modified albumin derivatives.

The results obtained with I give some evidence that the single high-affinity binding site of the intravenous biliary contrast agents (5) might be identical with the warfarin binding site of human serum albumin. This conclusion can be made from the strong displacement of bound warfarin, the large reduction of the extrinsic Cotton effects of I bound to XII–albumin at 310 nm that are associated only with binding to the high-affinity binding site, and the large reduction of the association constant of the high-affinity binding site for XII–albumin or XIII–albumin. By contrast, binding of I to the diazepam binding site may be negligible, as shown by the lack of any displacement of human serum albumin-bound diazepam and by the small effects of the tyrosine modification on the binding parameters of I.

With the oral biliary contrast agents, the specificity for one of the two sites of human serum albumin is not so pronounced. However, as revealed by their displacing potencies for diazepam and warfarin and their binding behavior for tyrosine- and tryptophan-modified albumin, VI is bound preferentially to the warfarin binding site but XI is bound to the diazepam binding site. This observation is interesting considering the small difference in the chemical structures of these contrast agents. A similar observation was made for the structurally related oral biliary contrast agents, iopanoic and iophenoxic acids, which differ only by the substitution of a phenolic hydroxyl group in iophenoxic acid and by an amino group in iopanoic acid (18). The data support earlier observations that the high-affinity binding sites of both drugs are different (18, 19); it seems that iophenoxic acid is bound preferentially to the warfarin site while iopanoic acid is bound preferentially to the diazepam binding site.

The latter results indicate that it will be difficult to find common characteristics for drugs bound specifically to the warfarin binding site and for drugs bound specifically to the indole and benzodiazepine binding site since only small changes in the chemical structure of the ligands can have pronounced effects on the binding site selectivity of the drugs.

In summary, the data clearly showed that the serum albumin binding of biliary contrast agents is quite unusual in respect to the structural parameters leading to strong binding to human and bovine serum albumin. Furthermore, small variations of the chemical structure of the contrast agents can effect large changes in the binding site selectivity. The diazepam and the warfarin binding sites of human serum albumin (two important drug binding sites of the protein) are involved in the binding of the biliary contrast agents. Since many other drugs also are bound to these sites, the biliary contrast agents must be considered as potent displacers of many drugs *in vivo*, especially with regard to their high plasma concentration *in vivo* (20, 21). However, the short plasma half-life of the intravenous biliary contrast agents or the short use of the oral biliary contrast agents makes it unlikely that such displacements are clinically important. However, evidence is accumulating that the plasma protein binding of the biliary contrast agents is extremely important for their distribution, hepatic uptake, and biliary and renal elimination (20–23). Therefore, exact knowledge about the mechanisms involved in the plasma protein binding of these drugs could be helpful for understanding the pharmacokinetics of the biliary contrast agents.

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Interaction of Xanthan Gum with Suspended Solids

JOSEPH S. TEMPIO * and JOEL L. ZATZ ˣ

Received August 18, 1980, from the *College of Pharmacy, Rutgers—the State University of New Jersey, Piscataway, NJ 08854.* Accepted for publication October 24, 1980.

*Present address: Smith Kline and French Laboratories, Philadelphia, PA 19101.

Abstract □ Xanthan gum was adsorbed significantly by magnesium carbonate, aluminum hydroxide, zinc oxide, and calcium carbonate, giving Langmuir-type isotherms. Saturation adsorption was higher from 0.9% NaCl than from water due to reduced mutual repulsion of polymer segments in the presence of the salt. Adsorption resulted from electrostatic attraction between positively charged particles and the negatively charged polymer. ζ-Potential measurements correlated with the adsorption data but were not predictive of the flocculation state. The results indicate that flocculation of magnesium carbonate and aluminum hydroxide by xanthan gum is consistent with a bridging mechanism.

