ulated at 6/min and the other at 60/min) provides a means for distinguishing pre- and postsynaptic activities. Contractions elicited at the lower rate are blocked preferentially by compounds that act postsynaptically, while contractions elicited at the higher rate are blocked preferentially by compounds that act presynaptically.]

2. The neuromuscular block was antagonized partially or completely by calcium chloride administration.

3. The cumulative neuromuscular blocking effect of polymyxin also was antagonized by calcium chloride administration.

This presynaptic action may involve diminution of the calcium-ion function in the nerve terminal, occasioning a decrease in the mobilization and release of acetylcholine, or it may involve occupation of the superficial neuronal membrane sites by the antibiotics resulting in decreased transmitter release, and these actions could be antagonized by calcium administration.

The characteristics of the neuromuscular block of polymyxin and colistin resembled those of magnesium in its direct effect on muscle fibers, posttetanic response potentiation, and less strikingly, calcium antagonism of the block.

It is concluded that the neuromuscular block of polymyxin B sulfate and colistin results predominantly from their postsynaptic, nondepolarizing action, which is noncompetitive, but also from their action to depress the direct excitability of the muscle fibers and from a presynaptic action resulting in reduced transmitter release. The neuromuscular blocking action does not involve the chelation of calcium ions, since polymyxin in paralyzing doses did not alter significantly the serum calcium-ion level.

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Influence of High-Viscosity Vehicles on Miotic Effect of Pilocarpine

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Received October 31, 1977, from the *Biopharmaceutics Group and Pharmacology Group, Department of Ophthalmology, Alcon Laboratories, Fort Worth, TX 76101.* Accepted for publication January 12, 1978.

Abstract □ Gel formulations containing 2% pilocarpine hydrochloride were prepared from ethylene maleic anhydride, carbomer, hydroxyethylcellulose, polyacrylamide, ethylhydroxyethylcellulose, hydroxypropylcellulose, and poly(methylvinyl ether–maleic anhydride). The viscosity characteristics of each formulation were evaluated from rheograms developed at 37° using a cone and plate viscometer. Single-point viscosities were determined at room temperature using a single-point rotational viscometer. Plastic viscosity parameters correlated to miosis durations in the rabbit following ophthalmic dosing of 50 μl. Carbomer formulations varying in concentration between 0.9 and 5.0% (w/w) showed a discontinuous relationship when either yield value or plastic viscosity was plotted against miosis durations. At carbomer concentrations above 3%, miosis durations increased 1.5-fold. Above and below this range, plastic parameters did not correlate to miosis duration. It was reasoned that the increased duration was a consequence of the gel's increased yield value such that appreciable *in vivo* thinning of the gel does not take place with eyelid and/or eyeball movements. As a result, the residence time of the drug in the eye would be expected to increase, thus promoting an increased duration.

Keyphrases □ Pilocarpine—miotic effect, influence of various high-viscosity vehicles in rabbits □ Vehicles, high viscosity—influence on miotic effect of pilocarpine in rabbits □ Viscosity, high—in various vehicles, influence on miotic effect of pilocarpine in rabbits □ Miotic effect—of pilocarpine, influence of various high-viscosity vehicles in rabbits □ Ophthalmic cholinergics—pilocarpine, miotic effect, influence of various high-viscosity vehicles in rabbits

Polymers have been added to aqueous solutions of ophthalmic drugs to lengthen the contact time of the drug with the eye. This method is based on the assumption that drug absorption and, hence, duration can be improved.

The use of viscous solutions to prolong the effect of pilocarpine has shown that, in rabbits, large decreases in the drainage rate can be obtained when the viscosity is increased from 1 to 12–15 cps (1). Above this level, however, further increases in viscosity do not appreciably decrease drainage rates. When compared to an aqueous solution of pilocarpine nitrate, the testing of viscous solutions (100 cps) indicated that there is a twofold increase in drug aqueous humor concentration with a 100-fold increase in viscosity at 30 min following dosing to rabbits (2). It was hypothesized that the shear created by blinking resulted in thinning such that a large increase in instilled solution viscosity would not appreciably improve contact time and, therefore, bioavailability (2). For solutions, the approach to increasing bioavailability by increasing the vehicle viscosity is limited.

