Potential Antitumor Agents: Procarbazine Analogs and Other Methylhydrazine Derivatives

JOHN A. BEISLER ˣ, GEOFFREY W. PENG *, and JOHN S. DRISCOLL

Abstract □ With the objective of developing new antitumor agents, two groups of hydrazine compounds, having structural features in common with the antitumor agents procarbazine and 1-acetyl-2-picolinoylhydrazine, were synthesized. The L-1210 leukemia system was used to evaluate compounds of both groups. The aliphatic procarbazines also were screened for antitumor activity as bis(benzyloxycarbonyl) derivatives and as derivatives having a phthalazine nucleus. No L-1210 antitumor activity was exhibited by these compounds.

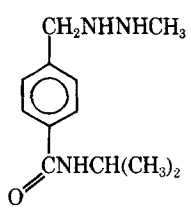
Keyphrases □ Hydrazines, substituted—synthesized, antitumor activity evaluated □ Procarbazine analogs—synthesized, antitumor activity evaluated □ Phthalazines, substituted—synthesized, antitumor activity evaluated □ Antitumor activity—evaluated in substituted hydrazines and phthalazines □ Structure-activity relationships—substituted hydrazines and phthalazines evaluated for antitumor activity

Hydrazine derivatives interact with biological systems to produce a wide range of responses. For example, isoniazid is a well-established tuberculostatic agent (1), and isocarboxazid finds clinical utility as a monoamine oxidase inhibitor (2). A recent survey (3) listed 19 hydrazine derivatives that are tumorigenic in animals, although hydrazine sulfate inhibited tumor growth in rats (4).

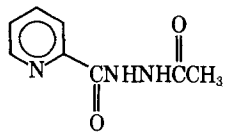
Procarbazine (I), a methylhydrazine derivative, displayed antitumor effects in a spectrum of animal neoplasms and is used clinically in the treatment of Hodgkin's disease (5). Although hydrazine and benzylhydrazine have considerable toxicity, they selectively inhibited Ehrlich ascites carcinoma in mice (6). The corresponding methyl derivatives (methylhydrazine and 1-methyl-2-benzylhydrazine) retained toxicity but exhibited an increased antitumor effect, apparently because the *N*-methyl groups metabolized to formaldehyde, which contributed an added cytotoxic effect. Thus, the *N*-normethyl analog of procarbazine was much less effective against Ehrlich ascites than procarbazine itself; however, both showed a diminished toxicity with respect to 1-methyl-2-benzylhydrazine.

A series of acylhydrazines and 1,2-diacylhydrazines showed activity in the Walker 256 carcinosarcoma test system with moderate toxicities in some instances, giving favorable therapeutic indexes (7). One member of the series, 1-acetyl-2-picolinoylhydrazine (II), was selected for clinical trials (8–10).

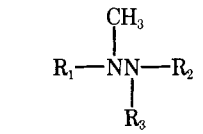
As part of a continuing interest in the development of new antitumor agents (11), a study was initiated to synthesize methylhydrazine derivatives for potential antitumor activity. Two groups of compounds were selected for



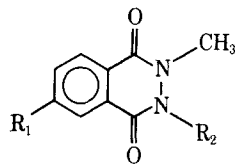
I



II



III: $R_1 = R_2 = H$, $R_3 = CH_2CH_3$
IV: $R_1 = CH_3CO$, $R_2 = R_3 = H$
V: $R_1 = R_2 = CH_3CO$, $R_3 = H$
VI: $R_1 = R_2 = C_6H_5CH_2OCO$, $R_3 = H$
VII: $R_1 = R_2 = C_6H_5CO$, $R_3 = H$



VIII: $R_1 = R_2 = H$
IX: $R_1 = CO_2H$, $R_2 = CH_3$

synthesis and antitumor evaluation against L-1210 leukemia. The first group consisted of simple methylhydrazines (III–IX), having structural attributes of both I and II. Accordingly, these hydrazines were provided with *N*-methyl groups in the hope of augmenting any emergent antitumor activity and acyl functions to moderate toxicity. In the second group, the structural importance of the phenylene group of I for antitumor activity was explored by replacing it with straight-chain aliphatic moieties. As in the first group, the methylhydrazine substructure was incorporated into the aliphatic procarbazine derivatives (Scheme I, XVI–XVIII), and provisions were made in the synthetic scheme to prepare acylated derivatives for antitumor testing.

