

Viscosity of Xanthan Gum Solutions at Low Shear Rates

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Abstract □ The viscosity of xanthan gum solutions in the low shear region was investigated with the aid of a Couette instrument. All solutions were highly pseudoplastic. Solutions containing 0.3–0.5% of the gum exhibited a highly ordered phase at very low shear. Viscosity, the degree of pseudoplasticity, and the value of the transition from soft gel to pseudoplastic behavior were directly related to gum concentration. The effect of the addition of a salt on viscosity depended on the xanthan gum concentration. The viscosity of a 0.3% xanthan gum solution was practically unaffected by the salts. Higher gum concentrations exhibited a viscosity increase when salt was present. Concentrations <0.3% exhibited a viscosity decrease in the presence of a salt. All viscosity effects seemed to reach limiting values at $\sim 10^{-3}$ to 3.3×10^{-3} *N* salt. No major differences were observed between sodium chloride, calcium chloride, and sodium citrate in their influence on xanthan gum viscosity.

Keyphrases □ Viscosity—xanthan gum in aqueous solutions, low shear rates, effect of added salts □ Xanthan gum—aqueous solutions, viscosity at low shear rates, effect of added salts □ Shear rate—low range, viscosity of xanthan gum in aqueous solutions, effect of added salts

Xanthan gum, an extracellular polysaccharide of the bacterium *Xanthomonas campestris* which was originally isolated and characterized by Jeanes and coworkers (1), has a wide variety of uses in the pharmaceutical, cosmetic, oil, and food industries. The polymer is an efficient thickening agent whose aqueous solutions are shear thinning (2, 3).

Examination of the molecular structure of xanthan gum offers insight into the basis for much of the physicochemical behavior of the substance in solution. Xanthan gum is structurally very complex. As proposed by Jansson and coworkers (4), the backbone of the molecule is a cellulose chain composed of [$\beta(1\rightarrow4)$ -D-glucose]. Every second residue of the chain has a $\beta(1\rightarrow3)$ substituted trisaccharide side chain of the [β -D-mannopyranosyl - (1 \rightarrow 4)- α -D-glucopyranosyl-(1 \rightarrow 2)- β -D-mannopyranoside-6-*O*-acetate] variety. Further, pyruvic acid substitution on the terminal mannose residue of the side chain (to the degree of 25–50%) has been reported and probably plays a key role in the molecular properties of xanthan gum in solution (5). The proposed structure of xanthan gum also suggests that the substituted trisaccharide side chains may lie close to the cellulose backbone at room temperature in some ordered, rod-like conformation held together loosely by short range van der Waals forces (6). At elevated temperatures,

however, it has been shown, *via* NMR relaxation procedures and optical methods such as circular dichroism and optical rotation, that there is a temperature-induced rearrangement within the molecular structure of the gum (7). It has been suggested that “chain melting” occurs, and the ordered, rod-like helix may become more flexible at elevated temperatures, with the trisaccharide side chains extending outward from the cellulose backbone. This structural change may be responsible for a sudden drop in viscosity of a 1% aqueous xanthan gum solution at elevated temperature (7).

The addition of salt to a water solution of purified xanthan gum raises the temperature at which structural rearrangement takes place, as shown by optical rotation and viscosity measurements (8). Calcium chloride was effective in much lower concentrations than sodium chloride, suggesting that stabilization of the helical, rod-like conformation was due to reduction in charge repulsion between the backbone and the side chains (8). The response of xanthan gum to variations of ionic strength is unlike that of most other polyelectrolytes. Normally, polyelectrolytes exhibit an expanded structure under conditions of low ionic strength as the result of neighboring group electrostatic charge repulsion. The addition of a salt results in a screening of the neighboring group repulsive forces and causes the molecule to collapse into a compact coil. Studies of the effects of salts on xanthan gum viscosity have produced somewhat contradictory results. In one case, the viscosity of a dilute xanthan gum solution was increased in the presence of sodium chloride (3). Another report shows a moderate decrease in viscosity under similar conditions (9), although the extent of viscosity reduction was not as pronounced as for typical polyelectrolytes. Symes (10) showed that the effect of 0.1 M KCl on xanthan gum solution viscosity depended on the gum concentration. At gum concentrations <0.25%, viscosity of aqueous solutions without added salt were higher than those containing potassium chloride. The reverse was true for solu-