This study was conducted to determine if high-viscosity polymer systems could overcome the suspected thinning that occurs because of eye movements and/or blinking of the eyelids and prolong pilocarpine effects in the rabbits. Carbomer gel systems were primarily chosen for study because of the possibility of formulating a wide variation of high viscosities.

EXPERIMENTAL

Carbomer Gel Preparation—A series of carbomer[1] gels was pre-

[1] Carbopol 940, B.F. Goodrich.

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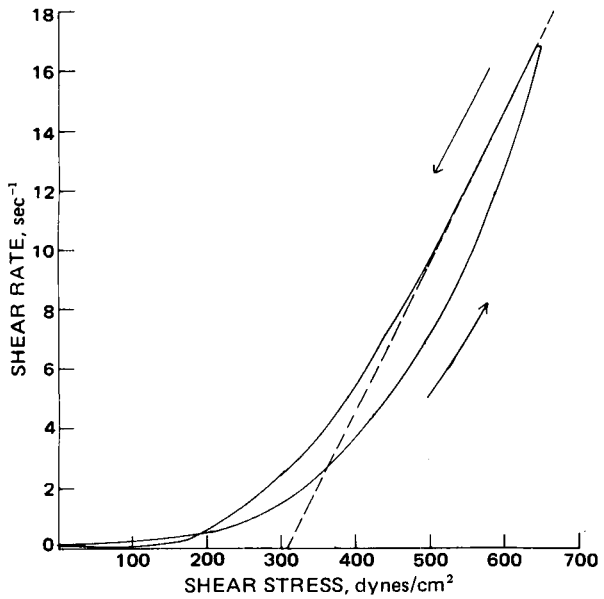

Figure 1—*Rheogram of a 5% carbomer preparation generated at 37°. The arrows indicate the upward and downward curves. When multiplied by the appropriate constants, the intersection of the dashed line with the abscissa represents the plastic yield value, whereas the slope of the line represents the plastic viscosity.*

pared. Each gel contained 2% pilocarpine hydrochloride[2], 0.01% benzalkonium chloride[2], 0.01% edetate disodium[2], 2% mannitol[2], purified water, and sufficient sodium hydroxide[2] to maintain a pH of 5.9–6.2. For gel preparations containing 0.9–2.0% carbomer, the addition of 2% pilocarpine hydrochloride produced a flocculated gel. However, within 24 hr, each mixture formed a cloudy gel. Sodium hydroxide (3 *N*) was added dropwise and stirred into the gel after each addition. As the pH rose above 5 and approached 6, the gels became rigid and clear. Gel preparations containing 2.35–5.0% carbomer did not flocculate upon the addition of pilocarpine hydrochloride. These gels became rigid and clear at lower pH values than those previously described.

Preparation of Other Gels—Ethylene maleic anhydride[3], hydroxyethylcellulose[4], polyacrylamide[5], ethylhydroxyethylcellulose[6], hydroxypropylcellulose[7], and poly(methylvinyl ether–maleic anhydride)[8] were used to prepare gels. Each polymer was hydrated according to the procedure specified in each manufacturer's technical bulletin. A stiff gel was prepared with ethylene maleic anhydride and poly(methylvinyl ether–maleic anhydride) by the addition of 2.3 and 1.6% (w/w) strong ammonia solution[9], respectively. Stiff gels were formed without the addition of base to the other hydrated polymers; however, 3 *N* NaOH was added dropwise to adjust the pH to 5.2.

