intramolecular charge repulsion is not a primary factor in these salt effects on viscosity. However, interpretation of these results is complicated by the fact that xanthan gum, as supplied by the manufacturer, contains some cellular material and ions. Typically, monovalent cations, (principally sodium and potassium) amount to 3–6% (w/w) of the finished product[3]. Divalent cations, principally calcium and magnesium, make up ~0.15–0.35% by weight of the commercial polymer[3]. For the same reason, it is difficult to compare results of this study with many previous reports for which purified gum was utilized.

The utility of xanthan gum as a stabilizer of aqueous suspensions and other disperse systems is due, in part, to the pseudoplastic nature of gum solutions. At high shear the viscosity is quite low, permitting shaking, pouring, and pumping without high resistance. On the other hand, the high viscosity augmented by existence of a gel-like state at very low shear accounts for the high resistance to particle sedimentation. Viscosity, the degree of pseudoplasticity, and the value of the transition from gel-like to pseudoplastic behavior are dependent on xanthan gum concentration. The effect of addition of a salt on viscosity of xanthan gum solutions is complex. A 0.3% xanthan gum solution exhibits negligible viscosity changes when a salt is added. Higher concentrations of xanthan gum show increased viscosity, and lower xanthan gum concentrations undergo a reduction in viscosity. All of these effects seem to reach limiting values at $\sim 10^{-3}$ *N* to 3.3×10^{-3} *N* salt concentration. Based on the small number of salts studied, viscosity changes appear to be independent of the salt. However, certain ions in particular pH ranges exhibit more specific effects on viscosity (11).

[3] J. Baird, Kelco Division of Merck and Co., Inc., personal communication.

REFERENCES

(1) A. Jeanes, J. E. Pittsley, and F. R. Senti, *Appl. Polymer Sci.*, **5**, 519 (1961).

(2) P. J. Whitcomb, B. J. Ek, and C. W. Macosko, *Am Chem. Soc. Symp. Ser.*, **45**, 160 (1977).

(3) P. J. Whitcomb and C. W. Macosko, *J. Rheol.*, **22**, 493 (1978).

(4) P. E. Jansson, L. Keene, and B. Lindberg, *Carbohydr. Res.*, **45**, 275 (1975).

(5) P. A. Sandford, J. E. Pittsley, C. A. Knutson, P. R. Watson, M. C. Cadmus, and A. Jeanes, *Am. Chem. Soc. Symp. Ser.*, **45**, 192 (1977).

(6) R. Moorhouse, M. D. Walkinshaw, and S. Arnott, *Am. Chem. Soc. Symp. Ser.*, **45**, 90 (1977).

(7) E. R. Morris, D. A. Rees, G. Young, M. D. Walkinshaw, and A. Darke, *J. Mol. Biol.*, **110**, 1 (1977).

(8) G. Holzwarth, *Biochemistry*, **15**, 4333 (1976).

(9) M. Rinaudo and M. Milas, *Biopolymers*, **17**, 2663 (1978).

(10) K. C. Symes, *Food Chem.*, **6**, 63 (1980).

(11) "Xanthan Gum," 2nd ed., Kelco Co., San Diego, Calif., 1978.

(12) J. G. Southwick, H. Lee, A. M. Jamieson, and J. Blackwell, *Carbohydr. Res.*, **84**, 287 (1980).

(13) J. R. Van Wazer, J. W. Lyons, K. Y. Kim, and R. E. Colwell, "Viscosity and Flow Measurement," Interscience, New York, N.Y., 1963, pp. 15, 16.

ACKNOWLEDGMENTS

The authors thank the Kelco Division of Merck and Co., Inc. for grant support and samples of KELTROL® xanthan gum, and Haake, Inc. for the use of the Rotovisco viscometer.

Syntheses and Evaluation of Some Mannich Bases Derived from Acetophenones Against P388 Lymphocytic Leukemia and Toxicological Assessment of 3-Dimethylamino-2-dimethylaminomethyl-1-(4-methoxyphenyl)-1-Propanone Dihydrochloride in Rats

J. R. DIMMOCK *[x], K. SHYAM *, B. M. LOGAN *, P. J. SMITH [‡], and B. M. CROSS [§]

Received September 7, 1982, from the **College of Pharmacy*, [‡]*Department of Chemistry, College of Arts and Science* and [§]*Department of Veterinary Pathology, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, Saskatchewan S7N 0W0 Canada.* Accepted for publication January 18, 1983.

Abstract □ A number of analogues of 3-dimethylamino-2-dimethylaminomethyl-1-(4-methoxyphenyl)-1-propanone dihydrochloride (IIa) and related compounds which showed activity against P388 lymphocytic leukemia were prepared, and of the 16 analogues, three met the criterion for activity in this screen. The toxicity of IIa was examined in rats and either a single dose of 25 mg/kg or nine daily doses of 12.5 mg/kg administered by the intraperitoneal route produced marked irritation and damage to the tissue with which it came into contact. Compound IIa did not show significant activity against eight other tumor systems.

Keyphrases □ Mannich bases—derived from acetophenones, antileukemic activity in the P388 screen, toxicological assessment in rats □ Antileukemic agents—potential, Mannich bases derived from acetophenones, P388 screen, toxicological assessment in rats □ 3-Dimethylamino-2-dimethylaminomethyl-1-(4-methoxyphenyl)-1-propanone dihydrochloride—synthesis, antileukemic activity in the P388 screen, toxicological assessment in rats

A number of Mannich bases have been synthesized and evaluated against murine P388 lymphocytic leukemia (1–3). Under certain conditions, Mannich bases undergo elimination leading to the formation of the corresponding α,β-unsaturated ketones (4, 5), which have a marked affinity for nucleophiles (6, 7). This property may account for certain of the biological properties of Mannich bases (8, 9).

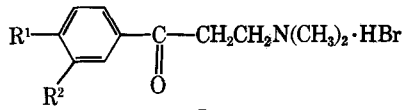
Series I was recently evaluated against P388 leukemia in mice and shown to be inactive (10). However, if a second dimethylaminomethyl group is inserted into the molecule, as in IIa, the deamination product would retain a dimethylaminomethyl function attached to the olefinic carbon atom α to the carbonyl group. Since, on occasions, the pH of tumor cells has been claimed to be more acidic than normal cells (11–13), deamination of IIa could give rise, possibly preferentially in malignant tissue, to a compound bearing a protonated nitrogen atom. Hence nucleophilic attack by cellular macromolecules would be enhanced since the intermediate formed as a result of Michael addition would be stabilized by two electron-withdrawing functions, namely the carbonyl group and the positively charged nitrogen atom.

