parabolic LD_{50} correlation with log P or the molecular weight also gave poorer results as compared to the molecular connectivity correlations. The parabolic relationship between LD_{50} and log P gave $r = 0.826$, $s = 0.249$, $n = 15$, and $F = 12.9$; with the molecular weight, the values were $r = 0.653$, $s = 0.334$, $n = 15$, and $F = 4.5$.

The very good correlations for the anesthetic and toxic activities were obtained with nonempirically based molecular connectivity terms. The equations describing the activity variations were not parabolic but contained two different connectivity terms. It is questionable whether the same structural features quantitatively affect the activity uniformly in a homologous series. The same features probably govern activity for smaller congeners up to the maximum activity; but beyond it, these factors may be somewhat different. In this respect, nonlinear correlations bring to light the flexibility and discriminating power of molecular connectivity as compared to the usual quadratic form of log P.

Many mechanistic explanations for parabolic relationships have been given (5–7). The usual explanation is based on a partitioning model. Alternative mechanistic explanations include the principle of bulk tolerance, limited solubility of the higher members of a congeneric series, conformational distortion of the active site, and metabolic transformation. These explanations imply that molecular size is the governing influence. The molecular connectivity indexes that mirror molecular connectedness are most readily identified with the size and shape of molecules. Murray *et al.* (8) obtained excellent parabolic relationships between molecular connectivity and biological activity. They discussed and endorsed the molecular size explanation, as modeled by molecular connectivity.

That the molecular connectivity indexes reflect the size and shape of molecules also can be seen when going through the congeneric series of Tables I and II. Thus, the correlations obtained would also support the mechanistic explanation for parabolic relationships implying molecular size. More specifically for the anesthetic activity, this molecular size explanation is in line with the Mullins critical volume hypothesis (9). This hypothesis states that anesthesia occurs when the volume of a hydrophobic region is caused to expand beyond a certain critical amount by the absorption of molecules of an inert substance. The results obtained here are also in agreement with previous studies of a mixed group of anesthetics (2) and a group of ethers (4) for which a molecular size explanation of the correlations with molecular connectivity indexes was proposed.

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Correlation of Quinidine Absorption with Disintegration and Dissolution Rates

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Abstract □ The dissolution profiles of four commercial quinidine sulfate tablets were determined using the USP rotating-basket dissolution apparatus. Substantial differences in dissolution half-times were noted and compared to previously reported disintegration times, absorption rate constants, and times of appearance of peak serum concentrations. Rank-order correlations were observed among all combinations of *in vivo* and *in vitro* parameters, indicating that the absorption rates of these tablets are controlled by both disintegration and dissolution.

Keyphrases □ Quinidine sulfate—four commercial tablets, dissolution profiles determined and related to disintegration and absorption □ Dissolution—quinidine sulfate, four commercial tablets, profiles determined and related to disintegration and absorption □ Disintegration—quinidine sulfate, four commercial tablets, related to dissolution profiles □ Absorption—quinidine sulfate, four commercial tablets, related to dissolution profiles □ Cardiac depressants—quinidine sulfate, four commercial tablets, dissolution profiles determined and related to disintegration and absorption

A recent report (1) presented the results of a comparative bioavailability study of four commercially available, chemically equivalent brands of quinidine sulfate. No statistically significant differences in the extent of absorption from the four brands were observed. However, significant differences in the times of peak serum concentration and absorption rate constants were found, indicating differences in the absorption rate among certain pairs of products. A rank-order correlation was observed when mean disintegration times for the four tablet formulations were compared with values for peak time and the absorption rate constant. It seemed appropriate, therefore, to determine the dissolution profiles of these four brands of quinidine sulfate tablets and to investigate the relationships among disintegration, dissolution, and absorption rate.

EXPERIMENTAL

The dissolution properties of six tablets of each of the four brands[1] of quinidine sulfate tablets employed in the study of Strum *et al.* (1) were determined in 900 ml of 0.1 *N* HCl at 37° using the USP rotating-basket dissolution apparatus[2] at 25 rpm. Following preliminary trials, sampling

[1] Treatment A: quinidine sulfate tablets USP, lot 76F83A, Eli Lilly & Co., Indianapolis, Ind.; Treatment B: quinidine sulfate tablets USP, lot 7088A, Philips Roxane Laboratories, Columbus, Ohio; Treatment C: Quinora tablets, lot 72755, Lakeside Laboratories, Milwaukee, Wis.; Treatment D: quinidine sulfate tablets USP, lot 15840, Stanlabs, Portland, Ore. These lots are the same as those used by Strum *et al.* (1).

[2] Hanson Research Corp., Northridge, Calif.

times were adjusted so that at least four data points were obtained above and below the apparent $t_{50\%}$ value.

