syrups. Recoveries from known mixtures ranged from 99 to 101%. These results and the specificity of the differential oxidation procedure suggest its superiority to the official assay procedures.

REFERENCES

(1) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975.

(2) "The National Formulary," 14th ed., Mack Publishing Co., Easton, Pa., 1975.

(3) A. G. Davidson, *J. Pharm. Pharmacol.*, **28**, 795 (1976).

(4) S. P. Massie, *Chem. Rev.*, **54**, 797 (1954).

(5) C. Bodea and I. Silberg, in "Advances in Heterocyclic Chemistry," vol. 9, A. R. Katritzky, Ed., Academic, New York, N.Y., 1968, p. 321.

(6) J. P. Billon, *Ann. Chim. (Paris)*, **7**, 183 (1962).

(7) T. N. Tozer and L. D. Tuck, *J. Pharm. Sci.*, **54**, 1169 (1965).

(8) P. Kabasakalian and J. McGlotten, *Anal. Chem.*, **31**, 431 (1959).

(9) J. P. Malrieu and B. Pullman, *Theoret. Chim. Acta*, **2**, 293 (1964).

(10) A. Pullman, *J. Chim. Phys.*, **61**, 1666 (1964).

(11) H. Gilman and R. D. Nelson, *J. Am. Chem. Soc.*, **75**, 5422 (1953).

(12) M. Nakanishi and N. Kuriyama, Japanese pat. 15,617 (1961); through *Chem. Abstr.*, **56**, 12908i (1962).

(13) G. P. Brown, J. W. Cole, and T. I. Crowell, *J. Org. Chem.*, **20**, 1772 (1955).

(14) D. Simov Antonov, *Izv. Khim. Inst., Bulgar. Nauk.*, **5**, 51 (1957); through *Chem. Abstr.*, **55**, 1655d (1961).

(15) C. Bodea and M. Raileany, *Ann. Chem.*, **614**, 171 (1958).

(16) L. K. Turner, *J. Forensic Sci.*, **4**, 39 (1963).

(17) J. A. Ryan, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 240 (1959).

(18) A. J. Kapadia, M. A. Barber, and A. E. Martin, *J. Pharm. Sci.*, **59**, 1476 (1970).

(19) S. Cooper, J. Albert, R. Dugal, and M. Bertrand, *J. Chromatogr.*, **150**, 263 (1978).

(20) E. C. Dinovo, L. A. Gottschalk, B. R. Nandi, and P. G. Geddes, *J. Pharm. Sci.*, **65**, 667 (1976).

(21) S. H. Curry, *Anal. Chem.*, **40**, 1251 (1968).

(22) R. G. Muusze and J. F. K. Huber, *J. Chromatogr. Sci.*, **12**, 779 (1974).

(23) D. H. Rodgers, *ibid.*, **12**, 743 (1974).

(24) A. DeLeenheer, *J. Assoc. Off. Anal. Chem.*, **56**, 105 (1973).

(25) A. G. Davidson, *J. Pharm. Pharmacol.*, **30**, 410 (1978).

(26) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., p. 761.

(27) J. B. Ragland and V. J. Kinross-Wright, *Anal. Chem.*, **36**, 1356 (1964).

(28) R. D. Kirchhoefer and J. W. Myrick, *J. Assoc. Off. Anal. Chem.*, **61**, 1519 (1978).

Pyridones as Potential Antitumor Agents II: 4-Pyridones and Bioisosteres of 3-Acetoxy-2-pyridone

DENG R. HWANG *, GEORGE R. PROCTOR ‡, and JOHN S. DRISCOLL ˣ

Received February 25, 1980, from the *Drug Design and Chemistry Section, Laboratory of Medicinal Chemistry and Biology, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, MD 20205.* Accepted for publication March 25, 1980. *Present address: Technicon Inc., Tarrytown, N.Y. ‡Present address: University of Strathclyde, Glasgow, Scotland.