RESULTS AND DISCUSSION

Chemistry—Compound III was synthesized using a modification of a literature procedure (12). Compounds IV–VIII were made according to established procedures (13–16, Table I).

The synthetic route to the aliphatic procarbazine derivatives (XVI–XVIII) utilized the approach developed by Zeller *et al.* (17), wherein the doubly blocked methylhydrazine (VI) served as a starting material. Thus, condensation of VI with the requisite bromo ester (Scheme I) gave the fully substituted hydrazines (X–XII). These compounds were converted to the *N*-isopropyl-substituted amides (XIII–XV) using a standard three-step synthetic sequence. As an inadvertant result, the lower homolog in the series (XIII) quantitatively lost a benzyloxycarbonyl substituent. The loss was probably due to the presence of the terminal carboxyl function, which is favorably disposed toward participation in a six-membered cyclic intermediate with the carbonyl of the near benzyloxycarbonyl group. Based on this reasoning, Structure XIII was assigned to this compound.

Hydrogenolysis smoothly removed the benzyloxycarbonyl-protecting groups to provide the substituted methylhydrazines, which were isolated as the semicrystalline hygroscopic dihydrochloride salts. Water solutions of the latter, when passed through an anion-exchange column (oxalate form), yielded oxalate salts after lyophilization as analytically pure, white solids (XVI–XVIII), which were not hygroscopic. Attempted recrystallization of the oxalates led to decomposition.

Reaction of the hydrazines, either as the oxalate or dihydrochloride salts, formed phthalazine derivatives (XIX–XXI). The three phthalazine

Table I—Experimental Data

Compound	Boiling Point (mm Hg) or Melting Point (Solvent)	Yield, %	Formula[a]	Analysis, %		Preparation Reference Number
				Calc.	Found	
III	149–150° (ethanol–acetone) [lit. (12) mp 141–143°]	52	$C_3H_{10}N_2 \cdot 2HCl$	C 24.50 H 8.22 Cl 48.22 N 19.05	24.64 8.33 48.20 18.71	—
IV	75° (2) [lit. (13) bp 103° (8)]	60	$C_3H_8N_2O$	C 40.90 H 9.15 N 31.79	40.50 9.15 31.97	13
V	120–125° (0.1) [lit. (14) bp 280° (760)]	70	$C_5H_{10}N_2O_2$	C 46.17 H 7.70 N 21.54	46.16 7.95 21.50	14
VI	72–73° (ether–cyclohexane) [lit. (15) mp 67–68°]	80	$C_{17}H_{18}N_2O_4$	C 64.95 H 5.77 N 8.91	65.13 6.01 9.01	15
VII	141–143° (ethanol) [lit.(14) mp 145°]	81	$C_{15}H_{14}N_2O_2$	C 70.85 H 5.55 N 11.01	71.04 5.67 10.67	14
VIII	239–240.5° (ethanol) [lit. (16) mp 238.5–240°]	58	$C_9H_8N_2O_2$	C 61.36 H 4.58 N 15.90	61.21 4.65 16.06	16
IX	282–285° (methanol)	52	$C_{11}H_{10}N_2O_4$	C 56.41 H 4.30 N 11.96	56.14 4.41 11.89	—
X	178° (0.005)[b]	77	$C_{22}H_{26}N_2O_6$	C 63.75 H 6.32 N 6.76	63.55 6.27 6.98	—
XI	182° (0.01)[b]	78	$C_{21}H_{24}N_2O_6$	C 64.46 H 6.59 N 6.54	64.27 6.44 6.66	—
XII	183° (0.01)[b]	78	$C_{24}H_{30}N_2O_6$	C 65.14 H 6.83 N 6.33	65.19 6.75 6.50	—
XIII	Oil[c]	43[d]	$C_{15}H_{23}N_3O_3$[e]	C 61.41 H 7.90 N 14.33	61.38 7.96 14.50	—
XIV	Oil[c]	62[d]	$C_{24}H_{31}N_3O_5$	C 65.28 H 7.08 N 9.52	64.99 7.00 9.45	—
XV	77–78° (ether–hexane)	69[d]	$C_{25}H_{33}N_3O_5$	C 65.91 H 7.30 N 9.23	65.92 7.23 9.23	—
XVI	Lyophilizate[f]	67	$C_7H_{17}N_3O \cdot (CO_2H)_2$	C 43.36 H 7.68 N 16.86 O 32.09	43.17 7.81 16.96 31.90	—
XVII	Lyophilizate[f]	82	$C_8H_{19}N_3O \cdot (CO_2H)_2$	C 45.62 H 8.04 N 15.96 O 30.38	45.52 8.04 16.11 30.41	—
XVIII	Lyophilizate[f]	99	$C_9H_{21}N_3O \cdot (CO_2H)_2$	C 47.64 H 8.36 N 15.15 O 28.85	47.44 8.59 15.18 28.68	—
XIX	146–147° (benzene–cyclohexane)	32	$C_{15}H_{19}N_3O_3$	C 62.26 H 6.62 N 14.52	62.53 6.84 14.61	—
XX	121–122° (benzene–cyclohexane)	35	$C_{16}H_{21}N_3O_3$	C 63.35 H 6.98 N 13.85	63.20 6.84 14.08	—
XXI	118–118.5° (benzene–cyclohexane)	31	$C_{17}H_{23}N_3O_3$	C 64.33 H 7.30 N 13.24	64.28 7.38 13.28	—