Two percent pilocarpine hydrochloride, 0.01% benzalkonium chloride, and 2% mannitol were first dissolved in about 10% of the water solution of each formulation and thoroughly incorporated into each gel. The final pH of all formulations ranged between 5.1 and 5.3. Viscosity readings were obtained in 2 days or more following preparation of each gel.

Petrolatum Preparation—A petrolatum ointment was prepared by levigating 2% pilocarpine hydrochloride with 6% mineral oil to produce a viscous but fluid mixture. The homogeneous mixture was then incorporated into petrolatum[10] USP by the method of geometric dilution.

Viscosity Measurements—A cone and plate viscometer[11], equipped with an *x–y* recorder[12] and a constant-temperature water bath[13], was used to generate rheograms at 35° in triplicate for ethylene maleic anhydride and carbomer formulations. The operating conditions were: 60-sec sweep, medium cone, B switch position, and a 2–5× scale reading. Viscosity measurements were made by applying a sufficient quantity of gel from the same syringes as were used to dose rabbits. The cone was brought in contact with the plate and was held stationary for 3–4 min to allow the gel to reach 35°. Standard operating procedures were followed[14].

Single-point viscosity measurements[15] also were made on each gel formulation. Although temperature was not controlled using this instrument, it ranged between 20 and 24°.

Miosis Measurements—New Zealand albino rabbits of either sex, free of gross ocular defects and weighing 1.8–2.5 kg, were positioned into restraining boxes and placed in a room with controlled rheostat lighting. A standard light intensity of 90–110 foot-candles was measured at the position of the rabbits' eyes. All rabbits were acclimated to the laboratory testing conditions for 30 min prior to initiating the study.

Two baseline pupillary diameters were measured to the nearest 0.1 mm with a micrometer[16] held at a fixed distance from each rabbit. All measurements were taken by the same individual. Rabbits were screened for a range in pupillary diameter of 4.0–5.2 mm; all others were excluded from the study.

Fifty microliters[17] of gel was dosed from a 1.0-ml tuberculin syringe. The filled syringes were centrifuged prior to dosing to remove trapped air. The eyelashes of test animals were trimmed to facilitate instillation of the test compounds. In dosing gel preparations, the right lower eyelid was pulled away from the globe and the dose or extruded ribbon was placed lengthwise along the lower portion of the conjunctival sac. The eyelid was immediately returned to its normal position.

Each treatment group consisted of five or six rabbits; no animal was used more than one time. Pupillary measurements were made on the treated eyes every 15 min for 1 hr and then every 30 min until the pupillary diameter returned to ±0.1 mm of the averaged baseline values for each individual rabbit for two successive readings.

The duration of response is defined as the point in time when the pupillary diameter first returned to baseline values. The duration associated with each rabbit was determined, and the results from the treatment group were expressed as an average ±*SD*. No more than two formulations were tested on a given day; however, a control gel formulation was used throughout the studies.

RESULTS

A rheogram, typical for either ethylene maleic anhydride or carbomer preparations, is depicted in Fig. 1. The flow curve for carbomer and ethylene maleic anhydride formulations produced a hysteresis loop in which the plastic downcurve was displaced to the left by a pseudoplastic upcurve. For this study, the limiting linear slope of the downcurve was used to calculate plastic viscosity; a yield value was obtained by extrapolating the linear portion of the downcurve to the shear stress axis. These two parameters, plastic viscosity and yield value, were used for correlation purposes and are listed in Table I along with the single-point viscosity determinations measured on each formulation.

Of the polymer materials tested, only carbomer and ethylene maleic anhydride produced rheograms in which a significant portion of the downcurve was linear, *i.e.*, plastic viscosity. The petrolatum preparation also exhibited plastic viscosity characteristics. Gels made from the other polymer materials produced a pseudoplastic upcurve as well as a hysteresis loop. However, the downcurve was mostly pseudoplastic in nature; a linear portion was not distinct.