Keyphrases □ Xanthan gum—interaction with magnesium carbonate, aluminum hydroxide, zinc oxide, and calcium carbonate □ Adsorption—xanthan gum by suspended solids □ Flocculation—bridging mechanism, magnesium carbonate and aluminum hydroxide with xanthan gum

Xanthan gum produces flocculation of pharmaceutical suspensions (1, 2). Studies utilizing sedimentation volume, microscopy, and particle-size measurement showed that changes in interparticulate structure could be induced by the polymer (2). Flocculation was attributed to the joining of several particles by adsorbed polymer molecules, which

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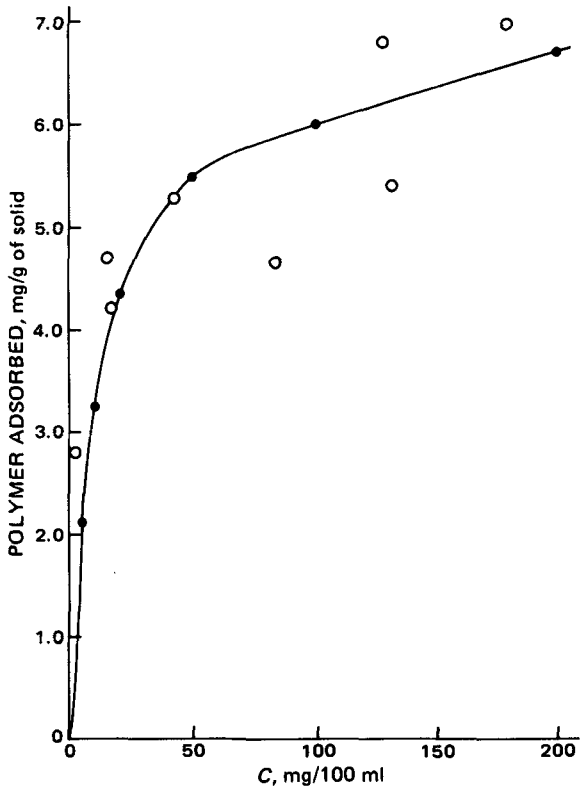

Figure 1—*Adsorption isotherm of xanthan gum from water onto magnesium carbonate. Key: ●, values calculated with Eq. 2; and ○, experimental values.*

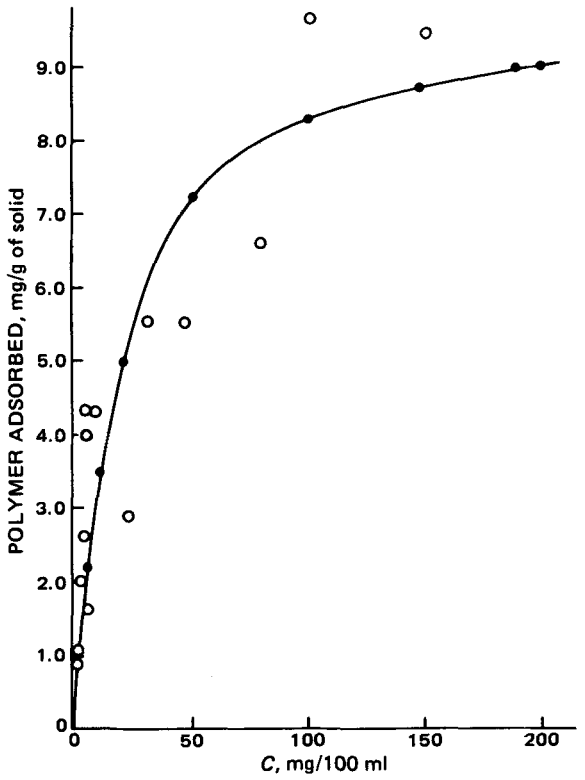

Figure 2—*Adsorption isotherm of xanthan gum from 0.9% NaCl onto magnesium carbonate. Key: ●, theoretical values calculated with Eq. 2; and ○, experimental values.*

are incorporated into the network of aggregated particles (1). Polymer adsorption is an essential feature of this flocculation mechanism. Microelectrophoretic measurements demonstrated that polymeric flocculants were adsorbed by suspended colloidal particles (3). In the presence of excess flocculant, the ζ-potential of several materials was controlled by the surface properties of the flocculant and was independent of the nature of the material. Electrostatic attraction often is involved in adsorption (4), but both adsorption and flocculation can occur if the polymer and particle surface carry the same charge, provided that the ζ-potential of the particle is not too high (5). In some systems, a given polymer functions as both flocculant and deflocculant, depending on its concentration at the particle surface (6).

This study investigated the adsorption of xanthan gum by the solids whose suspension properties were reported previously (2). Adsorption is a prerequisite for flocculation by bridging, and these data are required to decide whether bridging is the mechanism of flocculation by xanthan gum, as was suggested (1).