[a] NMR and IR spectra were consistent with structure assignments. [b] The temperature indicated is that of the heating block of a short path distillation apparatus. The recorded temperatures are not corrected. [c] The analytical sample was prepared by condensing the necessary amount on a cold finger under high vacuum. [d] Percentage yield over three synthetic steps. [e] One benzyloxycarbonyl blocking group was lost (NMR) using the general synthetic procedure. [f] The melting points of the lyophilized oxalates were broad and variable, although the compounds were spectrally and analytically pure.

homologs gave mass spectra (Table II) characterized by three common ions at m/e 189 $[C_6H_4(CON)_2CH_3(CH_2)]^+$, 162 $[C_6H_4(CO)_2NHCH_3]^+$, and 89 $[CONHC_3H_7]^+$. The balance of the fragmentation patterns for each phthalazine could be readily interpreted in terms of stepwise scissions of the respective side-chain elements.

Biology—The synthesized compounds, including synthetic intermediates, were evaluated for antitumor activity in the mouse L-1210 leukemia system according to established protocols (18). Compounds III–XXI showed no significant activity (Table III), as indicated by the ratio of the mean survival time of the test animals over that of the control animals expressed as a percentage (%T/C). A %T/C value greater than 125 is considered indicative of activity in this test system.

The murine tumor systems used to evaluate I and II, as well as their respective analogs, were Ehrlich carcinoma, Sarcoma 180, and Walker carcinosarcoma 256 (6, 7). However, the L-1210 system was chosen for screening the present series of compounds because of its greater predictive value for clinically useful drugs (19).

The nonacylated methylhydrazine, 1-ethyl-2-methylhydrazine (III), exerted a general toxicity on L-1210 tumor-bearing mice (Table III). Addition of acyl groups to methylhydrazine (IV–VII) neither ameliorated toxicity nor elicited antitumor activity. Compounds VIII and IX were both nontoxic and inactive.