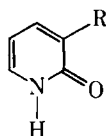
Abstract □ Pyridone structural requirements for activity against murine P-388 leukemia have been extended to isosteric analogs of 3-hydroxy-4-pyridone, a compound previously found to have activity. An amino group can be substituted for the 3-hydroxyl function with retention of activity. A sulfur, but not an amino function, can replace the lactam oxygen in the 2-position. Relocation of the lactam oxygen from the 2- to the 4-position in the pyridine ring also produces active pyridones, including 2-methyl-3-acetoxy-4-pyridone. This compound, which has a T/C value of 179%, is the most active material discovered thus far in the pyridone studies.

Keyphrases □ Pyridones—4-pyridones and bioisosteres of 3-acetoxy-2-pyridone, synthesis and evaluation for antitumor activity □ Antitumor agents, potential—4-pyridones and bioisosteres of 3-acetoxy-2-pyridone, synthesis and evaluation for activity □ Structure-activity relationships—4-pyridones and bioisosteres of 3-acetoxy-2-pyridone, synthesis and evaluation for antitumor activity

It was reported recently that 3-hydroxy- (I) and 3-acetoxy-2-pyridone (II) have reproducible activity against murine P-388 lymphocytic leukemia (1). Eight additional derivatives of 3- and 5-hydroxy-2-pyridone also were active, and a tentative structure–activity relationship was established between antitumor activity and the position of the hydroxyl group relative to the 2-pyridone lactam function. The present investigation extends the study of

0022-3549/80/0900-1074$01.00/0

© 1980, American Pharmaceutical Association



I: R = OH
II: R = $OCOCH_3$
III: R = NO_2
IV: R = NH_2
V: R = $NHCOCH_3$
VI: R = $NHCONHCH_3$

pyridone antitumor activity to 2-pyridones that are bioisosteres of I and to the 4-pyridone system.

RESULTS

An earlier study (1) established that hydroxyl substitution at the 3-position produced optimal P-388 activity in the 2-pyridone series. For this reason, the 2,3-relationship was maintained in the study of the effect of bioisosteric functional groups on 2-pyridone antitumor activity. The objective of the present 2-pyridone study was the determination of the effect on P-388 activity of replacing the oxygen functionality in I and II with nitrogen- and sulfur-containing groups.

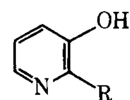
3-Amino-2-pyridone (IV) was synthesized by the nitration of 2-pyridone to produce 3-nitro-2-pyridone (III) and subsequent catalytic reduction to produce IV. Compound IV was reacted with acetic anhydride to give V, an analog of II, and with methyl isocyanate to give VI. Both V and VI are nitrogen isosteres of oxygen analogs previously found to be active (1). The importance of the oxygen functionality in the 2-position of I was studied by replacing it with nitrogen- (VII), chlorine- (VIII), and sulfur- (IX) containing groups. 3-Hydroxy-2-thiopyridone (IX) was *O*-acetylated to produce X, a sulfur analog of II, the most active oxygen-containing compound.

Another objective of this investigation was to study the effect of moving the lactam oxygen function in I from the 2-position to the 4-position to produce the other pyridone isomer. The commercially available pyrone plant product, maltol (XI), provided an entry to the desired 4-pyridone series. By a method similar to that of Fisher and Hodge (2), maltol was methylated to give XII, which was reacted with ammonia to produce the 4-pyridone (XIII). Methoxy cleavage with hydrobromic acid produced the target compound, 2-methyl-3-hydroxy-4-pyridone (XIV). The urethan (XV) and acetoxy (XVI) analogs were prepared for the reason mentioned previously.

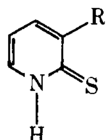
Compounds III–XVI were evaluated using the standard National Cancer Institute protocol for P-388 lymphocytic leukemia (3). The data for the reproducibly active members of the series, as well as the activities reported (1) for I and II which are shown for comparison, are given in Table I. Duplicate dose-response tests were carried out with each compound. An active test is defined (3) as one that produces a T/C value[1] of ≥125%. Active compounds are defined as those that give active tests in two separate experiments. The compounds among I–XVI that are not shown in Table I were inactive in duplicate experiments.

