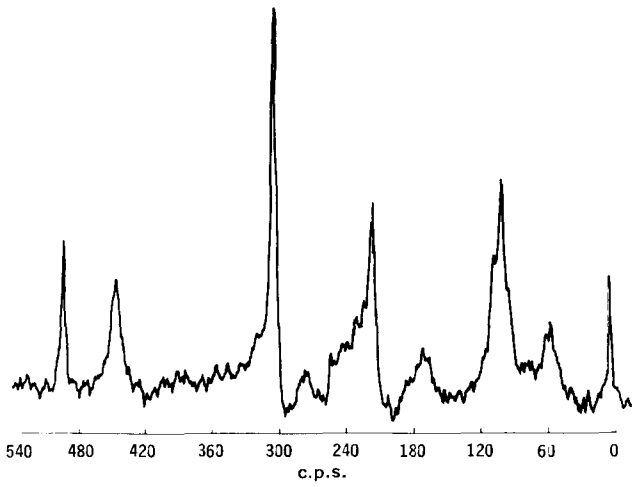

Figure 3—*NMR spectrum for SK&F 33134-A solution diluted with methanol-d_4.*

verely inhibited. Raising the temperature of this solution in small increments and recording the NMR spectra at selected temperature intervals resulted in spectra having increasing resolutions, with corresponding increases in signal intensities. The spectrum for SK&F 33134-A at 75° is also shown in Fig. 1. The sharpening of the spectrum with an increase in signal intensity suggests the gradual breakdown of the micellar structure as the temperature increases. The resolution reaches its maximum at approximately 60°. We assume that the micellar structure is completely disrupted at this temperature. The effect is further illustrated in Fig. 2, which contains a plot of band width at half-height of the aromatic protons on the iodinated benzene ring at 504 c.p.s. (resolution) *versus* temperature. The fact that band width at half-height reaches a minimum constant value at approximately 60° again illustrates the apparent breakdown of the micellar structure at this temperature.

Water-miscible organic solvents have been shown to have some effect on micelle formation (4). Figure 3 illustrates the effect of the addition of methanol-d_4 to the micellar solution of SK&F 33134-A at 25°. The NMR spectrum becomes highly resolved, indicating that the micelle has been disrupted.

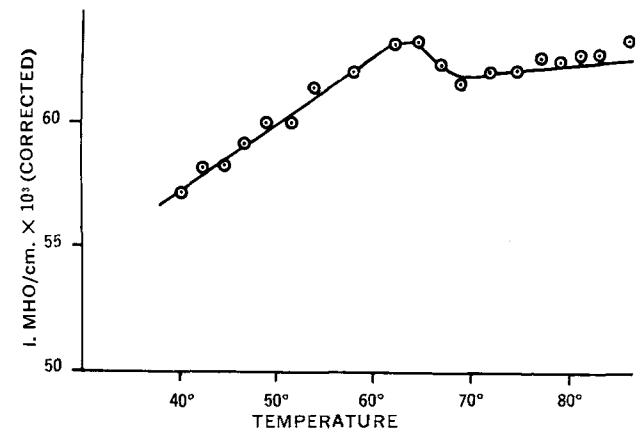

Figure 4—*Plot showing the effect of temperature on the specific conductance of a 5% aqueous solution of SK&F 33134-A.*

To substantiate the effect of temperature on the micellar state of SK&F 33134-A, conductivity studies were done over the same temperature range. A Serfass conductivity bridge, model RCM15B1, and a Beckman K 1.00/cm. conductivity cell were used. An aqueous solution of SK&F 33134-A was poured into two small jacketed glass vessels connected to each other and to a constant-temperature bath. The conductivity cell was immersed into one vessel and a thermometer into the other vessel. The temperature of the water bath was increased slowly. The temperature and the conductivity of the test solution were recorded. The results are shown in Fig. 4. The conductivity increases gradually to 60° and then becomes relatively constant. These conductivity data are in good agreement with the NMR data, indicating the presence of micelles at 25° and the subsequent complete destruction of the micelles as the temperature is increased. In both cases the temperature effect is reversible.