The more fully elaborated methylhydrazines (XVI–XVIII) patterned after procarbazine demonstrated a nonselective toxicity, which was

Table II—Mass Spectral Data for the Phthalazines[a]

Compound	M+	M − 28	M − 29	M − 58	M − 100	189	Base	M − 175	89
XIX	289 (7.8)	261 (20.3)	260 (16.6)	231 (4.4)	189 (6.9)		162 (100)	114 (19)	89 (9.4)
XX	303 (81.7)	275 (9.4)	274 (8.7)	245 (12.2)	203 (10)	189 (8.5)	162 (100)	128 (93)	89 (76)
XXI	317 (7.1)	289 (6.9)	288 (7.5)	259 (14)	217 (0.7)	189 (10.7)	162 (100)	142 (63)	89 (15.7)

[a] The tabulated values are mass-charge ratios *(m/e)* followed by the relative intensities (indicated in parentheses) as percentages of the base peak.

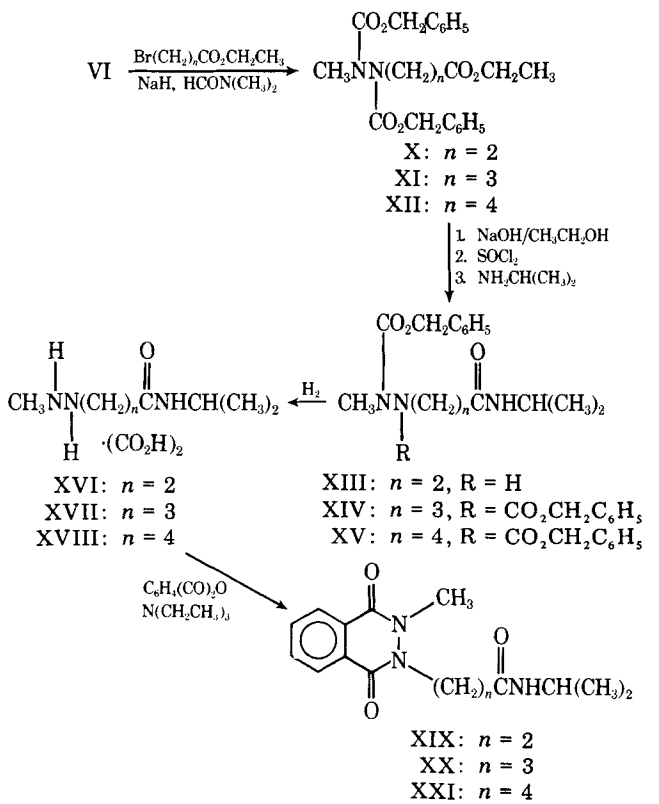
eliminated when they were tested as bis(benzyloxycarbonyl) derivatives (XIV and XV) but without a concomitant appearance of antitumor effects. Methylhydrazine XVIII has a calculated partition coefficient that is nearly identical to the measured value (20) of procarbazine (log P = 0.06, octanol). The lack of activity shown by XVIII and its derivatives (XV and XXI) was, therefore, particularly disappointing.

Derivatizing the aliphatic procarbazine analogs with phthalic anhydride gave water-soluble phthalazines (XIX–XXI), which were nontoxic and inactive.

EXPERIMENTAL[1]

1-Ethyl-2-methylhydrazine Dihydrochloride (III)—A procedure (12) for the synthesis of 1,2-dimethylhydrazine dihydrochloride was modified for the preparation of III. Accordingly, a twofold excess of ethyl bromide was reacted with 7.6 g (0.03 mole) of VII in ethanolic potassium hydroxide solution.

6-Carboxy-2,3-dihydro-2-methyl-1,4-phthalazinedione (IX)—1,2,4-Benzenetricarboxylic anhydride (9.6 g, 0.05 mole) and 1,2-dimethylhydrazine dihydrochloride (6.6 g, 0.05 mole) were refluxed in a mixture of 100 ml each of triethylamine and dimethylformamide for 18 hr. After solvent evaporation, the residue was treated with dilute hydrochloric acid and the product was extracted with ether–ethyl acetate (1:1). Evaporation of the dried extracts gave 6.1 g of IX after recrystallization.