EXPERIMENTAL

Materials—Xanthan gum, dried aluminum hydroxide gel, magnesium carbonate, calcium carbonate, and zinc oxide were the same materials used in a previous study (2). Silica[1] was 80–100 mesh. Water was distilled. All other materials were USP or reagent grade.

Preparation of Suspensions—The procedure used was described previously (2).

Polymer Analysis—Polymer samples were analyzed for the concentration of xanthan gum by the Seliwanoff reaction. This method is valid for systems where xanthan gum is the only carbohydrate present.

A 1-ml sample of polymer solution (containing 5–250 ppm of xanthan gum) was pipetted into a 10-ml screw-capped culture tube. Then 1 ml of a 4% resorcinol solution in distilled water (prepared fresh daily) was added, followed by 6 ml of concentrated sulfuric acid. The acid was added rapidly, and the tube was mixed with a vortex mixer. Heat and gas were evolved in most cases. The tubes then were placed in an ice water bath for ~5 min until cooled to near room temperature and then were allowed to stand at room temperature for 10–25 min. The concentrations were determined spectrophotometrically at 494 nm within ~1 hr of preparation (7, 8). The absorbance of the samples was read in 1-cm silica cells on a spectrophotometer[2].

Reagent and polymer blanks were run with each analysis. The Beer's law plot in water and 0.9% NaCl was linear throughout the concentration range of interest ($y = 50.8x - 0.10$ and $y = 45.9x + 0.0085$, respectively, for concentrations of 0.005–0.03%).

Adsorption Determinations—The amount of polymer adsorbed was determined indirectly from the difference between the initial polymer concentration and the amount found at equilibrium upon analysis of the supernate after drug addition. Kinetic studies indicated that 3–7 days was required for equilibrium.

Flasks containing the suspensions were placed in a shaker bath[3] at 25 ± 1°. Agitation was at a level sufficient to maintain the bulk of the powders in suspension in all samples. After 7 days, the samples were removed from the shakers, and 1-ml aliquots were withdrawn and diluted, if necessary, for analysis.

When the supernate was not clear, it was decanted from the settled fraction and centrifuged[4] at 2000 rpm for 20 min.

ζ-Potential—The ζ-potential of the suspensions was measured by electrophoresis[5]. All samples were diluted with distilled water prior to the measurement of the electrophoretic mobility. ζ-Potentials were calculated by the Helmholtz–Smoluchowski formula (9):

$$\zeta = \frac{\nu_e 4\pi\eta}{\epsilon} \qquad \text{(Eq. 1)}$$

where ν_e is the electrophoretic mobility of the particle, η is the viscosity, and ϵ is the dielectric constant of the suspending medium.

[1] MCB.

[2] Gilford model 222.
[3] Gyrotary model G-76, New Brunswick Scientific, New Brunswick, N.J.
[4] Damon International centrifuge model CU-5000.
[5] Zeta Meter, Inc., New York, N.Y.

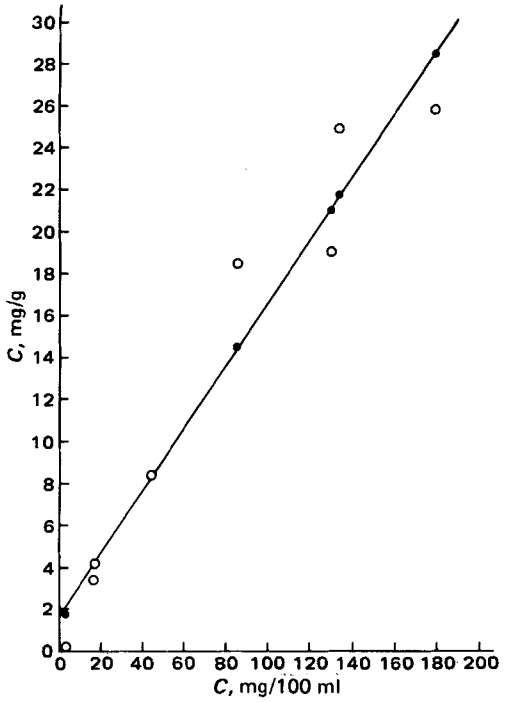

Figure 3—*Linearized Langmuir plot of xanthan gum from water onto magnesium carbonate. Key:* ●, *theoretical values calculated with Eq. 3; and* ○, *experimental values.*

Surface Tension—Surface tensions of the xanthan solutions were determined using the Wilhelmy plate method. A roughened platinum plate was employed, and double-distilled water was used as a standard.