A representative compound, IIa, was synthesized and shown to increase the median survival time in mice with P388 lymphocytic leukemia by 28 and 24% at dose levels of 25 and 12.5 mg/kg, respectively. A comparison of the bioactivities of IIb–f

0022-3549/84/0400-0471$01.00/0

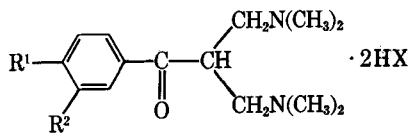
with Ia–e was made in order to explore the generality of this molecular modification on antileukemic activity. It was found that IIb–f increased the median survival time by 36, 38, 17, 16, and 8%, respectively, and this gradation in biological activity followed, in general, the values of the Hammett σ constants of −0.27, −0.17, 0.00, 0.23, and 0.60 for the nuclear substituents of IIb–f, respectively (10). The stabilities of representative compounds in I and II which possessed extremes of Hammett σ values (Ia,e and IIb,f) were examined under simulated physiological conditions (phosphate buffer, pH 7.4, at 37°C). While I was stable for at least 1.5 h, IIb and f broke down to the corresponding olefinic ketones at rates which seemed to suggest that elimination was favored by electron-withdrawing substituents on the aromatic ring. It was considered possible that an optimal rate of breakdown was associated with anticancer activity, *i.e.*, if decomposition was too rapid (as in the case of IIf), then the α,β-unsaturated ketone generated was sequestered prior to interaction with leukemia cells, whereas if it was too slow or even refractory to deamination (as suggested by the data for I), there would be insufficient α,β-unsaturated ketone present for presumed nucleophilic attack.

The aims of the present investigation were twofold. First, since the promising lead compounds IIa–c possessed nuclear methoxyl and methyl groups with Hammett σ values of $\sim$−0.2, it was proposed to synthesize III, which principally contained these groups and in which the Hammett σ value for the substituents on the aromatic ring for IIIa–f were +0.12, −0.15, −0.03, −0.37, −0.07, and −0.24, respectively. Thus, the rate of release of the α,β-unsaturated ketone would be expected to vary, and the validity of the rate of breakdown of III with antileukemic activity could be explored further. However, the rate of release of the conjugated styryl ketones *in vivo* could also be influenced by the pK_a of the basic group and, hence, the preparation of IV was envisaged. The pK_a values for dimethylamine, pyrrolidine, piperidine, morpholine, and trimethylamine are 10.77, 11.27, 11.22, 8.70, and 9.80, respectively (14), and thus the rate of decomposition predicted is IVd > IVe > IVa > IVb,c. Since the dibasic compounds in II were, in general, more active *versus* P388 lymphocytic leukemia than I, a comparison of the antineoplastic activities of III and IV with the monobasic derivatives V and VI was deemed profitable to shed more light on the generality of this observation. Second, IIa has been designated a Selected Agent Compound by the National Cancer Institute, and it seemed of importance, therefore, to explore the toxicity of IIa in order to further evaluate its potential as a candidate anticancer drug.



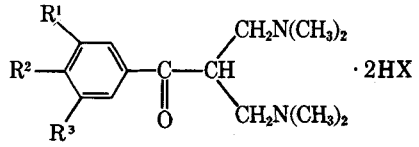
I

a. $R^1 = OCH_3$; $R^2 = H$
b. $R^1 = CH_3$; $R^2 = H$
c. $R^1 = R^2 = H$
d. $R^1 = Cl$; $R^2 = H$
e. $R^1 = R^2 = Cl$



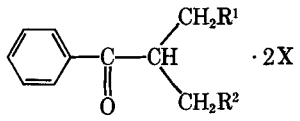
II

a. $R^1 = OCH_3$; $R^2 = H$; X = Cl
b. $R^1 = OCH_3$; $R^2 = H$; X = Br
c. $R^1 = CH_3$; $R^2 = H$; X = Br
d. $R^1 = R^2 = H$; X = Br
e. $R^1 = Cl$; $R^2 = H$; X = Br
f. $R^1 = R^2 = Cl$; X = Br



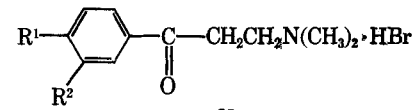
III

a. $R^1 = OCH_3$; $R^2 = R^3 = H$; X = Cl
b. $R^1 = R^2 = OCH_3$; $R^3 = H$; X = Br
c. $R^1 = R^2 = R^3 = OCH_3$; X = Br
d. $R^1 = R^3 = H$; $R^2 = OH$; X = Br
e. $R^1 = CH_3$; $R^2 = R^3 = H$; X = Br
f. $R^1 = R^2 = CH_3$; $R^3 = H$; X = Br



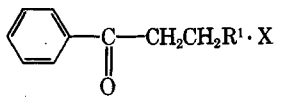
IV

a. $R^1 = N(CH_3)_2$; $R^2 =$  ; X = HBr
b. $R^1 = R^2 =$  ; X = HBr
c. $R^1 = R^2 =$  ; X = HBr
d. $R^1 = R^2 =$; X = HBr
e. $R^1 = R^2 = \overset{(+)}{N}(CH_3)_3$; X = $\overset{(-)}{Br}$



V

a. $R^1 = H$; $R^2 = OCH_3$
b. $R^1 = OH$; $R^2 = H$
c. $R^1 = H$; $R^2 = CH_3$



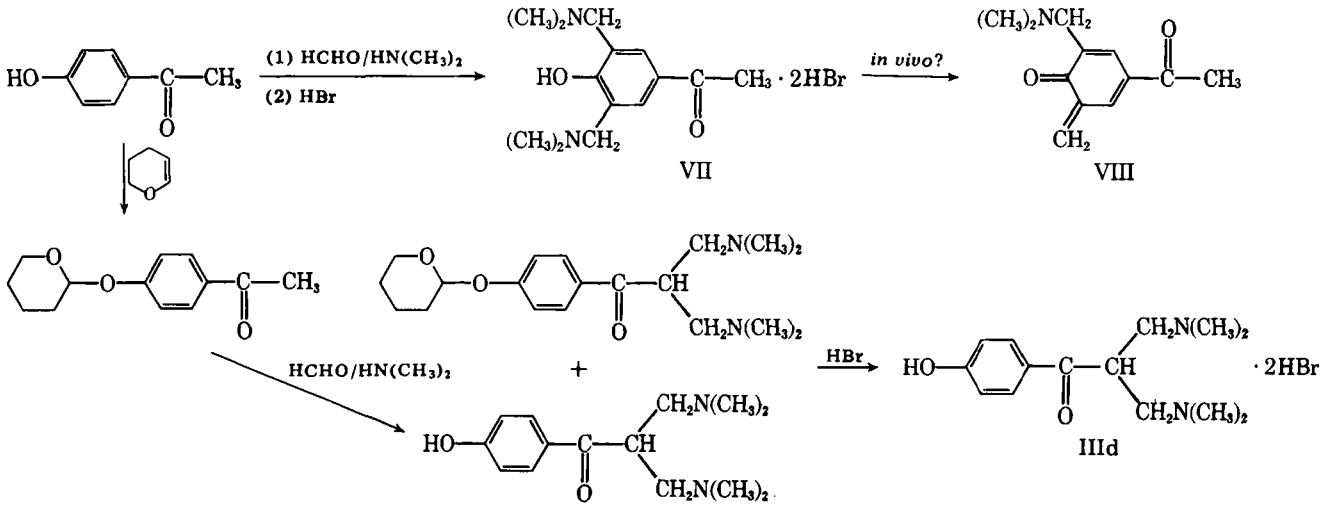
VI

a. $R^1 =$  ; X = HBr
b. $R^1 =$  ; X = HBr
c. $R^1 =$  ; X = HBr
d. $R^1 = \overset{(+)}{N}(CH_3)_3$; X = $\overset{(-)}{Br}$

RESULTS AND DISCUSSION

Compounds IIa, IIIa–c, e, f, and IVb–d were prepared by treating acetophenone or a substituted acetophenone with an excess of formaldehyde and amine and converting the products into the corresponding dihydrohalide salts. Utilization of this general procedure in attempting to prepare IIId gave rise to the nuclear bis(aminomethyl) product, VII (Scheme I). To obtain exclusively side chain aminomethylation, the nuclear hydroxyl group of *p*-hydroxyacetophenone was protected by a tetrahydropyranyl function (15), and TLC of the product of a Mannich reaction with this ketone showed a mixture of diamines was formed in which both protected and free hydroxyl groups were present. The mixture was then treated with hydrogen bromide to give the desired product IIId (Scheme I).