Scheme I

Bis(phenylmethyl) 1-(5-Ethoxy-5-oxopentyl)-2-methyl-1,2-hydrazinedicarboxylate (XII): General Preparation for X and XI—To a stirring suspension of 0.72 g (30 mmoles) of sodium hydride in 70 ml of dry dimethylformamide was added, in parts, 9.42 g (30 mmoles) of VI. The reaction mixture was protected with a calcium sulfate drying tube and stirred for 30 min after the addition. A solution of 6.27 g (30 mmoles) of ethyl 5-bromovalerate in 20 ml of dry dimethylformamide was added dropwise to the reaction solution over 10 min, producing a mild exothermicity. After the reaction solution was stirred for 20 hr, it was poured into 500 ml of saline and the product was removed by extraction with ether. The dried extracts were evaporated, and the residual oil was vacuum distilled in a short path apparatus to give 11.46 g of XII.

Bis(phenylmethyl) 1-Methyl-2-[5-[(1-methylethyl)amino]-5-oxopentyl]-1,2-hydrazinedicarboxylate (XV): General Preparation for XIII and XIV—A solution of XII (11.3 g, 25.5 mmoles) in 100 ml of 95% ethanol was treated with 35 ml of 2 N sodium hydroxide solution, stirred at room temperature for 4 hr, and then poured into 500 ml of cold saline. Neutral materials were removed by extracting twice with ether. Ice chips were added to the aqueous solution, the solution was acidified with concentrated hydrochloric acid, and the acidic product was collected by three ether extractions. The combined extracts were dried and evaporated to yield quantitatively the carboxylic acid.

The carboxylic acid (10.1 g) was stirred with 50 ml of thionyl chloride for 30 min at room temperature and subsequently refluxed for 30 min. Excess thionyl chloride was removed under vacuum, and the residue was dissolved in 100 ml of dry tetrahydrofuran. While the latter solution was stirred, protected with a drying tube and cooled with an ice bath, a solution of 10 ml of isopropylamine in 100 ml of dry tetrahydrofuran was added dropwise over 20 min. The resulting solution mixed with a copious precipitate was stirred 1 hr at ice temperature and 1 hr at room temperature and was then poured into saline made basic with sodium hydroxide solution. The product was removed by three ether extractions. The combined dried extracts were concentrated to about 100 ml on a steam bath, and 150 ml of hexane was slowly added to give a saturated solution at a boil. Allowing the solution to crystallize at room temperature gave 8.02 g of XV in two crops.

Compounds XIII and XIV could not be induced to crystallize and were purified by column chromatography on alumina. After eluting with benzene, the pure product was obtained by eluting with benzene–ethyl acetate (4:1).

***N*-(1-Methylethyl)-5-(2-methylhydrazino)pentanamide Ethanedioate (1:1) (XVIII): General Preparation for XVI and XVII**—A solution of 4.56 g (10 mmoles) of XV in 50 ml of 95% ethanol was placed in a 500-ml pressure bottle containing 0.5 g of 10% palladium-on-charcoal catalyst and hydrogenated at 2.67 kg/cm^2 (38 lb/in.^{2}) pressure with shaking for 18 hr. Immediately after venting the apparatus, the reaction mixture was treated with 10 ml of 10% hydrochloric acid. The catalyst was removed by filtering through a pad of diatomaceous silica[2].

The filtrate was concentrated under vacuum, and the residue was partitioned between 140 ml of distilled water and 100 ml of ether and separated. The ether layer was washed once with 10 ml of distilled water, and the combined aqueous layers were lyophilized to give the dihydrochloride as a partially crystalline, hygroscopic glass. The glass in 10 ml of water was applied to a strongly basic, 20–50-mesh, anion-exchange column[3] (3.5 × 20 cm, oxalate form) and eluted with 400 ml of water to give 2.76 g of XVIII as a white nonhygroscopic cake after lyophilization of the fractions.