Table I lists the viscosities obtained for each preparation. As the percent of carbomer in the preparation increased, the single-point viscosities also increased.

Averaged miosis intensity results in Fig. 2 show a comparison of the 3% carbomer gel formulation, a petrolatum formulation, and an aqueous solution of pilocarpine hydrochloride containing hydroxypropyl methylcellulose[18]. The peak response was lower for the carbomer gel in comparison to the viscous solution or the petrolatum preparation. The time to peak of each preparation was within 30 min of one another; however, the duration associated with the carbomer gel preparation was twice that of the viscous solution and 1.75 times greater than that of the petrolatum preparation.

[2] USP grade.
[3] EMA-91, 3.4 and 5% (w/w), Monsanto Co., St. Louis, Mo.
[4] Natrosol 250G, 12% (w/w), Hercules Inc., Wilmington, Del.
[5] Cyanamer P-250, 9% (w/w), American Cyanamid Co., Wayne, N.J.
[6] Ethulose E1200, 5% (w/w), Chemaster Corp., Long Island City, N.Y.
[7] Klucel HF, 5.5% (w/w), Hercules Inc., Wilmington, Del.
[8] Gantrez AN 179, 10% (w/w), GAF Corp., New York, N.Y.
[9] NF, reagent grade, Mallinckrodt, St. Louis, Mo.
[10] Alcon lot RPA 3658.
[11] Ferranti-Shirley viscometer, Ferranti, Ltd., Manchester, England.
[12] Model HR-92, Houston Instrument Co., Bellaire, Tex.
[13] Haake type K41.
[14] Operating handbook, Ferranti-Shirley viscometer system, Ferranti Bulletin No. B/12587-113.
[15] Spindle No. 7, 20 rpm, Brookfield RVT Synchro-Lectric viscometer, Brookfield Engineering Laboratories, Stoughton, Mass.
[16] Starrett.
[17] Fifty microliters was chosen as a dosing volume because it approximates the length of ribbon commonly used for semisolids.
[18] Isopto Carpine 2%, Alcon lot WBBC.

Table I—Viscosity and Corresponding Rabbit[a] Miosis Durations Obtained for Each Gel Formulation

Polymer and Concentration, % w/w	Plastic Viscosities[b], cps	Yield Value, dynes/cm²	Brookfield RV1[c] Viscosities, cps	Mean Miosis Duration, hr	Area under Response Curve
Carbomer					
0.9	100[d] (22)[e]	2,964 (379)	23,800	6.45 (0.53)	1.35 (0.27)
1.25	207 (21)	3,835 (696)	40,000	6.86 (0.93)	1.45 (0.30)
1.65	270 (31)	6,483 (440)	70,000	5.72 (0.58)	0.927 (0.328)
2.0	359 (21)	7,714 (403)	80,000	5.27 (0.32)	0.899 (0.061)
2.35	369 (63)	8,215 (667)	101,000	6.24 (0.71)	1.18 (0.23)
2.70	421 (50)	9,862 (303)	107,000	5.52 (0.94)	0.979 (0.21)
3.00	603 (24)	11,188 (460)	115,000	8.20 (1.1)	1.58 (0.40)
3.50	490 (59)	10,263 (587)	—	8.43 (1.06)	1.74 (0.33)
4.0	613 (59)	12,318 (453)	118,000	10.09 (1.19)	2.53 (0.47)
4.5	695 (88)	12,685 (686)	118,000	8.11 (0.84)	2.01 (0.279)
5.0	786 (73)	14,227 (838)	129,000	8.84 (1.08)	2.03 (0.20)
Ethylene maleic anhydride					
3.4	384	7,078	123,000	8.50 (0.57)	1.93 (0.30)
5.0	558	11,046	109,000	10.70 (1.58)	2.35 (0.69)
Hydroxyethylcellulose, 12	—	—	171,000	4.93 (0.34)	1.05 (0.16)
Polyacrylamide, 9	—	—	184,000	6.18 (0.87)	1.39 (0.18)
Ethylhydroxyethylcellulose, 5	—	—	92,000	4.55 (0.59)	0.885 (0.216)
Hydroxypropylcellulose, 5.5	—	—	193,000	4.66 (0.31)	0.963 (0.043)
Poly(methylvinyl ether-maleic anhydride), 10	—	—	80,000	5.33 (0.87)	1.021 (0.189)
Petrolatum	—	—	25,000	4.70 (0.71)	1.06 (0.15)