The mass spectrum of this compound was of interest insofar as the base peak



Scheme I

differed from four related compounds IIb and d–f, although common fragmentation pathways were found in all five compounds (Table I; Scheme II). The peak due to the dimethyl(methylene)ammonium ion (f, *m/z* 58) is the base peak except for IIId, in which case it is the acylium ion (g) *m/z* 121. Stabilization of the positive charge in the acylium ion by the powerful electron-releasing mesomeric effect of the hydroxyl group ($\sigma_p^+ = -0.85$) (16) could account for this phenomenon (Scheme III). It is of interest to note that a major ion in the fragmentation pattern of IIb is *m/z* 135, due to the related *p*-methoxy acylium ion. Other observations of interest from Scheme II are as follows.

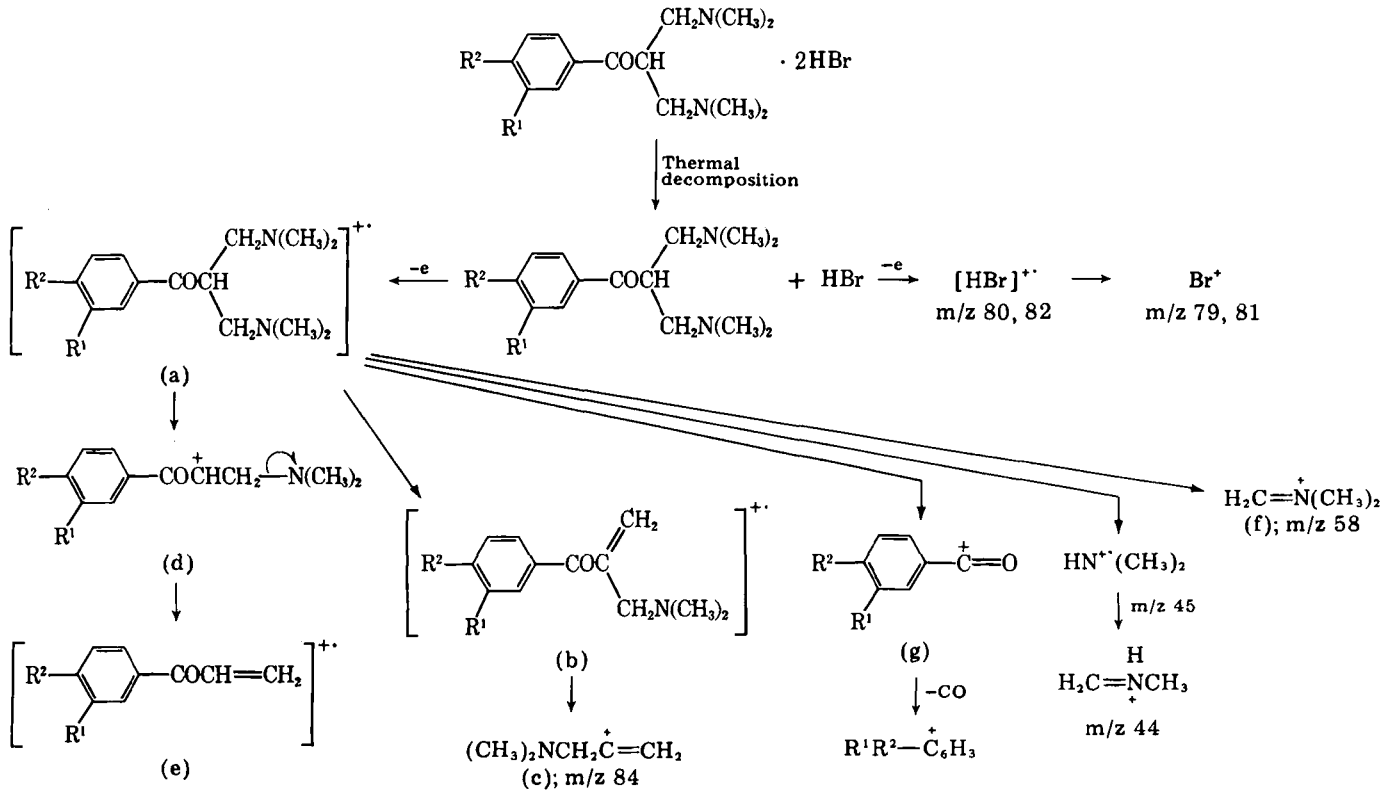
1. The radical ion of the free diamine (a) which could be formed is absent in all five cases. On the other hand, each spectrum shows peaks of equal intensity at *m/z* 80 and 82 due to $[HBr]^+$ and also at *m/z* 79 and 81 due to Br^+.

2. The peak due to the radical ion of 1-aryl-2-dimethylaminomethyl-2-propen-1-one (b), which could arise from loss of dimethylamine from a, is also absent. This pathway, however, cannot be ruled out since the data obtained suggest that ion b is formed, but is of low intensity because of its fragmentation to give c, *m/z* 84.

3. The carbocation (d) may account for the peak having the highest mass-charge ratio in each case. Homolytic fission of the bond γ to the carbonyl function in d gives the radical ion of the acrylophenone (e).

Compound IVa was prepared by Mannich condensation of Ic with pyrrolidine and formaldehyde, and quaternization of the free base of IId and Ic with methyl bromide gave IVe and VId, respectively. The remaining compounds in series V and VI were prepared essentially by the method of Maxwell (17). The physical data of IIa and III–VII and the efficacy of most of the compounds against P388 lymphocytic leukemia are given in Table II.

Compounds IIIb, d, and f, like the active diamines IIb and c, have nuclear substituents with an average Hammett σ value of ~−0.25, and both IIIb and f are active against P388 lymphocytic leukemia while IIId possesses marginal activity. It is conceivable that facile *O*-glucuronidation minimizes the antileukemic efficacy of IIId. The remaining three compounds IIIa, c, and e, with an average nuclear Hammett σ value of 0.02, were inactive. There was slightly higher activity in the case of IIIa, d, and e (average T/C% = 115) than with their monobasic counterparts Va–c (average T/C% = 105). No correlation between the predicted ease of breakdown in series IV with anticancer activity was apparent, and compounds VIa, b, and d were inactive. However, two



Scheme II

Table I—*m/z* (Relative Intensity) Values of the Principal Ions Observed in the 70-eV Mass Spectra of the 1-Aryl-3-dimethylamino-2-dimethylaminomethyl-1-propanone Dihydrobromides IIb, d–f, and IIId