DISCUSSION

Both 3-hydroxy-2-pyridone (I) and its acetyl derivative (II) have P-388 activity (Table I), with the latter compound being the best among 10 previously reported active analogs (1). Replacement of the 3-hydroxyl group in I with a nitro group (III) resulted in inactivity. However, an amino group in the same position provided a compound (IV) with approximately the same level of activity as its bioisostere, I. Acetylation of IV to produce V, instead of enhancing activity as in the case of II, abolished activity. While the formation of the methylaminocarbonyl derivative of I increased the activity of the resulting urethan (1), the opposite was the case when IV was treated in a similar manner.



VII: R = NH_2
VIII: R = Cl



IX: R = OH
X: R = $OCOCH_3$

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

Table I—Pyridones Active against P-388 Lymphocytic Leukemia[a]

Compound	Optimum Dose[b], mg/kg/day	T/C[c]	T − C[d]
I	400	138	−2.4
II	600	163	−2.8
IV	200	133	−4.1
IX	200	139	−0.9
XIV	200	153	0.0
XVI	400	179	−3.1

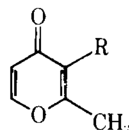
[a] With 10^6 cells implanted intraperitoneally in CDF_1 mice. [b] Dose giving the maximum T/C value on the QD 1–9 treatment schedule. [c] At least one other active test was obtained in a separate, duplicate experiment. [d] Weight difference, in grams, between treated and control mice 5 days after tumor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

The replacement of the lactam oxygen function of I with an amino group to give VII, the position isomer of active IV and the bioisostere of active I, resulted in inactivity. This result may be related to the fact that 2-hydroxypyridines exist mainly in the lactam form while the amino form predominates in 2-aminopyridines (4). A similar replacement with chlorine (VIII), which possesses no tautomeric possibilities, also resulted in inactivity. However, when the same replacement was made with sulfur to produce 3-hydroxy-2-thiopyridone (IX), activity was retained. 2-Mercapto- as well as 2-hydroxypyridines exist as the amide tautomer (pyridone or lactam form) in >99% (4). Acetylation of IX to form X reduced activity (T/C 133, 120, and 110%), contrary to what was observed with I but similar to the finding with IV.

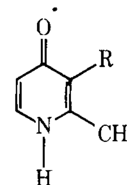
In the isomeric 4-pyridone series, the starting material, maltol (XI), its *O*-methylated derivative (XII), and the 3-methoxy-4-pyridone (XIII) obtained from XII did not possess P-388 activity. However, demethylation of XIII gave 2-methyl-3-hydroxy-4-pyridone (XIV), a compound with an activity level greater than that of I and similar to that of II, the most active compound in the 2-pyridone series. Preparation of a urethan (XV), which had increased activity relative to I in the 2-pyridone series, abolished activity in the 4-pyridone case. However, XVI, the *O*-acetyl derivative of XIV, was the most active compound in either the 2- or 4-pyridone series, producing T/C values of 179 and 176%. Compound XVI also proved active against the less sensitive murine tumor model, L-1210 lymphoid leukemia (T/C 157 and 138), and presently is being evaluated in the National Cancer Institute tumor panel (5).

The mechanism of antitumor activity for the pyridones has not been established. A similarity with the catechol-*ortho*-quinone series involving possible sulfhydryl reactivity was noted (6). Another possible parallel exists between the antitumor activity observed here and the catechol-*O*-methyl transferase inhibitory activity of the 3-hydroxypyridones demonstrated by Borschardt (7). Aminopyridones also were potent inducers of erythroid differentiation in Friend leukemia cells (8).