RESULTS AND DISCUSSION

Surface Tensions—At concentrations up to 0.3%, xanthan gum lowered the surface tension of water or 0.9% NaCl by no more than 3 dynes/cm. Thus, this polymer exhibited little surface activity in aqueous solution.

Adsorption Isotherms—Isotherms for xanthan gum adsorption by magnesium carbonate from solution in water and 0.9% NaCl are plotted in Figs. 1 and 2, respectively. The isotherms appear to be the Langmuir type, represented by:

$$Y = Y_m bC/(1 + bC) \qquad \text{(Eq. 2)}$$

where Y is amount adsorbed (in milligrams per gram), Y_m is the amount adsorbed at saturation of the solid surface, C is the equilibrium polymer concentration, and b is a constant. Taking the reciprocal and multiplying through by C yield:

$$C/Y = 1/Y_m b + C/Y_m \qquad \text{(Eq. 3)}$$

This equation is recognizable as the equation of a line with a slope of $1/Y_m$ and intercept $1/Y_m b$.

The adsorption data are plotted according to Eq. 3 in Figs. 3 and 4. The curves are linear; correlation coefficients were significant at the 95% confidence level.

Figures 1–4 were typical of all isotherms. Equation 3 was used to determine the parameters of the isotherms (Tables I and II). For each solid, the saturation adsorption, Y_m, from the salt solution (Table II) was greater than that from water (Table I). The amount of polymer that can be accommodated at a saturated surface depends on the available surface area and the area required for each polymer unit. When polymer segments are charged, as xanthan gum is, mutual repulsion prevents close approach of the segments to each other. Polymer–polymer repulsion is reduced in the presence of 0.9% NaCl, permitting closer packing of the polymer segments at the solid–liquid interface, thereby reducing the average area occupied by each polymer unit and raising the Y_m value.

Adsorption alone is insufficient to define a flocculation mechanism. The essential question is whether adsorption is extensive enough in the suspensions to make bridging possible. The adsorption isotherms represent a plot of adsorption *versus* the equilibrium polymer concentrations. The total amount of polymer in the system is the sum of the amount adsorbed and the amount remaining in solution:

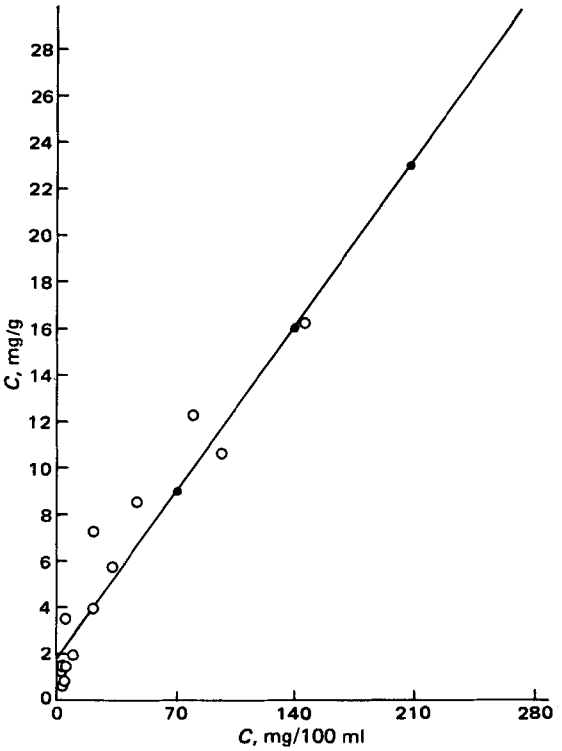

Figure 4—*Linearized Langmuir plot of xanthan gum from 0.9% NaCl onto magnesium carbonate. Key:* ●, *theoretical values calculated with Eq. 3; and* ○, *experimental values.*

$$\text{total polymer} = YA + VC \qquad \text{(Eq. 4)}$$

where A is the amount of adsorbent present (in grams) and V is the volume of liquid in contact with the adsorbent. Half-coverage at the solid–liquid interface (*i.e.*, $Y = \frac{1}{2}Y_m$) is taken to represent sufficiently extensive adsorption for bridging (10).