Compound	*m/z* (Relative Intensity) of Principal Ions
IIb	206(18), 202(6), 162(35), 135(78), 107(11), 92(18), 84(12), 82(28), 81(11), 80(28), 79(11), 77(24), 58(100), 45(16), 44(32)
IId	176(23), 172 (4), 132(18), 105(44), 84(13), 82(24), 81(8), 80(24), 79(8), 77(33), 58(100), 45(11), 44(21)
IIe	212(3), 210(9), 206(6), 141(18), 139(53), 113(7), 111(22), 84(8), 82(18), 81(6), 80(20), 79(7), 75(15), 58(100), 45(14), 44(27)
IIf	246(3), 244(6), 240(3), 202(9), 200(14), 117(4), 175(27), 173(42), 149(2), 147(11), 145(16), 109(10), 84(9), 82(21), 81(8), 80(22), 79(8), 75(6), 74(8), 58(100), 45(15), 44(27)
IIId	192(11), 188(4), 148(41), 121(100), 93(22), 84(8), 82(21), 81(8), 80(21), 79(8), 65(23), 58(93), 45(24), 44(44)

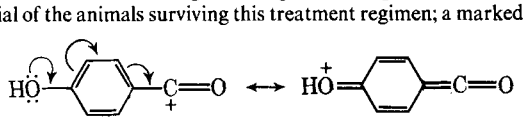
compounds (IVa and d) increased the median survival time in mice with P388 lymphocytic leukemia by ~20%. It was hoped that VII would give rise to the *ortho* quinone VIII *in vivo* (Scheme I), but the lack of both antineoplastic activity and marked murine toxicity suggested that this pathway did not materialize. The screening results observed in this study reveal a continuation of a trend observed earlier (10) that, in general, higher anticancer activity is found among dibasic derivatives of substituted acetophenones than with the corresponding monobasic analogues.

The second phase of this investigation was to examine the disposition of IIa. As mentioned earlier, significant antineoplastic activity was found at dose levels of 12.5 and 25 mg/kg. During the first trial with IIa, a single 12.5-mg/kg ip injection was administered to rats. Three test and one control rats were killed 2, 4, 6, 8, 10, and 15 d postinjection. During the second trial, three rats were given a single 25-mg/kg injection of IIa. The rats were closely observed, and one rat was killed 5, and two others at 30, and 48 h postinjection, Following this, a single 12.5-mg/kg injection of IIa was repeated in three animals. One of the test rats and one control were killed 24, 48, and 84 after the injection. In the final trial, it was proposed to give nine daily injections of IIa (12.5 mg/kg) to nine rats and to examine the animals 3, 8, and 15 after the ninth injection.

The results obtained were as follows. On both occasions a single 12.5-mg/kg injection of IIa produced no gross or microscopic lesions in the rats. After the single 25-mg/kg injection of IIa, the rats appeared very depressed, were reluctant to move and were "hunched over." One rat (no. 1) was killed 5 h after injection. Twenty-four hours after injection, the remaining rats (nos. 2 and 3) were depressed and reluctant to move. Porphyrin stained the forelimbs, faces, and heads; the hair coats were rough and spiky. The abdomen of one animal was tense and contracted.

At necropsy, all three rats were observed to have hydroperitoneum. The proximal intestine was flaccid, dilated, and fluid filled. The contents of the distal jejunum, ileum, and large intestine were very dry. Numerous white opaque areas of coagulation necrosis and saponification were scattered throughout the abdominal fat and the fat associated with the spermatic cords in rats 2 and 3. The cecal wall of rat 1 was edematous and contained a perforated ulcer at the distal end. Microscopic examination revealed interlobular pancreatic edema and edema of the colonic muscularis. Rat 2 was killed 30 h after the injection. Opaque areas present in the pancreas represented acute necrosis of the peripheral lobules. The subserosal longitudinal muscle of the stomach, small intestine, and colon had also undergone acute necrosis. The myonecrosis ranged from focal to diffuse; in places it extended through the circular muscle into the submucosa and was accompanied by hemorrhage. The walls of the seminal vesicles and coagulating glands were similarly affected, with the necrosis extended through the entire wall in areas. Rat 3 was killed 48 h after injection. A fibrinous peritonitis was present with fibrinous adhesions joining the liver to the diaphragm and the pancreas to the stomach, and fibrin coated the seminal vesicles, coagulating glands, and the mesentery. Petechial hemorrhages were visible on the serosa of the cecum, colon, and rectum. The histopathological lesions were similar to those of rat 2. The necrosis and hemorrhage in the wall of the stomach and intestine were more diffuse and often extended into the lamina propria. Small ulcers were present in the squamous portion of the stomach.

Table III indicates the changes in weight resulting from the multiple-injection trial of the animals surviving this treatment regimen; a marked weight



Scheme III

Table II—Physical Data on the Mannich Bases IIa and III–VII and Activity Against P388 Lymphocytic Leukemia in Mice

Compound	Yield, %	Melting Point, °C	Formula[a]	Maximum C%[b]	Toxicity in mice[c]
IIa	31	175–177	$C_{15}H_{26}Cl_2N_2O_2$	128(25)	0/6(100), 2/6(50), 6/6(25)
IIIa	21	161–163	$C_{15}H_{26}Cl_2N_2O_2$	114(12.5)	0/6(50), 6/6(25)
IIIb	58	200–203	$C_{16}H_{28}Br_2N_2O_3$	124(12.5)	0/6(100, 4/6(50), 6/6(25)
IIIc	61	208–211	$C_{17}H_{30}Br_2N_2O_4$	111(50)	0/6(100), 5/5(50)
IIId	34	193–195	$C_{14}H_{24}Br_2N_2O_2$[d]	118(6.25)	0/5(50), 6/6(25)
IIIe	28	196–198	$C_{15}H_{26}Br_2N_2O$	114(25)	0/5(100), 1/6(50), 6/6(25)
IIIf	59	205–207	$C_{16}H_{28}Br_2N_2O$	128(12.5)	0/5(50), 6/6(25)
IVa	41	191–192	$C_{16}H_{26}Br_2N_2O$	121(12.5)	0/6(100), 6/6(50)
IVb	43	177–179	$C_{18}H_{28}Br_2N_2O$[e]	102(50)	0/6(100), 6/6(50)
IVc	19	184	$C_{20}H_{32}Br_2N_2O$	—	—
IVd	54	188	$C_{18}H_{28}Br_2N_2O_3$	119(50)	0/6(200), 6/6(100)
IVe	64	208–211	$C_{16}H_{28}Br_2N_2O$[f]	108(12.5)	0/6(50), 3/6(25), 6/6(12.5)
Va	50	147	$C_{12}H_{18}BrNO_2$	106(50)	1/6(200), 6/6(100)
Vb	58	192–193	$C_{11}H_{16}BrNO_2$	106(200)	6/6(200)
Vc	41	164–166	$C_{12}H_{18}BrNO$	103(50)	0/6(200), 4/6(100), 6/6(50)
VIa	63	187–188	$C_{13}H_{18}BrNO$	100(25)	0/6(100), 3/6(50), 6/6(25)
VIb	54	194–195[g]	$C_{14}H_{20}BrNO$	95(25)	0/6(100), 4/6(50), 6/6(25)
VIc	67	191–192[h]	$C_{13}H_{18}BrNO_2$	—	—
VId	48	197–198[i]	$C_{12}H_{18}BrNO$	99(12.5)	0/6(100), 3/6(50), 5/5(25)
VII	43	225	$C_{14}H_{24}Br_2N_2O_2$	101(50)	5/5(200)

[a] Elemental analyses for C, H, and N were conducted for all compounds. Unless otherwise noted, all values were within ±0.4% of the theoretical values. [b] Ratios of the survival time of the treated (T) to control (C) animals expressed as a percentage. Compounds were initially screened at 200, 100, and 50 mg/kg; if mortalities occurred at these doses, they were reduced to nonlethal levels. A compound should increase the median survival time by at least 20% to be considered active. The dose in mg/kg is in parentheses. [c] Numbers of survivors 5 d after commencement of the dosage schedule of nine daily doses, except for IIIb–f, IVb, IVe (50-mg/kg dose), and VII in which cases five daily doses were administered. [d] Calc. for C, 40.79; found, 39.96. [e] Calc. for C, 48.23; found 47.77. [f] Calc. for C, 45.30; found 44.88. [g] Lit. (18) mp 197.0–197.5°C. [h] Lit. (19) mp 189.5–190.5°C. [i] Lit. (20) mp 238°C.

loss was observed after completing the injection schedule, although 15 d after the last injection, some weight gain was noted (rats 5 and 6).