The oxalate (XVIII, XVI, and XVII) lyophilizates were analytically pure. Attempts to recrystallize them resulted in decomposition.

1-[3,4-Dihydro-3-methyl-1,4-dioxo-2(1*H*)-phthalazinyl]-*N*-(1-

[1] NMR spectra were determined with a Varian T-60 spectrometer. IR spectra were recorded with a Perkin-Elmer model 621 spectrometer in chloroform. Mass spectra were obtained by direct probe insertion with a DuPont 21-492 spectrometer with a 75-ev ionizing voltage. Combustion analyses were performed by the National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Md., and by Galbraith Laboratories, Knoxville, Tenn. All melting points are uncorrected and were determined with a Thomas-Hoover capillary melting-point apparatus. Organic extracts were dried over anhydrous sodium sulfate in all cases. The alumina for column chromatography was neutral alumina, 100–200 mesh, Brockmann Activity III.

[2] Celite, Johns-Manville Co.

[3] Amberlite IRA-401S, Rohm & Haas Co., Philadelphia, Pa.

Table III—Mouse L-1210 Antitumor Evaluation

Compound[a]	%T/C (Dose)[b]	T − C[c]	NSC Number
III	108 (200)[d]	−1.1	237649
IV	105 (200)[d]	0.5	235817
V	120 (200)[e]	−0.3	235818
VI	110 (400)	−1.5	235821
VII	126 (200)[d,e]	0.3	235819
VIII	103 (400)	1.2	235820
IX	98 (400)	0.0	237651
X	100 (400)	−0.5	264080
XI	101 (400)	0.1	249986
XII	97 (400)	−1.0	249988
XIV	95 (400)	0.5	264081
XV	95 (400)	−1.1	264082
XVI	91 (200)[d]	−3.0	266768
XVII	112 (200)[d]	−4.4	266767
XVIII	101 (100)[f]	0.1	266769
XIX	101 (400)	−0.9	267970
XX	98 (400)	−0.8	267971
XXI	104 (400)	−0.8	267972

[a] Test compounds were administered intraperitoneally on Days 1, 5, and 9 following intraperitoneal tumor implantation. [b] The tabulated dose (milligrams per kilogram) was the highest dose given producing the indicated %T/C in a dose–response assay. [c] The difference of the average body weight change in grams of the test group (T) and the control group (C) measured on Day 5. [d] Toxic at 400 mg/kg. [e] Activity could not be reproduced. [f] Toxic at 200 mg/kg.

methylethyl)pentanamide (XXI): General Preparation for XIX and XX—A mixture of XVIII (0.77 g, 2.96 mmoles) as the crude dihydrochloride salt (use of the oxalate salt gave similar results) and phthalic anhydride (0.48 g, 3.26 mmoles) was combined with 50 ml of triethylamine and refluxed with stirring for 4 hr. Most of the triethylamine was removed by flash distillation (bath 45°), and the residue was partitioned between 50 ml of 10% hydrochloric acid and 100 ml of chloroform and separated. The aqueous layer was extracted twice with chloroform; the organic layers were combined, dried, and evaporated, yielding 0.69 g of a yellow syrup, which crystallized. The crystals in 5 ml of chloroform were chromatographed on 37 g of alumina. Elution with 200 ml of chloroform gave 290 mg of white crystals of XXI after recrystallization.

REFERENCES

(1) A. Lewis and R. G. Shepherd, in "Medicinal Chemistry," A. Burger, Ed., Wiley–Interscience, New York, N.Y., 1970, p. 435.

(2) C. Kaiser and C. L. Zirkle, in *ibid.*, p. 1483.

(3) B. Toth, *Cancer Res.*, **35**, 3693 (1975).

(4) J. Gold, *Oncology*, **25**, 66 (1971).

(5) D. J. Reed, in "Antineoplastic and Immunosuppressive Agents," part II, A. C. Sartorelli and D. G. Johns, Eds., Springer-Verlag, Berlin, Germany, 1975, p. 747.