Previous studies on suspensions containing the same solid drugs contained 5 g of solid (except for the calcium carbonate suspension, which used 10 g of solid) and 30–200 mg of xanthan gum in 100 ml of suspension medium (2). The adsorption isotherms and Eq. 4 were used to calculate the amount of xanthan gum at half-coverage in those systems (Table III). The amount required was 23–81 mg, and these values fell within the range of xanthan gum amounts that were actually utilized. Thus, it may be concluded that adsorption is extensive enough to allow flocculation by polymer bridging.

Table I—Adsorption of Xanthan Gum from Water at 25°

Substance	Y_m, mg/g	Intercept of Linearized Plot, g/100 ml[a]	r
Magnesium carbonate	6.67	1.6	0.972
Aluminum hydroxide	16.6	1.1	0.944
Calcium carbonate	3.59	4.8	0.961
Zinc oxide	4.55	2.7	0.964

[a] According to Eq. 3.

Table II—Adsorption of Xanthan Gum from 0.9% NaCl Solution at 25°

Substance	Y_m, mg/g	Intercept of Linearized Plot, g/100 ml[a]	r
Magnesium carbonate	9.83	1.8	0.949
Aluminum hydroxide	22.6	1.1	0.972
Calcium carbonate	11.1	2.3	0.947
Zinc oxide	7.30	2.9	0.949

[a] According to Eq. 3.

Table III—Total Amount of Xanthan Gum in Pharmaceutical Suspension at Half-Coverage

Substance	Total Xanthan Gum, mg	
	Water	0.9% NaCl
Magnesium carbonate[a]	27	43
Aluminum hydroxide[a]	60	81
Calcium carbonate[b]	35	81
Zinc oxide[a]	23	39

[a] Using 5 g + 100 ml of suspension medium. [b] Using 10 g + 100 ml of suspension medium.

Desorption—Several samples that had reached adsorption equilibrium were centrifuged to separate solid material from the liquid phase. Fifty milliliters of the liquid medium was replaced with medium containing no xanthan gum and then agitated for 7 days in the shaker bath. When the samples were reanalyzed, the xanthan gum concentration in solution did not exceed half its value prior to dilution. This finding indicated that the adsorbed polymer molecules were not desorbed upon dilution.

ζ-Potential and Surface Charge—The zero point of charge is the condition when the charge at a solid interface is zero. For solids dispersed in water, pH values may be used as an indication of the surface charge, provided that hydrogen or hydroxyl ions are potential-determining ions. This appears to be the case for oxides, hydroxides, and carbonates in aqueous systems (11–14).

A slightly soluble hydroxide like aluminum hydroxide has a positive surface charge below the pH of the zero point of charge due to the dissociation of amphoteric surface hydroxide groups and the adsorption from solution of metal–hydroxo complexes (11). The surface potential of calcium carbonate is due to the hydrolysis or adsorption of surface ions or complexes. The hydroxide ion is dominant (13). At pH below the point of zero charge, the surface potential of zinc oxide is expected to be dominated by the Zn^{2+} ion and adsorption of H^+ and metal–hydroxo complexes (14).

The pH values for a suspension supernate were compared with reported values of the zero point of charge for the various solids (Table IV). The ζ-potential values are believed to be a more reliable indication of the surface condition. The zero point of charge for a particular sample of substance depends markedly on the history of the sample, and literature zero point of charge values for different samples of the same material vary widely (17).

Classical theory dictates that high absolute values of ζ-potential are associated with deflocculated systems. The potential energy–distance curves for such systems show a primary minimum at short distances, due to van der Waals attractive forces, and a relatively steep threshold, due to charge–charge repulsion. However, only one system studied, calcium carbonate, was deflocculated in water. Parodoxically, calcium carbonate had the lowest ζ-potential.

The measurement of ζ-potential of concentrated suspensions containing polymers by electrophoresis is complicated because dilution is required. Dilution of systems containing adsorbed materials can result in desorption, with consequent alterations in the measured potential. Since xanthan gum did not undergo desorption upon dilution, this measurement was feasible.

The addition of xanthan gum to the suspended solids caused a reduction in ζ-potential and a reversal in sign to negative values (Fig. 5). The curves resemble the adsorption isotherms in that the potentials approach limiting values. The ζ-potential curves confirm polymer adsorption and indicate that the potential is determined largely by the layer of adsorbed polymer, which is negatively charged.

In the presence of xanthan gum, aluminum hydroxide and magnesium carbonate are flocculated (2). The fact that the ζ-potential is not negligible for these systems again illustrates its limited utility in predicting flocculation behavior. ζ-Potential measurements are of value, but they must be combined with other techniques to obtain a complete view of a disperse system.