Four animals (nos. 4 and 7–9) died before the termination of the multiple-injection trial. Porphyrin staining of the faces was marked in all the rats. Necropsy revealed mild hydroperitoneum, a dilated fluid-filled proximal small intestine, and a large intestine filled with dry ingesta. Rat 7 was killed after it had received its second 12.5-mg/kg injection of IIa. The animal was very quiet, reluctant to move, had a tense contracted abdomen and a spiky coat. Histopathological examination revealed acute degeneration and necrosis of the subcapsular muscle fibers of the seminal vesicles with infiltration by granulocytes. The bladder wall was edematous, and the subserosal myofibers had undergone acute necrosis. The intestinal serosal mesothelium was hypertrophied.

A second rat (no. 8) died after it had received its second injection. In addition to those necropsy findings previously mentioned, all serosal blood vessels were very congested. Areas of necrosis were scattered throughout the abdominal fat and the fat associated with the reproductive organs. Numerous small ulcers extended into the submucosa of the squamous stomach. Throughout the intestine and bladder there was necrosis of subserosal muscle. Fibers were eosinophilic and shrunken. Nuclei were absent, pycnotic, and karyorrhectic. Peripheral pancreatic acini had undergone acute necrosis, and granulocytes had infiltrated the affected areas.

A third test rat (no. 9) died after receiving its fifth injection of IIa. Hematuria had been reported on the previous day. In addition to heavy porphyrin staining of the face and forepaws, blood stained the fur around the prepuce.

Table III—Weight Changes of Male Wistar Rats after Intraperitoneal Injection of IIa and Saline for Nine Consecutive Days

Rat[a]	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Weight Difference Between Days 1 and 9, g	Weight, g Day 12	Day 17	Day 24	Weight Difference Between Day 1 Day of Examination, g
1	350	340	330	325	320	305	290	300	295	−55	295			−55
2	348	328	315	328	325	305	295	290	295	−53	285			−63
3	360	345	340	315	310	300	310	295	305	−55		305		−55
4	380	368	355	340	340	355	335	330	325	−55		[b]		
5	334	315	320	305	292	275	270	270	270	−64			335	+ 1
6	380	370	365	360	355	330	320	300	315	−65			375	− 5
7	350	330	[c]											
8	354	335	[d]											
9	342	335	325	305	290	[e]								
Control 1	358	352	355	355	355	350	335	350	355	− 3	360			+ 2
Control 2	330	340	345	340	335	330	335	335	335	+ 5		340		+10
Control 3	355	340	330	315	320	335	340	345	340	−15			375	+20

[a] Rats 1-9 were injected with IIa at 12.5 mg/kg, while controls 1-3 were injected with 0.9% NaCl (saline). [b] Rat 4 died on Day 14. [c] Rat 7 was killed after receiving a second injection. [d] Rat 8 died after receiving a second injection. [e] Rat 9 died after a fifth injection.

The fluid contained in the stomach, duodenum, and jejunum was blood stained. There were areas of hemorrhage and necrosis in the pancreas, circular hemorrhages in the cecal mucosa, and blood in the urinary bladder. Histopathological examination revealed an acute diffuse peritonitis, characterized by the presence of fibrin and granulocytes on the intestinal serosa and in the connective tissue and fat associated with the seminal vesicles, coagulating glands, and the right spermatic cord. The duodenal serosa was coated with granulocytes, which extended through the edematous muscularis in some areas to the submucosa. Acute myonecrosis was noted in the duodenal wall. Similar lesions were scattered throughout the wall of the intestine and bladder. An ulcerative cystitis consisted of areas of mucosal necrosis, granulocyte infiltration into an edematous submucosa, and necrosis of single mucosal cells which sloughed into a blood-filled lumen.

The fourth animal (no. 4) died 5 d after the ninth injection of IIa. The animal was autolyzed; however, a large area of necrosis bounded by hemorrhage was noticed in the right inguinal subcutis and body wall.

Two test animals (nos. 1 and 2) and one control (no. 1) were killed 3 d after the ninth injection. One of the test animals was lame in the right hind limb. In both test animals, fibrous adhesions joined large areas of the subcutaneous tissue and body wall in the right inguinal region. In each rat, an area of necrosis, 1-1.5 cm in diameter, in the body wall was bounded by a distinct red line; grossly, the viscera appeared normal. The coagulation necrosis extended through the body wall to the peritoneum. Many of the necrotic muscle fibers were calcified. Granulation tissue has replaced much of the necrotic tissue, and muscle fibers bordering the areas of necrosis showed signs of regeneration with very long, plump nuclei and multinucleate areas. The necrotic subcutaneous fat had been replaced with granulation tissue. In the intestine and bladder, areas of the serosa and outermost muscularis had been replaced by regenerating muscle fibers, fibroblasts, and capillaries. The orientation of the regenerating fibers was irregular. Areas of mesenteric fat necrosis had been replaced by granulation tissue and lymphocytes.

One rat (no. 3) was killed 8 d after the last injection. This rat was also lame in the right hind limb. During necropsy, a large area of necrosis was found in the subcutis of the right inguinal area. A severe chronic peritonitis was present; all intestine loops were tightly adhered to each other, the bladder, seminal vesicles, and sublumbar musculature. The intestines were dilated and contained fluid. Normal fecal pellets were present in the rectum. Areas of the intestinal wall were thickened; however, the intestine was patent although the lumen was greatly reduced. A mass 1.5 cm in diameter occupied a position in the dorsal body wall midway between the right kidney and the bladder. The mass had a fibrous wall, was filled with clear fluid, and involved the right ureter and sublumbar muscles. The right ureter proximal to the mass was dilated with clear fluid. There was hydronephrosis of an enlarged right kidney. The right seminal vesicle was shrunken; atrophy of the right testis was seen during microscopic examination. Few spermatogonia were present in the seminal tubules; however, spermatozoa were present in the epididymal tubules. The walls of the intestines, seminal vesicles, and coagulating glands were thickened with a layer of granulation tissue. Areas of abdominal fat necrosis had been walled off with fibrous tissue; many of these areas had calcified. Fibrous tissue thickened the pancreatic capsule and extended between acini. Gastric ulcers extended into the muscularis mucosa. Beneath the ulcers, the muscularis and submucosa were infiltrated by fibroblasts, angioblasts, and numerous eosinophils. The medulla of the right kidney was compressed, and there was perivascular and cortical edema.