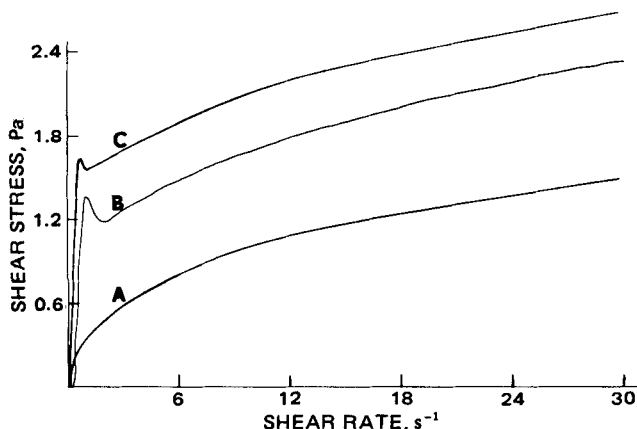


Figure 1—Shear stress versus shear rate for three aqueous xanthan gum solutions with a scan time of 4 min. Key: (A) 0.133%; (B) 0.3%; (C) 0.5%.

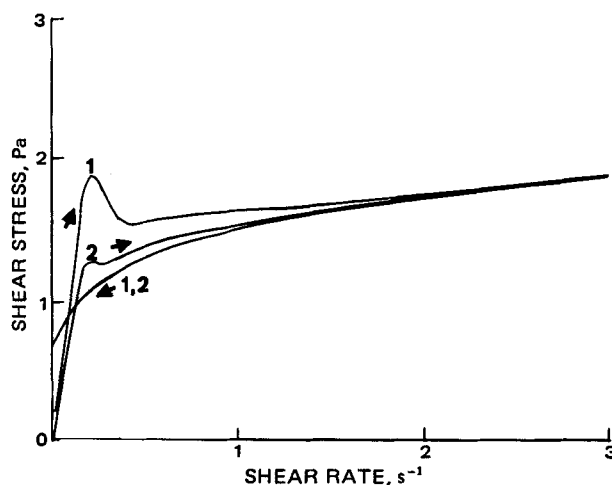


Figure 2—Shear stress versus shear rate for a 0.5% aqueous xanthan gum solution. Scan time for a complete cycle was 8 min. Numbers indicate the order of execution of the shearing cycles, and arrows indicate the direction of shear rate change.

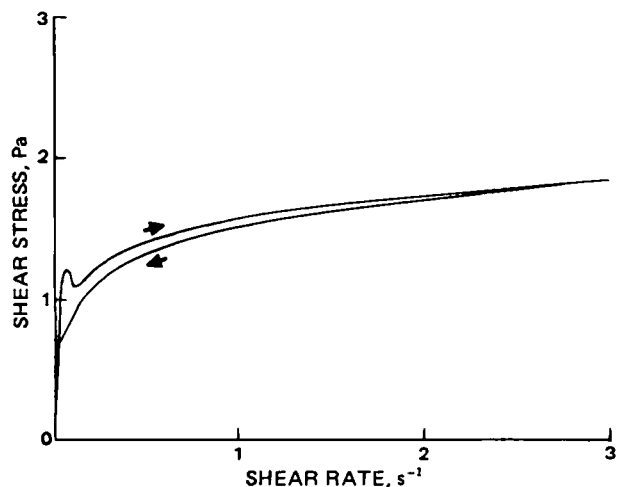


Figure 3—Shear stress versus shear rate for a 0.5% aqueous xanthan gum solution. Scan time for the complete cycle was 2 h. Arrows indicate the direction of shear rate change.

tions containing >0.25% xanthan gum. The relative stability of viscosity of xanthan gum solutions to ionic strength, temperature, and pH variation (11) has been ascribed to the rod-like shape of the molecule and the importance of hydrogen bonding in intermolecular interaction (12).

In considering the application of xanthan gum as a suspending agent and emulsion stabilizer, viscosity characteristics in the very low shear region are of great importance. The only previous investigation in which very low shear viscosity was studied (2, 3) utilized a purified xanthan gum preparation. In the present study, a new instrument based on the Couette principle and capable of measurements at very low shear was utilized to investigate the rheological behavior of solutions prepared from commercial food-grade xanthan gum. The influence of several salts on solutions containing various xanthan gum concentrations was also studied.

EXPERIMENTAL

Xanthan gum¹ was utilized as received. All salts and preservatives were reagent or USP grade. Deionized water was used in the preparation of solutions.