[a] Mean values are averages of six to 10 rabbits. [b] Values were determined from rheograms using a Ferranti-Shirley viscometer at 35°. [c] Single-point determinations were made using a No. 7 spindle at 20 rpm and 20–24°. [d] Mean values are averages of three determinations. [e] Values in parenthesis represent 1 *SD*.

It has been hypothesized that the longer durations achieved with either the carbomer or ethylene maleic anhydride gels can be attributed in part to the gel's longer retention in the conjunctival sac of the rabbit eye. Eye retention of the gel was approximately 4–6 hr. The gradual decline in miosis shown in Fig. 2 is consistent with this finding. The intensity curve associated with carbomer following 6 hr began to decline at a slope approximately parallel to the decline associated with either petrolatum or the viscous solution between 1 and 4 hr. This result indicates that the corneal absorptive phase was over by 6 hr. As observed in Fig. 2, the miosis intensities representing the 3.4% ethylene maleic anhydride preparation nearly identically followed the 3% carbomer preparation; the 5% ethylene maleic anhydride preparation paralleled the 3% carbomer formulation but at values about 10–20% higher.

The longer retention time is considered to be a consequence of the plastic viscosity characteristics of carbomer or ethylene maleic anhydride. Figure 3, which represents the data generated for carbomer preparations, shows that a correlation is apparent when miosis durations are plotted against yield values. Although the relationship did not increase linearly, it was statistically significant [$r = 0.654$, $p < 0.05$ (3)]. When a correlation was tested between plastic viscosity or single-point rotational viscosity and miosis durations, similar results were found.

Figure 3 suggests a discontinuous type of relationship; that is, at a certain point on the abscissa, miosis durations significantly increase. For the yield value data, discontinuity occurred between 9862 and 11,188 dynes/cm² (Table I). An ANOVA was performed on the data as outlined by Hays (4). When all 11 groups were tested for a difference between mean miosis durations, a highly significant result was obtained ($F = 2.63$, $p < 0.01$). The treatment groups were then divided into two distinct groups, those below the discontinuity point (0.9–2.7% carbomer) and those above it (3.0–5.0% carbomer). The miosis duration differences were highly significant ($F = 7.08$, $p < 0.01$). However, statistical differences not related to viscosity also were found within each group (for 0.9–2.7% carbomer, $F = 3.82$; $p < 0.05$; for 3.0–5.0% carbomer, $F = 5.25$, $p < 0.01$). The treatment effect within each group, independent of yield value, could have been due to the relatively small numbers of rabbits used in each treatment group. In addition, as the yield value increased, the plastic viscosity or the single-point rotational viscosity increased linearly (Pearson $r = 0.982$ or 0.970, respectively).

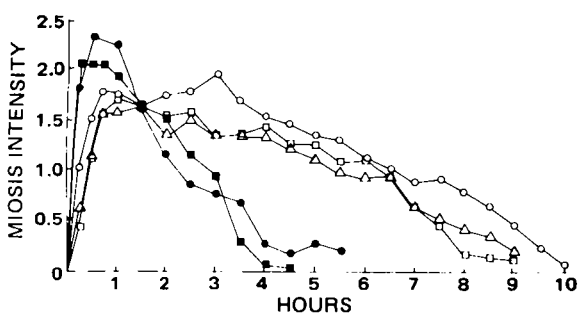

Figure 2—*Averaged (n = 5 or 6) durations of various ophthalmic preparations containing 2% pilocarpine hydrochloride. Each rabbit was dosed topically with 50 µl. The miosis intensity, in millimeters, represents a difference in pupil diameters of time zero and time t. Key: O and □, 5 and 4% ethylene maleic anhydride, respectively; Δ, 3% carbomer; ●, petrolatum; and ■, 2% hydroxypropyl methylcellulose.*