In summary, it has been found that relative to the 2-pyridone lead compound, I, an amino group can be substituted for the 3-hydroxy group with retention of activity and that a sulfur, but not an amino or a chloro function, can successfully replace the lactam oxygen in the 2-position. Changing the lactam oxygen from the 2- to the 4-position of the pyridine ring produces 3-hydroxy-4-pyridone derivatives with better P-388 leukemia activity than similar 2-pyridones. 2-Methyl-3-acetoxy-4-pyridone (XVI) is the most active compound found thus far in these studies. The 4-pyrone (XI), which differs from the 4-pyridone (XIV) only in the heterocyclic atom, is inactive. The inactivity of the 3-methoxy analog (XIII) is consistent with previous observations that the two vicinal oxygen functions capable of being oxidized further are required for P-388 activity in the pyridones (1) and in a similar, but nonheterocyclic, series of catechol derivatives (6).



XI: R = OH
XII: R = OCH_3



XIII: R = OCH_3
XIV: R = OH
XV: R = $OCONHCH_3$
XVI: R = $OCOCH_3$

EXPERIMENTAL[2]

3-Nitro-2(1*H*)-pyridone (III)—Compound III, mp 224–225° [lit. (9) mp 224–225°], was prepared from 2-pyridone on a 30-g scale by the method of Binz and Maier-Bode (9); NMR: 6.32 (t, 1, CH), 7.78 (m, 1, CH), 8.33 (m, 1, CH), and 12.77 (broad, 1, NH); UV: 361 (3.83) and 248 (3.43); IR: 1675 and 1640.

Anal.—Calc. for $C_5H_4N_2O_3$: C, 42.83; H, 2.88; N, 20.06. Found: C, 42.94; H, 2.89; N, 20.13.

3-Amino-2(1*H*)-pyridone (IV)—3-Nitro-2(1*H*)-pyridone (7.00 g, 0.05 mole) dissolved in 100 ml of methanol was hydrogenated in a Parr shaker (45 psi) in the presence of 10% palladium-on-carbon (400 mg). The catalyst was filtered, and the solution was stirred with activated carbon. The solution was filtered and evaporated to yield 5.47 g (99%) of a pink-white, light-sensitive solid, mp 123–125°; NMR: 4.66 (broad, 2, NH_2), 6.00 (t, 1, CH), and 6.63 (m, 2, CH); UV: 309 (3.94) and 253.5 (3.75); IR: 1650.

Anal.—Calc. for $C_5H_6N_2O$: C, 54.48; H, 5.49; N, 25.52. Found: C, 54.46; H, 5.56; N, 25.18.

3-Acetamido-2(1*H*)-pyridone (V)—A stirred mixture of sodium acetate (7.84 g, 0.08 mole), acetic anhydride (10 ml), and dry IV (8.45 g, 0.077 mole) was refluxed for 2 hr and then stirred for 16 hr at a temperature just high enough to keep the mixture fluid. The excess acetic anhydride was evaporated *in vacuo*, and the resulting solid was extracted first with hot methylene chloride (100 ml) and then with hot ethyl acetate (125 ml). Evaporation of the solvents gave a pink solid, which was dissolved in a limited amount of methanol and stirred with decolorizing carbon. Filtration of the solution and cooling gave 6.70 g (57%) of white crystals, mp 209–211°; NMR: 2.08 (s, 3, CH_3), 6.13 (t, 1, CH), 7.03 (m, 1, CH), 8.17 (m, 1, CH), and 9.12 and 11.82 (broad, 2, NH); UV: 308 (4.00), 256 (3.91), and 247.5 (3.98); IR: 1635 and 1605.

Anal.—Calc. for $C_7H_8N_2O_2$: C, 55.21; H, 5.29; N, 18.48. Found: C, 55.13; H, 5.31; N, 18.28.

3-[[(Methylamino)carbonyl]amino]-2(1*H*)-pyridone (VI)—Methyl isocyanate (3.00 ml, 0.051 mole) was added by syringe to a cold (2°) stirred solution of IV (5.50 g, 0.05 mole) and triethylamine (0.5 ml) in dry dimethylformamide (30 ml). Stirring was continued for 3 hr in the cold and for 50 hr at room temperature. Evaporation of the solvent *in vacuo* gave a brown solid, which was recrystallized from methanol (charcoal) to give 5.76 g (69%) of a white solid, mp >300°; NMR: 2.60 (d, 3, CH_3), 6.10 (t, 1, CH), 6.87 (broad, 2, CH, NH), 7.97 (m, 1, CH), and 8.15 and 11.70 (broad, 2, NH); UV: 305 (4.04) and 251 (4.01); IR: 1640–1605.