Xanthan gum solutions (2%) containing 0.1% methylparaben and 0.03% propylparaben served as a stock preparation of the gum. Desired electrolyte

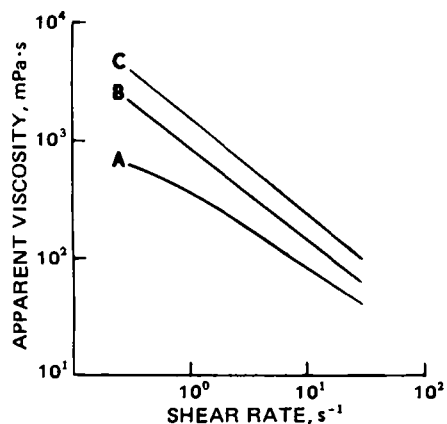


Figure 4—Logarithm of apparent viscosity as a function of the logarithm of shear rate for xanthan gum solutions. Key: (A) 0.133%; (B) 0.3%; (C) 0.5%.

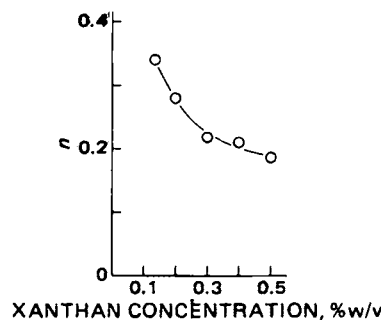


Figure 5—Power law constant, n , as a function of xanthan gum concentration in aqueous solution.

concentrations were obtained by dilution of 0.1 N stock solutions containing the parabens. Dilutions were made with deionized water containing methyl- and propylparabens. The diluted solutions were mixed using a low-torque mixer until they were homogeneous. Several samples were taken at various locations in the solution and examined rheologically to assure homogeneity of the mixed solutions. It was found that a 2-min mixing time, even at the highest concentration of xanthan gum used, was sufficient to ensure solution homogeneity.

Rheological measurements were made with a commercial instrument² that utilizes the Couette principle, with an air bearing to maintain the position of an inner cylinder while the outer cylinder rotates. The torque on the inner cylinder is measured. Both shear rate and shear stress are determined with high precision and plotted automatically as a flow curve (shear stress versus shear rate) while the properties of the sample are explored. Sensitivity and scaling factors are adjustable to cover a wide range of shear rates and material characteristics. Sample properties can be measured by increasing shear rate, decreasing shear rate, or cycling back and forth, and the time period during which these measurements are made may be selected from within a wide range.

RESULTS AND DISCUSSION

Flow curves for aqueous solutions containing three xanthan gum concentrations are presented in Fig. 1. To obtain these curves the instrument was set so that scanning of the shear rates covered ($0-30 \text{ s}^{-1}$) took 4 min. The curve for 0.133% xanthan gum solution exhibited continuous curvature with no evidence of a yield point or discontinuity. The pseudoplastic behavior of the solution is evident. At 0.3% xanthan gum the flow curve rises steeply at first, reaches a peak, drops sharply, and then rises smoothly again. The abrupt change in slope signals a different type of behavior than that observed at lower concentrations. At shear values beyond the discontinuity, the 0.3% solution exhibits typical pseudoplastic behavior. Shear stress values for the 0.5% xanthan gum solution fall above that of the 0.3% solution, indicating that the apparent viscosity is higher at all values of shear rate. However, the flow curves for the 0.3 and 0.5% solutions are qualitatively similar.

The effect of changing the direction of shear rate change and of a second shearing cycle on the flow curve of a 0.5% xanthan gum solution are shown in Fig. 2. A complete shear cycle consists of having the shear rate increase from zero to a preset value (in this case, 3 s^{-1}) and then decrease again to zero. Arrows in Fig. 2 indicate whether a curve was generated from left to right (increasing shear rate) or right to left (decreasing shear rate). The instrument was programmed so that each complete cycle was executed during 8 min. A 1-min rest period separated the onset of the second shearing cycle (cycle 2 in Fig. 2) from completion of the initial cycle (cycle 1). The initial scan (cycle 1 going from 0 to 3 s^{-1}) was not retraced by the return curve (cycle 1 from 3 to 0 s^{-1}). Also, when the sample was sheared a second time (cycle 2) only the return curve coincided with that from the first shearing cycle. The curve generated by increasing the shear rate during cycle 2 fell between that of the initial trace in the same direction and the return curves, although closer to the latter. The behavior of 0.3% xanthan gum solutions was similar to that of the 0.5% solution, but the difference in magnitude between the various curves was smaller.