The thick fibrous wall of the fluid-filled mass extended into the adipose tissue and the muscles of the dorsal abdominal wall. It surrounded blood vessels, nerves, and sublumbar lymph nodes. Areas of mineralizing necrotic muscle were present in the mass; lymphocytes and multinucleate giant cells were prominently associated with these areas. Thrombosed blood vessels and areas of fat necrosis were also trapped in the mass. The central cavity appeared to be lined by fibroblasts.

The last two test animals (nos. 5 and 6) were sacrificed 15 d after the ninth injection. Hematuria had been reported in one of these animals after the eighth and ninth injections. Diarrhea was reported at the same time for the other rat. An ulcer 1 cm long was present in one animal in the skin fold between the right stifle and right inguinal area. Further examination revealed ulceration, necrosis, and replacement with granulation tissue that extended through the dermis and subcutis and into the body wall. Fibrous adhesions between abdominal viscera were extensive in both rats; adhesions trapped the right testes, epididymes, and spermatic cords in the scrotal sacs. The right testis from one rat was extremely small and lacked spermatogonia. The seminal vesicles and bladder were adhered together. Areas of necrotic seminal vesicle had undergone mineralization. Epididymal fibrosis was prominent in the rat no. 6; no spermatozoa were present in the epididymal or seminal tubules. Large numbers of abnormal cells, including multinucleate giant cells, were present in the seminal tubules. Sertoli cells were very prominent.

One may summarize these disposition studies by noting that when the rats received a single 25-mg/kg injection of IIa, it appeared that any portion of the abdominal viscera coming into contact with the substance underwent necrosis. Adynamic ileus, produced by peritonitis and pain, resulted in a large volume of fluid pooling in the anterior intestine and probably caused severe electrolyte imbalance. Acute gastric ulceration was probably also a manifestation of the stress produced by abdominal pain. Although a single dose of 12.5 mg/kg produced no gross or light microscopic lesions, nine daily doses at the same level resulted in severe myonecrosis and peritonitis. Throughout the series of injections, the rats exhibited behavioral manifestations of stress and pain and lost a significant amount of weight. After cessation of injections there was tissue healing; however, the permanent damage produced would interfere with intestinal, reproductive, and (in one instance) renal function. It must be concluded that the compound, at a single 25-mg/kg dose or a series of 12.5-mg/kg doses, is very irritating and severely damages any tissue with which it comes into contact.

Finally, the screening of the Selected Agent Compound IIa *versus* a number of tumors (21) was undertaken (Table IV). In tumor systems 3-8 inclusive, IIa was inactive and although some reduction in tumor weight was found in the colon and lung xenografts, it was insufficient to meet the criteria for activity.

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were undertaken locally[1], and organic extracts were dried with anhydrous magnesium sulfate. TLC was carried out using sheets of silica gel with fluorescent indicator[2] and a solvent mixture of toluene–methanol (9:1). Mass spectra[3] were run at 70 eV, and the 60-MHz NMR spectra[4] were determined in deuterochloroform or deuterium oxide using internal standards of tetramethylsilane and sodium 2,2-dimethyl-2-silapentane-5-sulfonate, respectively.

Syntheses of Compounds—*1-Aryl-3-dimethylamino-2-dimethylamino-*

[1] Mr. R. E. Teed, Department of Chemistry, College of Arts and Science, University of Saskatchewan, Saskatoon.
[2] Eastman-Kodak Co.
[3] VG Micromass MM16F mass spectrometer with 2025 data system.
[4] Varian T-60 spectrometer.

Table IV—Evaluation of IIa Against Various Tumors in Mice

Tumor	Treatment Schedule	Maximum T/C%[a]	Toxicity[b]
CX-1 Colon xenograft	Four daily injections	38(25)	0/6(100), 3/6(50), 6/6(25)
LX-1 Lung xenograft	One injection every 4 d; total of three injections	64(50)	0/6(100), 6/6(50)
MX-1 Breast xenograft	One injection every 4 d; total of four injections	101(12.5)	0/6(100), 5/6(50), 6/6(25)
$CD8F_1$ Mammary tumor	One injection	103(7.81)	1/10(125), 3/10(62.5), 10/10(31.25)
Colon 38	One injection every 7 d; total of two injections	102(25)	0/10(100), 1/10(50), 10/10(25)
B16 Melanocarcinoma	Nine daily injections	102(25)	0/10(50), 10/10(25)
L 1210 Lymphoid leukemia	Nine daily injections	110(25)	1/6(50), 6/6(25)
Lewis lung carcinoma	Nine daily injections	105(12.5)	1/10(50), 10/10(25)
P388 Lymphocytic leukemia	Nine daily injections	128(25)	0/6(100), 2/6(50), 6/6(25)

[a] Figures for tumors 1–5 are the weight differences of the treated animals compared with controls expressed as a percentage. A value of <20 for the first four tumors indicates activity; values of <42 in the case of the colon 38 tumor are considered active. The figures for tumors 6–9 are the ratios of the median survival time of treated animals compared with controls expressed as a percentage. A compound should increase the survival time by 25, 25, 40, and 20%, respectively, to be considered active. Doses in mg/kg are in parentheses. [b] At day 5; doses are in parentheses.

methyl-1-propanone Dihydrohalides (*IIa*, *IIIa–c,e,f*)—A mixture of the substituted acetophenone (0.05 mol), aqueous solutions of formaldehyde (37% w/v, 0.15 mol) and dimethylamine (25% w/v, 0.15 mol), and ethanol (25 mL) was heated under reflux for 3 h (IIa, IIIa,e), 24 h (IIIb,f), or 30 h (IIIc). The solvent was removed *in vacuo*, and the mixture was extracted with ether (3 × 20 mL). The combined ethereal extracts were washed with water, dried, and then the solvent was removed under reduced pressure to give the Mannich base, which was dissolved in acetone and treated with either hydrogen chloride or hydrogen bromide. The colorless solid which precipitated was removed by filtration, dried, and recrystallized from methanol to give the desired Mannich base salts.

3-Dimethylamino-2-dimethylaminomethyl-1-(4-hydroxyphenyl)-1-propanone Dihydrobromide (*IIId*)—A mixture of 4-hydroxyacetophenone (13.6 g, 0.1 mol), 2,3-dihydro-4*H*-pyran (10.4 g, 0.12 mol), an acidic ion-exchange resin[5] (1.5 g), and benzene (125 mL) was stirred vigorously at room temperature for 24 h. The reaction was monitored by following the disappearance of 4-hydroxyacetophenone (R_f 0.65) using TLC. After removal of the resin by filtration, the mixture was passed through a column of silica gel (60–200 mesh, benzene). The resultant yellow solution was washed with aqueous sodium hydroxide solution (10% w/v, 3 × 20 mL) and then with water (4 × 20 mL). After drying, the benzene was removed *in vacuo* to give a yellow solid, which was recrystallized from *n*-hexane to give 4-(2-tetrahydropyranyloxy)-acetophenone (15.6 g, 71%) as yellow crystals, mp 84–86°C [lit. (22) mp 89.5–91.0°C]; R_f 0.82; ^{1}H-NMR ($CDCl_3$): δ 7.82 (d, 2, ArH at C_2 and C_6), 7.00 (d, 2, ArH at C_3 and C_5), 5.45 (t, 1, tetrahydropyranyl H at C_2), 3.68 (m, 2, tetrahydropyranyl H at C_6), 2.54 (s, 3, CH_3), and 2.20–1.40 ppm (m, 6, tetrahydropyranyl H at C_3, C_4, and C_5).