Table IV—pH of Supernate of Suspended Solids

Substance	Supernatant pH	Zero Point of Charge	Reference
Magnesium carbonate	9.2	8.5	11
Aluminum hydroxide	6.3	8.5	12
Calcium carbonate	11.1	10.8	15
Zinc oxide	7.2	9.0	16

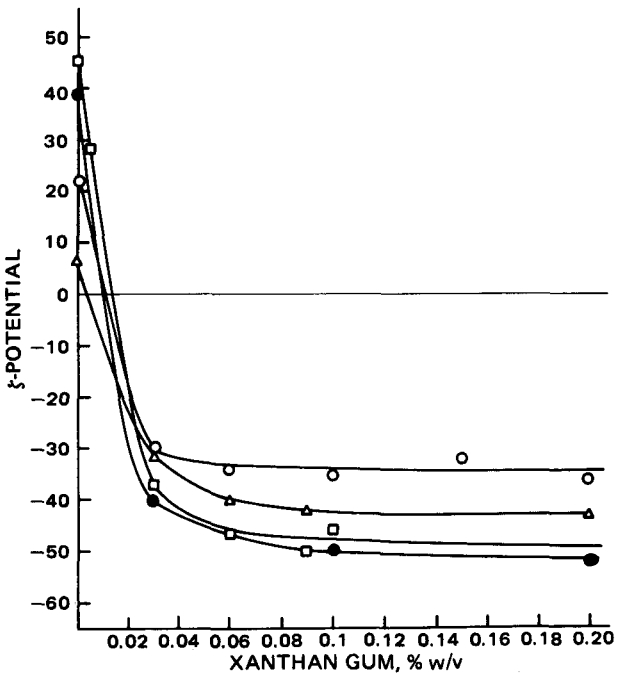

Figure 5—*ζ-Potential of solid drugs as a function of xanthan gum concentration. Key:* □, *aluminum hydroxide;* ●, *zinc oxide;* ○, *magnesium carbonate; and* △, *calcium carbonate.*

The adsorption mechanism of xanthan gum by the solids investigated is most likely electrostatic. The positively charged surfaces are expected to attract strongly the oppositely charged polymer molecules. Since xanthan gum has little surface activity, an adsorption mechanism based on hydrophobic interaction with the surface is not likely.

Experiments with silica provide an interesting comparison. The ζ-potential of silica in water was 55 mv. Suspensions containing 5 g of silica in 100 ml of water were deflocculated, with a sedimentation volume of 0.05. There was no change in sedimentation volume upon addition of xanthan gum. Adsorption studies revealed that xanthan gum was not adsorbed to any significant extent. In this case, the negative potential on the particles prevented polymer adsorption and precluded flocculation by bridging.

Conclusion—The results provide evidence for bridging as a flocculation mechanism of xanthan gum. Significant adsorption occurred on solids that underwent a change in flocculation state because of the gum. ζ-Potential measurements confirmed polymer adsorption. Previously, it was shown that salt effects on the flocculation of aluminum hydroxide, magnesium carbonate, zinc oxide, and calcium carbonate were minimal and that double-layer repulsion alteration by the electrolyte was not important in the flocculation–deflocculation behavior of these suspensions (2). The lack of correlation between the ζ-potential and the flocculation state is another indication that double-layer effects do not play a major role in controlling flocculation of these materials by xanthan gum.

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Synthesis and Structure–Activity Relationships of Selected Tricyclic Oxime *O*-Ethers as Potential Anticholinergic Agents

VILAS A. PRABHU *, ROBERT G. BROWN, and JAIME N. DELGADO ˣ

Received September 29, 1980, from the *College of Pharmacy, University of Texas at Austin, Austin, TX 78712.* Accepted for publication November 3, 1980. *Present address: College of Pharmacy, Southwestern Oklahoma State University, Weatherford, OK 73096.

Abstract □ Selected isomeric and nonisomeric oxime *O*-ether derivatives of thioxanthone oxime were synthesized and evaluated for anticholinergic activity. The oxime *O*-ethers were prepared *via O*-alkylation of the oximate anion with appropriate aminoaklyl halides. Separation and isolation of the structural isomers were accomplished through dry-column chromatography. The racemic α-methyl isomer was resolved *via* formation of tartrate diastereomers, which were subsequently isolated. All synthesized compounds exhibited significant antimuscarinic activity. A comparison of the antimuscarinic activities of these compounds revealed that the racemic α-methyl isomer was the most potent and that the racemic β-methyl isomer was the least potent. Structure–activity relationships among the oxime *O*-ether derivatives synthesized are discussed.

