inum oxide was added, and hydrogen was admitted to the system at atmospheric pressure. The solution absorbed 400 ml. (13.6 mmoles) of hydrogen in 30 min., after which no further uptake was observed. The reaction mixture was filtered to remove platinum and evaporated to dryness, leaving 0.851 g. of residual oil.

The crude product was separated by chromatography on 20 g. of silica gel into two main fractions, which were eluted from the column with acetone. The first of these weighed 0.451 g. and crystallized as long needles. Recrystallization from hexane gave material melting at 53–56° [lit. (4) m.p. 54–56°] and having the properties expected of 4-methyl-2-pyrrolidinone; mass spectrometry: M^+, *m/e* 99; ν_{max}^{CHF}: 3460 (m), 3240 (s), 3020 (s), and 1700 (s) cm.$^{-1}$; NMR (60 MHz.): δ 1.3 (3H, doublet), 1.8 (1H, multiplet), 2.4 (2H, unresolved), 3.4 (2H, two doublets), and 7.4 (1H, broad).

Anal.—Calc. for C_5H_9NO: C, 60.61; H, 9.09; N, 14.14; mol. wt. 99. Found: C, 60.79; H, 8.84; N, 14.33; *m/e* 99.

The second fraction, 0.364 g., did not crystallize. The IR spectrum differed from that described for the first fraction in having strong, broad absorption near 3300 cm.$^{-1}$. The NMR spectrum had a peak at δ 5.3 (1H) that was removed when deuterium oxide was added to the solution. This material, presumably a mixture of 5-hydroxy-4-methyl-2-pyrrolidinones, was not investigated further.

Oxidation of Jatropham—A solution of 0.815 g. (7.2 mmoles) of lactam in 40 ml. of acetone was cooled to 5°, and a solution of chromic acid (5) was added slowly with occasional addition of portions of anhydrous magnesium sulfate until the red-orange color of the oxidizing agent persisted. The mixture was filtered, the insoluble portion was washed thoroughly with acetone, and the solution was evaporated to dryness. The residue weighed 0.62 g. (78%). The material was recrystallized from carbon tetrachloride, giving a sample melting at 99–102°. This sample was further purified by sublimation, yielding long needles, m.p. 103–105°. The purified material was identical in IR spectrum (chloroform solution), TLC behavior, and mixed melting point (103–105°) with a sample of citraconic acid imide, m.p. 104–105°, synthesized by heating citraconic anhydride with ammonium hydroxide (6).

Anal.—Calc. for $C_5H_6NO_2$: C, 54.05; H, 4.50; N, 12.61; mol. wt. 111. Found: C, 54.35; H, 4.54; N; 12.32; *m/e* 111.

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COMMUNICATIONS

Dissolution Rates of Cholesterol Monohydrate Crystals and Human Cholesterol Gallstones in Bile Acid–Lecithin Solutions: Enhancing Effect of Added Alkyl Quaternary Ammonium Salts

Keyphrases □ Cholesterol monohydrate crystals and human cholesterol gallstones—dissolution in bile acid–lecithin solutions, effect of alkyl quaternary ammonium salts □ Cholate–lecithin dissolution media for cholesterol dissolution—effect of alkyl quaternary ammonium salts on interfacial barriers □ Benzalkonium chloride—effect on cholesterol dissolution in cholate–lecithin solutions □ Quaternary ammonium compounds—effect on cholesterol dissolution in cholate–lecithin solutions □ Bile acid–lecithin solutions—cholesterol dissolution, effect of alkyl quaternary ammonium salts □ Gallstone dissolution in bile acid–lecithin solutions—effect of quaternary ammonium salts

Sir:

Recent experiments on cholesterol dissolution in micellar bile salt solutions showed that added lecithin decreases the dissolution rates even though it increases the solubility of cholesterol monohydrate crystals in the solvent media (1, 2). From these data, effective crystal–solution interfacial barriers for the dissolution process were deduced, assuming a model based upon the interfacial barrier in series with a Nernst diffusion layer. Table I shows: (*a*) the dissolution rates of a compressed cholesterol monohydrate pellet (J/A), and (*b*) the solubilities (C_s) and diffusivities (D) of cholesterol molecules in various media determined by reported methods (2). The total transfer resistance (R) was calculated as the sum of diffusional resistance (h/D) and interfacial resistance ($1/P$). For example, in 2% cholate–1% lecithin solution, the interfacial resistance for cholesterol dissolution is nearly 20 times the diffusional resistance based upon the benzoic acid dissolution experiment. These findings are important in view of the recent clinical studies showing that *in vivo* diminution of cholesterol gallstones may be controlled by dissolution kinetics. This communication reports findings with benzalkonium chloride and other quaternary ammonium compounds in counteracting or eliminating the interfacial barriers present in the cholate–lecithin media for cholesterol dissolution.