Anal.—Calc. for $C_7H_9N_3O_2$: C, 50.24; H, 5.42; N, 25.22. Found: C, 50.13; H, 5.50; N, 25.21.

3-Acetoxy-2(1*H*)-thiopyridone (X)—Acetic anhydride (3.82 ml, 0.0405 mole) was added by syringe to a dry, stirred solution of IX (5.09 g, 0.04 mole) and pyridine (0.0405 mole, 3.3 ml) in acetone (30 ml), which had been freshly distilled from phosphorus pentoxide. The solution was refluxed for 23 hr under nitrogen, during which time the product precipitated from solution. The mixture was stirred at room temperature for an additional 42 hr. The light-yellow product was filtered and then recrystallized from methanol–ethanol to give 5.82 g (86%) of a light-yellow solid, mp 167–171°; NMR: 2.20 (s, 3, CH_3), 6.68 (t, 1, CH), 7.74 (m, 2, CH), and 13.8 (broad, 1, NH); UV: 361.5 (3.89) and 279.5 (4.05); IR: 1765, 1365, and 1310.

Anal.—Calc. for $C_7H_7NO_2S$: C, 49.67; H, 4.17; N, 8.31. Found: C, 49.78; H, 4.40; N, 8.41.

2-Methyl-3-methoxy-4-pyrone (XII)—Compound XII was prepared in a 73% yield on a 20-g scale from XI by the method of Fisher and Hodge (2). The crude product was used immediately for the next reaction without further purification.

2-Methyl-3-methoxy-4(1*H*)-pyridone (XIII)—Crude XII (20.63 g, 0.146 mole) was dissolved in concentrated ammonium hydroxide (600 ml), and the light-yellow solution was refluxed for 12 hr. The reaction mixture was cooled to room temperature, more ammonium hydroxide was added (50 ml), and stirring was continued for 4 hr. Evaporation of the solvent *in vacuo* gave a yellow solid, which was recrystallized from acetone to give 16.39 g (80.5%) of product. Further recrystallization from acetone–ethanol gave analytically pure XIII, mp 155–156° [lit. (2) mp 155–156°]; NMR ($CDCl_3$): 2.33 (s, 3, CH_3), 3.75 (s, 3, OCH_3), 6.40 (d, 1, CH), 7.48 (d, 1, CH), and 9.97 (broad, 1, NH); UV: 264 (4.14); IR: 1620.

Anal.—Calc. for $C_7H_9NO_2$: C, 60.39; H, 6.52; N, 10.10. Found: C, 60.37; H, 6.63; N, 10.05.

2-Methyl-3-hydroxy-4(1*H*)-pyridone (XIV)—A solution of XIII (8.35 g, 0.06 mole) in 48% hydrobromic acid (120 ml) was heated at 140–150° for 4 hr, cooled to room temperature, and concentrated to 30–40 ml. The resulting red crystalline solid was isolated and dissolved in a small amount of water, and the solution was carefully neutralized with sodium carbonate. At pH 6–7, a red-brown solid precipitated. This solid was filtered, dissolved in boiling water, and decolorized with charcoal. A light red-brown product was isolated (5.81 g, 77%), mp 285–288° dec. [lit. (2) mp >250° dec.]; NMR: 2.13 (s, 3, CH_3), 6.03 (m, 2, CH + exchangeable), and 7.3 (m, 2, CH + exchangeable); UV: 276.5 (4.17); IR: 1635.

Anal.—Calc. for $C_6H_7NO_2$: C, 57.57; H, 5.63; N, 11.24. Found: C, 57.30; H, 5.77; N, 11.28.