Several conclusions may be drawn from the data in Fig. 2 and similar data for 0.3% solutions:

1. Initial disturbance of a sample encounters high resistance. This is shown by the high slope found in the flow curve when shear is first applied.

2. A transition in behavior is found when the shear rate is increased to slightly higher values (but the shear rate at which this transition occurs is still quite small).

¹ KELTROL; Kelco, Div. Merck and Co., Inc., San Diego, Calif.

² Haake RV 100/CV 100; Haake, Saddle Brook, N.J.

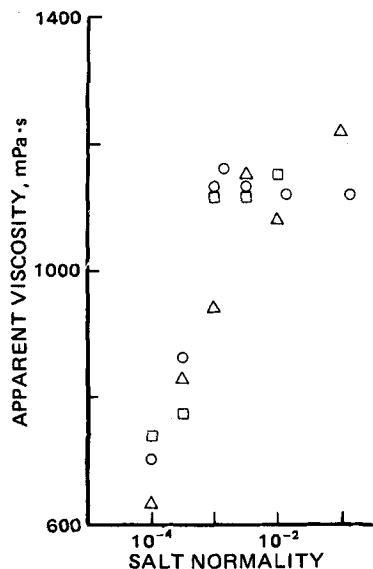


Figure 6—Effect of various salts on the apparent viscosity of 0.5% solutions of xanthan gum at a shear rate of 3.0 s^{-1} . Key: (O) calcium chloride; (Δ) sodium chloride; (\square) sodium citrate.

3. Viscosity in the low shear region is dependent on the recent history of the sample. In other words, some thixotropy is evident.

Figure 3 shows results for a single shearing cycle of a 0.5% xanthan gum solution in which the low shear rates were scanned at a rate equal to 1/15 that used in the previous experiments. Comparison of the curve in Fig. 3 arising from increasing the shear rate with that of the corresponding curve for cycle 1 in Fig. 2 shows that although there are some differences in magnitude in the very low shear rate area, the same general pattern is found. After a sharp increase in shear stress, the curve in Fig. 3 peaks, drops, and then follows the pattern of a pseudoplastic material as the shear rate rises. The return curve ($3 \text{ to } 0 \text{ s}^{-1}$) in Fig. 3 does not coincide with the initial tracing. In fact it is identical to the return curves obtained at the faster scan rate (Fig. 2).

Using the same scan rate as for the work in Fig. 3, the discontinuity in the flow curve of a 0.4% xanthan gum solution was still quite marked. With a 0.3% solution it was not so sharp, but still discernable. Reducing the rate of change of the shear rate increased the extent to which the structural architecture could adjust in response to changing shear conditions. Although the difference in magnitude between the two curves that comprise a complete shear cycle was reduced at the slower scan rate, the existence of a structural change at very low shear was still evident.

The viscosity behavior of xanthan gum solutions must be described in terms of intermolecular networks formed by the extremely long, rigid, highly asymmetric polymer molecules (10). At concentrations of 0.3–0.5% (in aqueous solution), network formation results in a system that may be described as a “soft gel” which persists as long as the system is not disturbed. At extremely low shear stress, particles of gel are the unit of flow, and the resistance

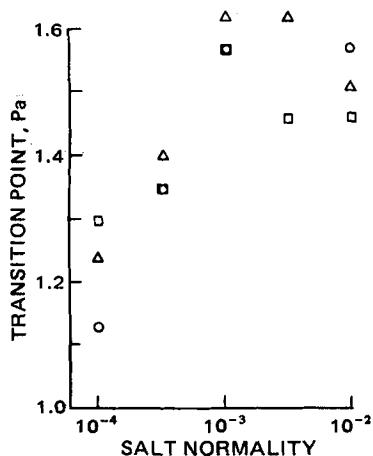


Figure 7—Effect of various salts on the gel transition point of 0.5% solutions of xanthan gum. Key: (O) calcium chloride; (Δ) sodium chloride; (\square) sodium citrate.