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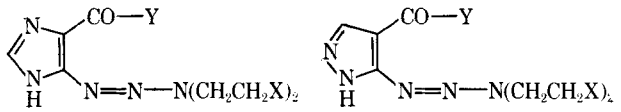
Imidazole and Pyrazole Bis(2-fluoroethyl)triazenes

Keyphrases □ Bis(2-fluoroethyl)triazene derivatives—synthesis □ Antileukemic activity—triazenoimidazoles

Sir:

Among a considerable number of 5-(disubstituted-triazeno) and 5-(monosubstituted-triazeno) derivatives of imidazole-4-carboxamide and of imidazole-4-carboxylic acid esters tested against lymphoid leukemia L-1210, 5-[3,3-bis(2-chloroethyl)-1-triazeno]imidazole-4-carboxamide (I, NSC-82196) has proved to be the most effective. In certain of the standard L-1210 tests, a majority of the afflicted mice treated with NSC-82196



I: Y = NH_2; X = Cl
II: Y = NH_2; X = F
III: Y = OCH_3; X = F
IV: Y = NH_2; X = F
V: Y = OC_2H_5; X = F

The data in Table I show that the two bis(2-fluoroethyl)triazenoimidazoles (II and III) increased the lifespan of leukemic mice by 50–70% at tolerated doses. By way of comparison, the doses of NSC-82196 reported (1, 2) to be most effective are 300–625 mg./kg. for single-dose treatment and 50–100 mg./kg./day for daily treatment. The data appear to justify the following conclusions: (*a*) the bis(2-fluoroethyl)triazenes are more toxic than is NSC-82196; (*b*) at doses tolerated by the host animals, II and III are less effective than NSC-82196; and (*c*) in the standard L-1210 test system, the increases in lifespan caused by II and III are comparable to those produced by the corresponding dimethyltriazenes of the amide (NSC-45388) (8) and methyl ester (NSC-87982) (5) series.

Both the v-triazole (9) and the pyrazole (10) analogs of 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (NSC-45388, DIC) cause significant increases in the lifespan of mice bearing L-1210, and other triazenopyrazole amides and esters have likewise demonstrated activity against L-1210 (7). However, in tests conducted in accordance with the protocols of the Cancer Chemotherapy National Service Center, amide IV displayed minimal activity, whereas the ethyl ester did not significantly increase survival time as a result of either the single-dose or the daily therapeutic regimens. Again, both are more toxic than NSC-82196.

Amides II and IV, like NSC-82196, undergo a change in aqueous solutions to ionic transformation products (11, 12), but the bis(2-fluoroethyl)triazeno derivatives are considerably more stable than NSC-82196. Esters III and V likewise undergo a change, presumed to be the same type. Obviously, the greater toxicity of II–V, in comparison with NSC-82196, may be due to replacement of chloro groups by fluoro groups. It is also conceivable that the lower toxicity of NSC-82196 results in part from its instability. If this is true, the instability may be advantageous.

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Aggregation Mechanisms in Pharmaceutical Suspensions

Keyphrases ☐ Suspensions, pharmaceutical—aggregation mechanism ☐ Flocculation, coagulation—suspensions

Sir:

The method of prevention of impaction and caking in pharmaceutical suspensions by controlled flocculation is usually credited to Haines and Martin (1). The work of these authors is, however, sometimes quoted in review articles (2, 3) without reference to the important criticisms subsequently published by Wilson and Ecanow (4) and Ecanow *et al.* (5). We have endorsed (6) some of these criticisms, but have suggested that several generalizations proposed by Ecanow and his coworkers were based on inadequately controlled experiments. The purpose of this communication is to clarify some aspects of suspension theory recently commented upon by Ecanow *et al.* (7), since this area is of considerable importance to the pharmaceutical formulator.

We are grateful to Ecanow *et al.* (7) for amplifying some points in their earlier paper (5), since we had previously found that the almost complete absence of experimental data, such as particle size of the drug and concentration of electrolyte, made an adequate appraisal impossible. Despite the recent criticisms of these authors, we see no reason to retract from our claim that Figure 1 in *Reference 6* demonstrates differences between coagulation and flocculation. Ecanow and coworkers appear to have forgotten that suspensions of drugs in anionic surfactants (1, 8) and cationic and nonionic surfactants (9) in the absence of electrolyte cake on storage. The control suspension described in the uppermost curve of Figure 1 in *Reference 6* caked after ultimate sedimentation. However, we do not consider it semantically or scientifically helpful to refer to this process as coagulation for the following reason. If the particles were slightly smaller, they would remain in permanent colloidal suspension due to Brownian motion