(6) G. Weitzel, F. Schneider, A. Fretzdorff, J. Durst, and W. D. Hirschman, *Hoppe Seyler Z. Physiol. Chem.*, **348**, 433 (1967).

(7) H. Rutner, N. Lewin, E. C. Woodbury, T. J. McBride, and K. V. Rao, *Cancer Chemother. Rep.*, **58**, 803 (1974).

(8) A. M. Vandermerwe, H. C. Falkson, and G. Falkson, *S. Afr. Cancer Bull.*, **14**, 75 (1970).

(9) J. Laszlo, J. Durant, and V. Loeb, *Cancer Chemother. Rep.*, **53**, 131 (1969).

(10) K. B. Olson, J. Horton, K. L. Pratt, W. J. Paladine, Jr., T. Cunningham, J. Sullivan, H. Hosely, and D. H. Treble, *ibid.*, **53**, 291 (1969).

(11) J. A. Beisler and S. S. Hillery, *J. Pharm. Sci.*, **64**, 84 (1975).

(12) F. E. Condon, *J. Org. Chem.*, **37**, 3615 (1972).

(13) *Ibid.*, **37**, 3608 (1972).

(14) A. Michaelis and E. Hadanck, *Chem. Ber.*, **41**, 3285 (1908).

(15) K. A. Jensen, U. Anthoni, B. Kagi, C. Larsen, and C. T. Pedersen, *Acta Chem. Scand.*, **22**, 1 (1968).

(16) E. H. White, D. F. Roswell, and O. C. Zafiriou, *J. Org. Chem.*, **34**, 2462 (1969).

(17) P. Zeller, H. Gutmann, B. Hegedus, A. Kaiser, A. Langemann, and M. Muller, *Experientia*, **19**, 129 (1963).

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

(19) A. Goldin, A. A. Serpick, and N. Mantel, *Cancer Chemother. Rep.*, **50**, 173 (1966).

(20) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).

ACKNOWLEDGMENTS AND ADDRESSES

Received July 23, 1976, from the *Drug Design & Chemistry Section, Laboratory of Medicinal Chemistry and Biology, Drug Research and Development Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, MD 20014.*

Accepted for publication August 17, 1976.

The authors thank Dr. J. A. Kelley of this laboratory for mass spectrometric data and Mr. Leo Dudeck and Mr. George Congleton, Hazleton Laboratories, Vienna, Va., for conducting the antitumor assays.

* National Institutes of Health Visiting Postdoctoral Fellow 1972–1974. Present address: University of Illinois Medical Center, Chicago, IL 60612.

[x] To whom inquiries should be directed.

Formulation Factors Affecting Strength and Dissolution of Uncoated Oxytetracycline Tablets

S. ESEZOBO and N. PILPEL [x]

Abstract □ The effect of various formulation and processing factors on the properties of 300-mg oxytetracycline tablets was studied. At a constant moisture level and packing fraction, an increase in gelatin concentration resulted in increased tensile strength, increased disintegration and dissolution times, and reduced capping tendency. The Wagner theory of dissolution applied satisfactorily to tablets containing up to 5% (w/w) gelatin but was less applicable at higher gelatin levels. Dissolution rate constants were calculated, and their values depended on the gelatin content and packing fraction of the tablets.

Keyphrases □ Oxytetracycline tablets—tensile strength and dissolution, effect of various formulation and processing factors □ Tablets, oxytetracycline—tensile strength and dissolution, effect of various formulation and processing factors □ Tensile strength—oxytetracycline tablets, effect of various formulation and processing factors □ Dissolution—oxytetracycline tablets, effect of various formulation and processing factors □ Dosage forms—oxytetracycline tablets, tensile strength and dissolution, effect of various formulation and processing factors

Recently, various investigators (1, 2) reported that commercial oxytetracycline hydrochloride capsules, nominally containing the same dose but produced by different manufacturers, are not biologically equivalent. Brice and Hammer (1) performed disintegration and dissolution tests and found that, in general, batches that gave poor