As shown in Table I, in 2% cholate–1% lecithin and in 5% cholate–2.5% lecithin, added benzalkonium chloride significantly reduced the large R values to

Table I—Dissolution Rates[a] of Cholesterol Monohydrate Pellet (J/A), Solubilities (C_s), and Diffusion Coefficients (D) Independently Determined in the Solvent Media at 37°

0.1 *M* Phosphate, pH 7.4						
Cholate, %	Lecithin, %	Benzalkonium Chloride, %	$(J/A)10^4$, mg. cm.$^{-2}$ sec.$^{-1}$	C_s, mg. cm.$^{-3}$	$D \times 10^6$, cm.^{2} sec.$^{-1}$	$R \times 10^{-3}$, sec. cm.$^{-1}$
2.0	—	—	0.67	0.53	2.17	7.91
2.0	—	0.5	4.82	0.63	1.92	1.31
2.0	1.0	—	0.16	1.05	1.49	65.63
2.0	1.0	0.5	4.82	1.37	1.50	2.84
5.0	—	—	1.95	1.34	1.90	6.87
5.0	—	1.25	8.95	1.71	1.54	1.91
5.0	2.5	—	0.56	3.0	1.30	53.57
5.0	2.5	1.25	8.33	3.27	1.10	3.93
Benzoic acid in 0.01 *N* HCl			131.0	4.70	14.0	3.59

[a] R was calculated from $J/A = C_s/R$, where $R = h/D + 1/p$ with h = Nernst diffusion layer thickness and p = effective interfacial permeability coefficient.

nearly that found with benzoic acid dissolution. Similar effects with benzalkonium chloride were also found in 2 and 5% cholate. Other dissolution studies in 2% cholate–1% lecithin showed that 0.5% cetylpyridinium chloride may have the same effect as benzalkonium chloride, giving $R = 4.85 \times 10^3$ sec. cm.$^{-1}$; 0.5% cetrimonium bromide was around 80% as effective as benzalkonium chloride, giving $R = 10.3 \times 10^3$ sec. cm.$^{-1}$. Experiments with human cholesterol gallstones were conducted by reported methods (2) in 2% cholate–1% lecithin solutions, with or without 0.5% benzalkonium chloride. Similar results as those shown in Table I for cholesterol monohydrate pellets were obtained: $R = 1.57 \times 10^3$ sec. cm.$^{-1}$ and $R = 61.76 \times 10^3$ sec. cm.$^{-1}$ with and without benzalkonium chloride, respectively.

The clinical implications of these findings with the quaternary ammonium compounds may be important in the medical treatment of the gallstone disease. Recent clinical studies of Danzinger *et al.* (3) showed that oral administration of chenodeoxycholic acid to patients with gallstones can lead to the undersaturation of the bile with respect to cholesterol and the dissolution of the stones. They found that, in six of the seven patients studied, gallstones progressively diminished in size during the 14–30 months of chenodeoxycholic acid treatment. In a different kind of study by Admirand[1] involving the dissolution of cholesterol gallstones retained in the common bile duct postoperatively *via* T-tube perfusion of 5% cholate, small stones of millimeter diameter were dissolved in 3–14 days while larger stones did not appear to diminish significantly. These studies support the idea that increasing the *in situ* gallstone dissolution rate should yield material patient benefits through reduced medical treatment times. The results and methodology reported with benzalkonium chloride and other quaternary ammonium compounds may prove valuable in finding or designing safe and efficacious agents or therapeutic regimens for the medical treatment of the gallstone disease.

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Obtaining Preliminary Estimates to Fit Two-Term Exponential Model to Blood Concentration Data

Keyphrases ☐ Absorption and elimination rate constants, preliminary estimates—obtained using exponential function curve fitting ☐ Blood concentration data—preliminary estimates for two-term exponential model, equations ☐ Rate constants, absorption and elimination—preliminary estimates for two-term exponential model, method, equations

Sir:

For a two-term exponential model, Wagner (1) discussed a graphical method of obtaining preliminary estimates of the elimination and absorption rate constants. In a later paper, Wagner and Metzler (2) concluded, by illustrating two examples, that graphical estimates (obtained by conventional feathering techniques) of the absorption rate constant and the elimination rate constant overestimate and underestimate the corresponding rate constants obtained by the least-squares solution. Wagner (1) noted that, if the starting values for the computer program are not close to the least-squares estimates, some computer programs may not necessarily converge at the global minimum because the error sum of squares may contain two minima. This communication presents another method of ob-