Samples of dissolution media, 5 ml, were withdrawn (and replaced with an equal volume of drug-free fluid) in a plastic disposable syringe[3] through an attached 3.81-cm, 22-gauge needle, the top of which was 5 cm beneath the surface of the fluid. These samples were immediately filtered through a 0.45-μm membrane[4] filter. The samples were then assayed spectrophotometrically[5] at 343 nm. It was determined that there was no interference in the readings due to tablet excipients. The observed concentrations were converted to amounts dissolved and, in turn, to percent dissolved by using the data from the content uniformity determinations reported by Strum *et al.* (1).

RESULTS AND DISCUSSION

The resulting percent dissolved *versus* time data for each tablet were then plotted on log probability graph paper according to the method of Wagner (2). A line of best fit was obtained by applying least-squares regression analysis to the transformed values of percent dissolved [transformed to z values as suggested by Lippmann (3)] *versus* logarithms of time. Linear plots were obtained in all cases with correlation coefficients ranging from 0.947 to 0.992. Values for $t_{50\%}$ were then calculated from the slopes and intercepts of the lines of best fit.

Means and standard deviations were calculated for each of the four products and are listed in Table I along with previously reported (1) mean disintegration times, t_{max} values, and k_a values. As can be seen from these results, rank-order correlations occur when both dissolution half-time and disintegration time are compared with the two *in vivo* parameters. Specifically, as the dissolution rate decreases, the absorption rate also decreases, as evidenced by decreasing k_a values and increasing t_{max} values. Similarly, increasing disintegration times (slower disintegration) also coincide with decreasing absorption rates. Because of the limited range of values and the lack of statistically significant differences between certain treatment pairs in the *in vivo* data, it was felt that it would be inappropriate to express these findings as linear relationships.

Based on the k_a values, it appears that dissolution $t_{50\%}$ values greater than 27 min and disintegration times greater than 7 min result in substantially decreased absorption rates. Thus, the absorption rates of these four brands of quinidine sulfate tablets apparently are controlled by both disintegration and dissolution.

Table I—Means and Standard Deviations of Dissolution Half-Time, Disintegration Time, Absorption Rate Constant, and Time of Peak Serum Concentration for Each of Four Commercially Available Brands of Quinidine Sulfate Tablets

Treatment	$t_{50\%}$, min	Disintegration Time, min[a]	k_a, hr^{-1}[a]	t_{max}, hr[a]
C	7.08 ± 0.76	1.00 ± 0.0	2.91 ± 2.17	1.63 ± 0.59
A	14.49 ± 1.20	4.08 ± 0.20	2.88 ± 2.47	1.84 ± 0.74
B	27.41 ± 1.63	7.16 ± 1.94	2.08 ± 2.21	2.27 ± 0.71
D	34.94 ± 3.98	17.83 ± 2.22	1.12 ± 0.46	2.54 ± 0.33

[a] Data from Ref. 1.

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[4] Millipore Corp., Bedford, Mass.
[5] Model DB-G spectrophotometer, Beckman Instruments, Fullerton, Calif.

Synthesis and Biological Activity of N^6-(n-Alkylureido)purine Ribonucleosides and Their 5′-Phosphates

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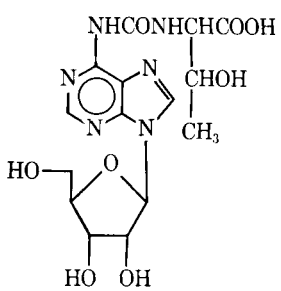
Abstract □ Syntheses and biological activities of 12 N^6-(n-alkylureido)purine ribonucleosides (alkyl chain length of 1–10, 16, and 18 carbons) and three N^6-(n-alkylureido)purine ribonucleoside 5′-phosphates (chain length of 4, 9, and 10 carbons) are described. The N^6-(n-alkylureido)purine ribonucleosides were prepared by a reaction of (2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine-6-carbamate and n-alkylamine in refluxing pyridine. The 5′-nucleotides were prepared by direct phosphorylation of the corresponding ribonucleoside with phosphorus oxychloride and triethyl phosphate. Some N^6-(n-alkylureido)purine ribonucleosides (n-octyl, n-nonyl, and n-decyl) and their nucleotides showed a marked antiproliferative activity against L-1210 cells in culture.

Keyphrases □ Purine ribonucleosides, substituted—synthesized, evaluated for cytotoxic activity *in vitro* □ Cytotoxic activity—various substituted purine ribonucleosides and 5′-phosphates evaluated *in vitro* □ Structure–activity relationships—various substituted purine ribonucleosides and 5′-phosphates evaluated for cytotoxic activity *in vitro*

In view of the growth-inhibitory activities by analogs of the anticodon-adjacent modified ribonucleoside *N*-(purin-6-ylcarbamoyl)-L-threonine ribonucleoside (I) against cells of leukemic origin grown in culture (1, 2), a series of N^6-(n-alkylureido)purine ribonucleosides of varying chain length (1–10, 16, and 18 carbons) were prepared for determination of structure–activity relationships.

Since the 5′-nucleotides had shown greater water solubility (3), as well as the ability to cross cell membranes (4), and acted as sustained-release forms for the nucleosides



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