DISCUSSION

Plastic flow occurs as a result of overcoming the weak attraction between dispersed polymer molecules held together by secondary valence forces (5). Below the yield value, the shearing stress produced in a rotational viscometer is not sufficient to bring about flow. But once the shearing stress exceeds that of the yield value, expressed in dynes per square centimeter, the secondary valence forces are no longer capable of holding the molecules in position and the shearing rate increases.

If eye movements or blinking can create a shearing force on viscous formulations when placed in the conjunctival sac, then appreciable thinning should occur once a particular shearing force is reached. Although carbomer and ethylene maleic anhydride could be used to for-

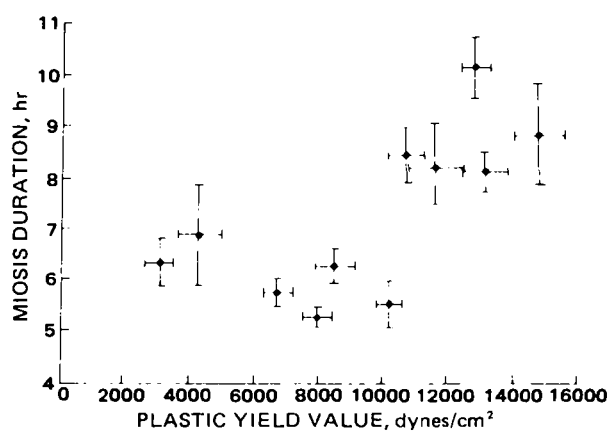

Figure 3—*Effect of plastic yield value (37°, n = 3) on the miosis duration of rabbits (n = 5 or 6) following ophthalmic dosing of 50 µl of carbomer gel preparations containing 2% pilocarpine hydrochloride. Each preparation varied in viscosity as a result of changes in carbomer concentration (0.9–5.0%; see Table I).*

mulate highly viscous, well-retained gels, other highly viscous polymer sols or gels were poorly retained in the rabbit eye and did not produce extended miosis duration. The carbomer data suggest that the increased duration was a result of the increased viscosity of the gels as expressed by a yield value above a certain value corresponding to 2.7–3.0% carbomer. As a consequence, it was not rapidly squeezed out of the eye and a significantly longer duration was achieved.

The viscosities measured with the single-point rotational viscometer did not correlate with miosis duration (Table I). This result illustrates the necessity for constructing a rheogram and identifying specific rheological characteristics that may correlate to the observed phenomenon and perhaps suggest an explanation for the results.

Insight into the mechanism of drug release for ethylene maleic anhydride and carbomer preparations can be speculated upon by analyzing the results of Fig. 2. It is reasoned that the time to peak, t_p, as well as peak miosis intensities, I_{max}, for each preparation are related to the corneal absorption rate; the latter can be altered depending on the degree of control of drug release exerted by the gel systems. The large improvement in eye retention observed for ethylene maleic anhydride and carbomer when compared to a solution dosage form would increase bioavailability, but the effect on t_p and I_{max} would depend on the release characteristics of the gel system.

In general, an improvement in retention followed by an increase in bioavailability could result in: (*a*) a large increase in I_{max} with no change in t_p if drug release from the gel preparations is rapid and uncontrolled, or (*b*) a decrease in I_{max} with a delay in t_p if release from the gel systems is controlled.