2-Methyl-3-[[(methylamino)carbonyl]oxy] -4(1*H*)- pyridone (XV)—To a stirred suspension of XIV (2.78 g, 0.02 mole) in dry dimethylformamide (15 ml) and triethylamine (5 drops) under nitrogen was added 1.21 ml (0.02 mole) of methyl isocyanate. During the addition (syringe through a flask septum), the suspended solid changed from red brown to white. After stirring 21 hr at room temperature, the solvent was evaporated, the resulting solid was triturated well with benzene and then ethyl acetate. A pink-white solid (3.61 g, 99%), mp 280–285° dec., was obtained; NMR: 2.08 (s, 3, CH_3), 2.57 (d, 3, NCH_3), 6.07 (d, 1, CH), 7.45 (broad, 2, CH, NH), and 10.2 (broad, 1, NH); UV: 258.5 (4.16); IR: 1730 and 1620.

Anal.—Calc. for $C_8H_{10}N_2O_3$: C, 52.71; H, 5.53; N, 15.43. Found: C, 52.40; H, 5.50; N, 15.13.

2-Methyl-3-acetoxy-4(1*H*)-pyridone (XVI)—A solution of XIV (3.64 g, 0.029 mole) in acetic anhydride (25 ml) was refluxed (130–140°) for 21 hr under a nitrogen atmosphere. Removal of excess acetic anhydride gave a dark oil, which was dissolved in ethyl acetate and cooled at 0°. A dark-brown solid (1.05 g, 22%) resulted, mp 205–208° [lit. (2) mp 205–208°, (10) 204–205°]; NMR: 1.20 (unresolved d, 6, CH_3), 6.12 (broad, 1, CH), and 7.53 (broad, 1, CH); UV: 260 (4.10); IR: 1760 and 1630.

Anal.—Calc. for $C_8H_9NO_3$: C, 57.46; H, 5.42; N, 8.41. Found: C, 56.57; H, 5.47; N, 8.24.

[2] All melting points were recorded on a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Services Section, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Md. Compounds were identified by NMR, UV, and IR spectroscopy. These spectra were determined in dimethyl sulfoxide-d_6, 95% ethanol, and nujol, respectively, unless otherwise indicated. NMR data are delta values relative to tetramethylsilane, UV values are in nanometers (log ϵ), and IR values are in reciprocal centimeters. Compounds I, II, VII–IX, and XI were purchased from Aldrich Chemical Co.

REFERENCES

(1) D. R. Hwang and J. S. Driscoll, *J. Pharm. Sci.*, **68,** 816 (1979).

(2) B. E. Fisher and J. E. Hodge, *J. Org. Chem.*, **29,** 776 (1964).

(3) R. I. Geran, N. H. Greenberg, M. M. Macdonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3,* **3**(2), 1 (1972).

(4) H. Tieckelmann, in "Pyridine and its Derivatives," vol. 14, Suppl. part 3, R. A. Abramovitch, Ed., Interscience, New York, N.Y., 1974, p. 733.

(5) S. A. Schepartz, DHEW Publication (NIH) 76-1200, 1976, pp. 13–25.

(6) J. S. Driscoll, *J. Pharm. Sci.*, **68,** 1519 (1979).

(7) R. T. Borschardt, *J. Med. Chem.*, **16,** 581 (1973).

(8) C. Li, L. S. Rittmann, A. S. Tsiftsoglou, K. K. Bhargava, and A. C. Sartorelli, *J. Med. Chem.*, **21,** 874 (1978).

(9) A. Binz and H. Maier-Bode, *Angew. Chem.*, **49,** 486 (1936).

(10) A. Peratoner and A. Tamburello, *Gazz. Chim. Ital.*, **36,** 33 (1906).

ACKNOWLEDGMENTS

The authors thank Mr. Leo Dudeck and Mr. George Congleton of Hazleton Laboratories for the determination of the antitumor test data under National Cancer Institute Contract N01-CM-57007.

D. R. Hwang was a National Institutes of Health Visiting Postdoctoral Fellow for 1976–1977. G. R. Proctor was a National Cancer Institute Visiting Expert for 1975–1976.