A mixture of 4-(2-tetrahydropyranyloxy)-acetophenone (2.2 g, 0.01 mol), an aqueous solution of formaldehyde (37% w/v, 2.4 mL, 0.03 mol), dimethylamine (25% w/v, 4.5 mL, 0.025 mol), and ethanol (10 mL) was heated at reflux for 30 h. The ethanol was removed *in vacuo*, the mixture was extracted with ether (2 × 10 mL), and the combined organic extracts were washed with water (3 × 5 mL) and dried. After filtration, an additional quantity of anhydrous ether (10 mL) was added, and the solution was treated with hydrogen bromide to give a light-yellow solid, which was recrystallized from methanolic hydrogen bromide (1% w/v) and then from methanol to give IIId (1.4 g) as a bright-yellow solid. ^{1}H-NMR (D_2O): δ 8.04 (d, 2, ArH at C_2 and C_6), 7.04 (d, 2, ArH at C_3 and C_5), 4.04–3.20 [m, 5, $C_2H(CH_2)_2$], and 2.95 ppm [s, 12, $2N(CH_3)_2$]. The yield is based on the use of 4-(2-tetrahydropyranyloxy)-acetophenone as the starting material.

3-Dimethylamino-1-phenyl-2-(1-pyrrolidinylmethyl)-1-propanone Dihydrobromide (*IVa*)—A mixture of 3-dimethylamino-1-phenyl-1-propanone hydrochloride (5.35 g, 0.025 mol) (17), an aqueous solution of formaldehyde (37% w/v, 24 mL, 0.03 mol), pyrrolidine (2.5 mL, 0.03 mol), and ethanol (35 mL) was heated at reflux for 3 h. The solvent was removed *in vacuo*, and water (40 mL) followed by excess aqueous sodium hydroxide (40% w/v) were added to the crude mixture; the aqueous phase was then extracted with ether (50 mL). The organic extract was dried, and removal of the ether gave an oil, which was dissolved in acetone and treated with hydrogen bromide. The resultant crude dihydrobromide salt was recrystallized from ethanol to give IVa as colorless prisms (4.3 g). The yield was based on the use of 3-dimethylamino-1-phenyl-1-propanone hydrochloride as starting material.

3-Amino-2-aminomethyl-1-phenyl-1-propanone Dihydrobromides (*IVb–d*)—These compounds were prepared using the general procedure described for the synthesis of IIa, IIIa–c, e, and f *vide supra*. In the synthesis of IVb–d, the time of heating at reflux in ethanol was 24, 3, and 24 h, respectively.

3-Dimethylamino-2-dimethylaminomethyl-1-phenyl-1-propanone Dimethobromide (*IVe*)—3-Dimethylamino-2-dimethylaminomethyl-1-phenyl-1-propanone dihydrochloride was prepared as colorless crystals, mp 163–164°C [lit. (23) mp 164–165°C] in 20% yield by a reported procedure (10), except that hydrogen chloride was passed through a solution of the free base in acetone and not hydrogen bromide. An aqueous solution of the diamine dihydrochloride (5.8 g, 0.02 mol) was cooled to 5°C and rendered basic to litmus with triethylamine. The mixture was stirred with ice-cooling for 15 min and extracted with ether (3 × 15 mL). The combined organic extracts were washed with water (3 × 10 mL) and dried, and then the solvent was removed under reduced pressure to give a pale-yellow oil, which was dissolved in dry acetone and treated with excess methyl bromide. The solid was removed by filtration, washed with dry acetone, dried, and recrystallized from acetone–methanol to give IVe as a colorless solid (5.4 g).

3-Dimethylamino-1-aryl-1-propanone Hydrobromides (*V*)—The substituted 1-propanone hydrochlorides were prepared by a literature method (17) and then converted into the hydrobromide salts by a reported procedure (10). The crude hydrobromides were recrystallized from acetone–methanol (Va and c) or methanol (Vb). The percentage yields listed in Table II are based on syntheses from the appropriate substituted acetophenone and not from the crude hydrochloride.

3-Amino-1-phenyl-1-propanone Hydrobromides (*VIa–c*)—The appropriate 1-propanone hydrochlorides were prepared essentially by a literature method (17) using the required amine hydrochloride in place of dimethylamine hydrochloride. The times of heating the reactants at reflux were 2 h (VIa and c) and 3 h (VIb). The hydrobromides were obtained from the hydrochloride salts by a literature method (10) and purified by recrystallization from acetone–methanol. The percentage yields in Table II are based on the quantity of acetophenone used.

3-Dimethylamino-1-phenyl-1-propanone Methobromide (*VId*)—Aqueous sodium carbonate solution (10% w/v) was added to an aqueous solution of crude 3-dimethylamino-1-phenyl-1-propanone hydrochloride (17) (4.27 g, 0.02 mol) in water until basic to litmus, and the mixture was extracted with chloroform (4 × 15 mL). After the combined organic extracts were washed with water (3 × 5 mL) and dried, the chloroform was removed *in vacuo* to give a pale-yellow oil, which was dissolved in anhydrous ether (15 mL) and treated with methyl bromide (1.6 mL, 2.77 g, 0.029 mol). The solution was cooled to −4°C for 3 h, and the precipitate was removed by filtration, washed with dry ether, dried, and recrystallized from methanol–acetone (4:1) to give VId as colorless crystals. The yield recorded in Table II was based on the quantity of acetophenone used.

3,5-Bis(dimethylaminomethyl)-4-hydroxyacetophenone Dihydrobromide (*VII*)—A mixture of *p*-hydroxyacetophenone (6.8 g, 0.05 mol), an aqueous solution of formaldehyde (37% w/v, 8.9 mL, 0.11 mol), dimethylamine (5.0 g, 0.11 mol), and ethanol (50 mL) was heated at reflux for 20 h. After removal of the ethanol and water *in vacuo*, the resultant viscous oil was dissolved in acetone and treated with hydrogen bromide. The precipitate was removed by filtration, washed with acetone, dried, and recrystallized from methanol to give VII as colorless prisms (8.8 g). ^{1}H-NMR (D_2O): δ 8.00 (s, 2, ArH at C_2 and C_6), 4.45 (s, 4, 2 × CH_2N), 2.98 [s, 12, 2 × $N(CH_3)_2$], and 2.62 ppm (s, 3, $COCH_3$).

Biological Evaluations—*Screening of Compounds*—The antineoplastic evaluation of the compounds described herein was undertaken by the National Cancer Institute, Bethesda, Maryland, using their protocols (24). The compounds listed in Table II were injected by the intraperitoneal route into male or female Swiss, $B_6D_2F_1$, or CD_2F_1 mice. The derivatives were dissolved in saline prior to injection, except for IVe and VId which were administered in hydroxypropyl cellulose; VIb was injected in both saline and saline containing polysorbate 80[6]. Compounds IVc and VI had been previously assessed by the

[5] Amberlyst H-15; Rohm and Haas, Philadelphia, Pa.

[6] Tween 80; Atlas Chemical Industries.

National Cancer Institute, although not against P388 lymphocytic leukemia.