The extent of the decrease in I_{max} as well as the delay in t_p depends upon the degree to which the release rate is controlled. It is possible, of course, to decrease significantly or even eliminate the response intensities if the release rate is reduced such that biophasic concentrations are insufficient to invoke a response. This is not of concern here, however.

The miosis intensities observed in Fig. 2 for the gel preparations show a reduced I_{max} and a delayed t_p in comparison to either the solution or petrolatum dosage forms. Consequently, some degree of control of the release rate can be attributed to ethylene maleic anhydride and carbomer. Within the gel, release could be controlled by diffusion and/or slow erosion of the gel surface with time. However, further work is necessary to describe more fully the nature of drug release as well as to estimate the physiological constraints of the precorneal area on the response duration.

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Reaction of Sodium Hydroxymethanesulfonate with Substituted Anilines

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Abstract □ The reactions of substituted anilines with sodium hydroxymethanesulfonate to form the anilinomethanesulfonates were studied in 50% ethanol–water at 0–50°. The Arrhenius rate constants were $5.4 \times 10^{10} \exp(-16{,}400/RT)\ M^{-1}\ min^{-1}$ for aniline, $4.8 \times 10^{11} \exp(-17{,}100/RT)\ M^{-1}\ min^{-1}$ for *p*-anisidine, $7.1 \times 10^{9} \exp(-14{,}500/RT)\ M^{-1}\ min^{-1}$ for *p*-toluidine, $1.5 \times 10^{13} \exp(-21{,}100/RT)\ M^{-1}\ min^{-1}$ for *p*-chloroaniline, and $1.1 \times 10^{12} \exp(-19{,}800/RT)\ M^{-1}\ min^{-1}$ for *p*-bromoaniline. Some equilibrium constants and hydrolysis rate constants of the products also were calculated. Hydrolysis rate constants were temperature independent. These reactions had a ρ value of −3.40 in the Hammett equation. The solvent concentrations used proved to be very convenient for obtaining high yields of the aminomethanesulfonates.

Keyphrases □ Anilines, various substituted—kinetics of reaction with sodium hydroxymethanesulfonate, equilibrium and hydrolysis rate constants calculated □ Sodium hydroxymethanesulfonate—kinetics of reaction with various substituted anilines, equilibrium and hydrolysis rate constants calculated □ Kinetics—reaction of various substituted anilines with sodium hydroxymethanesulfonate, equilibrium and hydrolysis rate constants calculated

The sodium salts of substituted methanesulfonic acids are of interest as both synthesis intermediates and pharmacological agents. Sodium *p*-phenetidinomethanesulfonate has been used as an antipyretic, and several other sodium α-aminoalkanesulfonates have antiviral and anticarcinogenic activities (1–3). Industrially, some primary aromatic amines such as aniline and α-naphthylamine have been transformed into their respective sodium methanesulfonates to avoid formation of the diazoamino group (N=NNH) during coupling in the formation of the azo dyes (4, 5). Hydrolysis of those compounds to obtain the desired azo dyes is then performed in appropriate media.

Numerous syntheses of this type of compound were reported (6, 7), but little research has been done on the formation kinetics of these products. Ikeda *et al.* (8) studied the formation of various substituted sodium anilinomethanesulfonates in water but calculated only overall rate constants. The same investigators (9–13) also studied the amine release from different substituted anilinomethanesulfonates in water and its pH dependence. This paper presents the results of research concerning the formation kinetics of anilinomethanesulfonates in mixed ethanol–water solvents at conditions where the syntheses of these compounds are favored.

EXPERIMENTAL

Materials and Apparatus—All reagents were proanalysis grade and were used without further purification except where indicated. The amines proved to be free of any interfering impurities when analyzed by GLC. Toluene did present an impurity peak with a retention time similar to that of aniline, but this impurity was easily removed by distillation.

The formaldehyde content of the mixture was analyzed by the Romijn method, and the metabisulfite content of the initial solutions was determined by iodometric titration.

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