Keyphrases □ Anticholinergics, potential—selected tricyclic oxime *O*-ethers, synthesis, structure–activity relationships □ Structure–activity relationships—selected tricyclic oxime *O*-ethers as potential anticholinergics, synthesis □ Antimuscarinic activity—comparison of synthesized tricyclic oxime *O*-ethers □ Oxime derivatives—synthesis, comparison as potential anticholinergics

Various structurally and stereochemically different esters exhibiting anticholinergic activity were studied previously (1–4) to obtain information concerning stereospecificity of the parasympathetic postganglionic acetylcholine receptor. One report (3), dealing with α- and β-methylcholine esters of 2-cyclohexyl-2-hydroxy-2-phenylacetic acid, concluded that α-methyl substitution significantly increased antimuscarinic activity and that such an increase was independent of the configuration of the α-substituted carbon atom. Based on these findings, the report indicated that the stereochemistry of the aminoalcohol moiety was not significant in determining antimuscarinic activity.

Previous work (5, 6) demonstrated that oxime derivatives are useful model compounds for the study of structure–activity relationships. More recent studies related geometric (7, 8) and enantiomeric (8) isomerism in oxime *O*-ethers to their anticholinergic activity. These findings (8), however, were not in complete agreement with earlier reports (1–3) concerning the stereochemical significance of the aminoalcohol moiety in determining antimuscarinic potency.

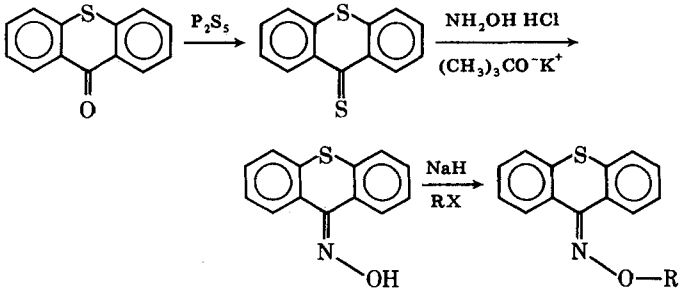
The present study was a further investigation of the possible relationships between structural and stereochemical properties and antimuscarinic activity among oxime *O*-ethers. Selected isomeric and nonisomeric oxime *O*-ethers of thioxanthone oxime (Table I) were synthesized, and a preliminary pharmacological evaluation was conducted to determined their antimuscarinic activity.

DISCUSSION

Preparation of the oxime directly from thioxanthone was attempted *via* methods described by Gomer *et al.* (6), for the synthesis of xanthoxime, and Wylie *et al.* (9), for the preparation of benzophenone oxime, but was unsuccessful. This failure can be explained by the fact that, in thioxanthone, the carbonyl carbon is considerably less electrophilic and, therefore, less susceptible to nucleophilic attack by the hydroxylamine nitrogen. Subsequently, thioxanthone oxime was prepared by a modified method of Nagrajan *et al.* (10). Accordingly, thioxanthone was converted first to the thione by refluxing it with excess phosphorus pentasulfide in xylene. The thione then was refluxed with hydroxylamine hydrochloride and potassium *t*-butoxide in anhydrous ethanol to yield the oxime in fair yields. Based on the reported mechanism (8, 11) involved in the synthesis of oximes from highly aromatic ketones, a general base-catalyzed mechanism was proposed for the synthesis of thioxanthone oxime. The oxime was quite unstable when exposed to direct sunlight, decomposing to the ketone. The major steps involved in the synthesis of the oxime and the oxime *O*-ethers are depicted in Scheme I.

The oxime *O*-ethers included in this study (Table I) were prepared *via O*-alkylation of the oximate anion with the appropriate aminoalkyl halides. The mechanism of *O*-alkylation involves a nucleophilic attack by the base-generated anionic oximate species on the aminoalkyl halide, resulting in the displacement of the halide ion (12).

The procedure of Huerta *et al.* (8) was used to prepare the α- and β-methylcholine *O*-ethers of the oxime. Accordingly, 2-chloro-*N*,*N*-



RX = aminoalkyl halide

Scheme I

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