The data in Table IV was generated as follows. Compound IIa was dissolved in saline and administered to mice hosting tumors 1–3 by the subcutaneous route and intraperitoneally in the remaining cases. The xenografts (tumors 1–3) were inoculated into NU/NU athymic Swiss mice by subcutaneous injection. The activity recorded is the mean tumor weight change between day 0 and the final evaluation days which were 15, 11, and 11 d, respectively. The $CD8F_1$ mammary and colon 38 tumors in $CD8F_1$ and $B_6C_3F_1$ mice, respectively, were evaluated after 34 and 20 d. The activity noted for the $CD8F_1$ mammary tumor was the median tumor weight change, and for the colon 38 tumor, the median tumor weight was estimated from the diameter of the tumor. The B16 melanocarcinoma was injected intraperitoneally into $B_6C_3F_1$ mice and evaluated on day 60. Both L1210 and P388 leukemias were injected by the intraperitoneal route into CD_2F_1 mice and evaluated on day 30. The Lewis lung carcinoma was injected intravenously into $B_6C_3F_1$ mice and evaluated on day 60. The activity of the last four tumors is expressed as the effect on median survival time. The toxicity of IIa *versus* the nine tumors listed in Table IV was evaluated on days 15, 11, 11, 34, 20, 5, 5, 5, and 5, respectively.

Disposition Studies with IIa—Dosed male Wistar rats, weighing 220–250 g (first trial), 285–300 g (second trial), and 240–250 g (third trial) were injected with IIa dissolved in sterile saline (0.9% w/v) by the intraperitoneal route, while control animals received sterile saline (0.9% w/v). All animals were necropsied after sacrifice, and the following tissues were fixed in 10% buffered formalin: lung, heart, thymus, trachea, thyroid, liver, spleen, pancreas, kidney, adrenal, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, lymph nodes, bladder, and reproductive organs. Tissues were processed routinely, sectioned at 5 μm, and stained with hematoxylin and eosin.

REFERENCES

(1) J. R. Dimmock, C. B. Nyathi, and P. J. Smith, *J. Pharm. Sci.*, **67**, 1543 (1978).

(2) J. R. Dimmock, G. B. Baker, and R. G. Sutherland, *Can. J. Pharm. Sci.*, **10**, 53 (1975).

(3) J. R. Dimmock and W. G. Taylor, *J. Pharm. Sci.*, **64**, 241 (1975).

(4) F. A. Carey and R. J. Sundberg, "Advanced Organic Chemistry, Part B: Reactions and Synthesis," Plenum, New York, N.Y., 1977, pp. 44, 46.

(5) F. F. Blicke, in "Organic Reactions," Vol. 1, R. Adams, Ed., Wiley, New York, N.Y., 1942, p. 303.

(6) F. W. Menger and J. H. Smith, *J. Am. Chem. Soc.*, **91**, 4211 (1969).

(7) C. E. Lough, D. J. Currie, and H. L. Holmes, *Can. J. Chem.*, **46**, 771 (1968).

(8) P. N. Gordon, J. D. Johnston, and A. R. English in "Antimicrobial Agents and Chemotherapy," G. L. Hobby, Ed., American Society for Microbiology, Ann Arbor, Mich., 1965, p. 165.

(9) H. Schönenberger, T. Bastug, L. Bindl, A. Adam, D. Adam, A. Petter, and W. Zwez, *Pharm. Acta. Helv.*, **44**, 691 (1969).

(10) J. R. Dimmock, K. Shyam, N. W. Hamon, B. M. Logan, S. K. Raghavan, D. J. Harwood, and P. J. Smith, *J. Pharm. Sci.*, **72**, 887 (1983).

(11) M. Eden, B. Haines, and H. Kahler, *J. Natl. Cancer Inst.*, **16**, 541 (1955).

(12) H. Kahler and W. v B. Robertson, *J. Natl. Cancer Inst.*, **3**, 495 (1943).

(13) K. A. Meyer, E. M. Kammerling, L. Amtman, M. Koller, and S. J. Hoffman, *Cancer Res.*, **8**, 513 (1948).

(14) A. Albert and E. J. Serjeant, "Ionisation Constants of Acids and Bases," Methuen, London, 1962, pp. 140–141.

(15) A. Bongini, G. Cardillo, M. Orena, and S. Sandri, *Synthesis*, **1979**, 618.

(16) F. A. Carey and R. J. Sundberg, "Advanced Organic Chemistry, Part A: Structure and Mechanisms," Plenum, New York, N.Y., 1977, p. 145.

(17) C. E. Maxwell, *Org. Syn.*, **23**, 30 (1943).

(18) A. H. Land, C. Ziegler, and J. M. Sprague, *J. Am. Chem. Soc.*, **69**, 125 (1947).

(19) A. L. Williams and A. R. Day, *J. Am. Chem. Soc.*, **74**, 3875 (1952).

(20) O. R. Hansen and R. Hammer, *Acta. Chim. Scand.*, **7**, 1331 (1953).

(21) A. Goldin, S. A. Schepartz, J. M. Vendetti, and V. T. DeVita, Jr., "Methods in Cancer Research," Vol. XVI Part A, Academic, New York, N.Y., 1979, p. 165.

(22) J. H. Burkhalter, W. D. Dixon, M. L. Black, R. D. Westland, L. M. Werbel, H. A. DeWald, J. D. Rice, G. Rodney, and D. H. Kaump, *J. Med. Chem.*, **10**, 567 (1967).

(23) H. A. Albrecht, J. T. Plati, and W. Wenner, U.S. Pat. 3,058,987, Oct. 6, 1962; Chem. Abstr., **58**, 5644c (1963).

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

ACKNOWLEDGMENTS

The authors thank the Medical Research Council of Canada for the award of an operating grant (MA-5538) to J. R. Dimmock and the University of Saskatchewan for the award of a Graduate Scholarship to K. Shyam. Appreciation is recorded to the National Cancer Institute, Bethesda, Md., who undertook the antineoplastic evaluation of most of the compounds reported in this investigation.

Tack Behavior of Coating Solutions II

S. K. CHOPRA and R. TAWASHI ˣ

Received November 17, 1982, *from the Faculty of Pharmacy, University of Montreal, Case Postale 6128, Succursale "A", Montreal, Quebec, H3C 3J7 Canada.* Accepted for publication March 9, 1983.

Abstract □ The tackiness of coating solutions containing high concentrations of polymers was determined using a parallel plate technique. Kinematics of the film-splitting process was also investigated using a high-speed movie camera. The results showed that the impulse required to split a liquid film of highly concentrated polymer solution (semisolid), in contrast to a dilute solution is related not to viscosity, but to the internal structures of the system. Evidence has been found that the materials that are considered to be tacky in practice, display "delayed elastic effects" and require far larger impulses than nontacky materials.

Keyphrases □ Film-coating solutions—tablets, tack behavior, viscosity, concentrated polymer solutions □ Viscosity—film-coating solvents for tablets, tack behavior, concentrated polymer solutions □ Polymers—concentrated solutions, viscosity, tack behavior, film-coating of tablets

The technique of film-coating solid dosage forms has grown at an accelerating rate, employing a wide variety of materials and coating systems (1–3). One of the factors affecting the tablet-coating process is the tackiness of the coating formulations. The concentration of the film formers used in these coating formulations depends on the molecular weight, grade, and chemical structure of the polymers (4). Generally, the concentration of a polymer used in a film-coating formulation ranges from 2 to 10% (5). During the drying phase of the coating process, evaporation of the solvent occurs. Consequently, the concentration of the polymer increases, giving rise to increasing tackiness until the deposited film is essentially