Table I—Effect of Salts on the Apparent Viscosity of Xanthan Gum Solutions at a Shear Rate of 3.0 s^{-1}

Xanthan Gum Concentration, % w/v	Apparent Viscosity, mPa·s					
	No Added Salt	10^{-4} M NaCl	10^{-3} M NaCl	10^{-2} M NaCl	10^{-3} M CaCl_2	10^{-2} M CaCl_2
0.133	186	—	—	80	83	76
0.2	340	265	210	220	—	—
0.3	414	460	430	450	415	410
0.4	580	670	670	740	—	—
0.5	620	630	940	1080	1160	1120

to deformation is very high. After the transition point, structure within the gel particles is affected. Partial breakdown of intermolecular linkages and spatial rearrangement of the polymer molecules accounts for the pseudoplastic behavior at shear rates higher than that at which the transition occurs. From the breaks in the consistency curves, the transition shear stress was estimated to be 1.1 Pa for the 0.5% solution, 0.9 Pa for the 0.4% solution, and 0.4 Pa for the 0.3% solution.

At xanthan gum concentrations $>0.5\%$, gel strength would be expected to increase. A yield value was reported for a 1% xanthan gum solution, but not for lower concentrations (2, 3). At concentrations $< \sim 0.3\%$, measurements in our laboratory failed to show a definite gel-like region and then a transition to a less-ordered state.

Apparent viscosity (shear stress/shear rate) was calculated for the xanthan gum solutions from first cycle flow curves using fresh solutions. Flow curves in which the maximum shear rate scanned was 3.0 s^{-1} were used to calculate apparent viscosity for shear rates ranging from 0.3 to 3.0 s^{-1} . All values calculated were for shear rates higher than those at which the transition from a gel state took place. Apparent viscosity for shear rates from 3.0 to 30 s^{-1} were obtained from flow curves for which the maximum shear rate setting was 30 s^{-1} . The logarithm of apparent viscosity is plotted as a function of the logarithm of shear rate in Fig. 4. These plots are linear for the 0.3 and 0.5% xanthan gum solutions; the 0.133% solution also exhibits a linear relationship except for the lowest shear rate values. The curves in Fig. 4, which follow the same general pattern as plots shown previously for other xanthan gum concentrations (2), indicate that the power law equation is applicable:

$$\eta = KD^{(n-1)}$$

where η is apparent viscosity, D is shear rate, K is the viscosity at 1 s^{-1} , and n is a constant that indicates the degree of pseudoplasticity. The minimum possible value of n , corresponding to the highest degree of pseudoplasticity, is zero (13). Values of n , calculated from the linear portion of log viscosity-log shear rate relations, are plotted as a function of xanthan gum concentration in Fig. 5. From Figs. 4 and 5, it is evident that an increase in xanthan gum concentration results in an increase in both viscosity and the degree of pseudoplasticity.

The addition of various salts to a 0.5% xanthan gum solution brought about an increase in apparent viscosity. Results for one shear rate, 3.0 s^{-1} , are shown in Fig. 6. Similar relationships were found by making comparisons at other shear rate values. The increase in viscosity reached a limiting value with increasing salt concentration, which was about the same for the three salts studied. Furthermore, the three salts appeared to be nearly equally effective. A concentration of 10^{-3} N CaCl_2 or NaCl brought viscosity to the plateau level. Sodium citrate required a concentration of $3.3 \times 10^{-3} \text{ N}$ to reach the same viscosity.

These salts also increased the magnitude of the shear stress at which the low shear transition from a gel state took place (Fig. 7). Transition points were estimated from the low shear range flow curves obtained under the same conditions as those shown in Fig. 3. The error in reading the transition points from the graphs was $\sim 0.1 \text{ Pa}$. The addition of a salt increases the magnitude of shear stress at which the transition from a gel occurs, and, as with the effect on viscosity, the transition shear stress reaches a limiting value with increasing salt concentration. All salts appear to be equally effective, reaching maximal shear stress at a concentration of 10^{-3} N .

Although the most extensive salt studies were performed on 0.5% xanthan gum solutions, some data were obtained with lower gum concentrations (Table I). The dependence of apparent viscosity on salt concentration varied with the xanthan gum concentrations. In a 0.5% xanthan gum solution, the addition of a salt nearly doubled the viscosity. The viscosity of a 0.4% xanthan gum solution was also increased by salt, but to a smaller extent. The viscosity of a 0.3% xanthan gum solution was hardly affected by salt, while solutions containing $\leq 0.2\%$ of the gum showed a decrease in viscosity. The decrease in viscosity was more pronounced at the lower xanthan gum concentration (0.133%). Sodium chloride and calcium chloride seemed to have equal effect on viscosity at all xanthan gum concentrations, suggesting that reduction of

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 product³. Divalent cations, principally calcium and magnesium, make up ~0.15–0.35% by weight of the commercial polymer³. 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 $3.3 \times 10^{-3} N$ 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.

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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

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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