

ml.). The solution was warmed to 65°, and diethylaminoethanol (1.24 Gm.) in anhydrous benzene (50 ml.) was slowly added dropwise; no visible reaction was observed. The reaction mixture was refluxed for 4 hours at 65°. After this time, the hydrochloride salt which had precipitated was removed by filtration, washed with two 50-ml. portions of anhydrous benzene, and dissolved in absolute methanol (100 ml.). Anhydrous ether was added until the solution became slightly cloudy; the solution was then stored in a refrigerator (6°) for 24 hours. The product was recrystallized twice using the above procedure. The reddish orange crystals which formed (1.03 Gm.) melted at 184–185° uncorrected. The product was not subjected to further purification. After drying under reduced pressure in the presence of a drying agent, the product melted at 184–185° uncorrected. Yield, 1.02 Gm. (25%).

*Anal.*—Calcd. for  $C_{24}H_{36}N_2O_6S_2$ : C, 46.99; H, 5.89. Found: C, 47.43; H, 6.51.

### CONCLUSION

The synthesis and chemical investigation of some alkyl and aminoalkyl esters of *p*- and *m*-azobenzenedisulfonic acid have been reported. Two homologous series of dialkyl esters ranging from dimethyl

to dibutyl and the hydrochloride salts of bis-(2-di-*n*-butylaminoethyl)-*m*-azobenzene-3:3'-disulfonate and bis-(diethylaminoethyl)-*p*-azobenzene-4:4'-disulfonate are reported. Discussion and references leading to the preparation of *p*- and *m*-azobenzenedisulfonic acids and their chlorides, metallic salt, and amide derivatives are also presented. The compounds were not subjected to pharmacological evaluation.

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## Stability Patterns of Vitamin A in Various Pharmaceutical Dosage Forms

By J. THURØ CARSTENSEN

Data presented show that the logarithm of the pseudo first-order rate constant for the degradation of vitamin A when moisture is abundantly present is linearly related to the water vapor pressure.

IT HAS BEEN established by us through numerous experiments that vitamin A in oil solution, when stored under an inert atmosphere, follows (a) a pseudo first-order degradation scheme and (b) lends itself to conventional Arrhenius plotting according to Garrett (1). This is exemplified in Figs. 1 and 2.

It has also been established that vitamin A acetate and palmitate encased in gelatin, acacia, and like substances, upon tableting into conventional uncoated tablets and/or chewable tablets, follow a similar pattern, provided that extrusion is allowed for. Examples of this are shown in Fig. 3.

While these facts are easily explained on a thermodynamical basis, we have encountered the somewhat surprising phenomenon that in the case where moisture is abundantly present, the logarithm of the pseudo first-order rate constant (*k*) is linearly related to the water vapor pressure (*p*). This holds true for water-micelle systems of vitamin A palmitate and also vitamin A acetate and palmitate beadlets in sugar coated tablets (see Figs. 4 and 5). To verify the better fit of a straight line (e.g., the data in Fig. 4), the least square fit lines were drawn (a) with respect to  $y = \log k = f(1/T)$  (*T* being absolute temperature) and (b)  $y = \log k = f(p)$ . The sum  $\Sigma(y_i - \alpha x_i - \beta)^2 = S^2$  is not, in this case, of good com-

parative measurement because of the different abscissa; however, the relative standard deviation of the slopes ( $\alpha$ ) calculated in cases (a) and (b) give relative comparisons of which abscissa gives the best linear fit.

The values  $S_{\alpha}/\alpha(1/T) = 0.485/3.463 = 0.14$  and  $S_{\alpha}/\alpha(P) = 0.000479/0.0132 = 0.036$  demonstrate numerically what is obvious to visual inspection. The important qualitative fact is that in the case of  $f(1/T)$  the intermediate points lie below the terminal line segment, whereas in case of  $f(p)$  the points scatter, implying curvature for  $f(1/T)$  but not for  $f(p)$ . There is no ready thermodynamic explana-

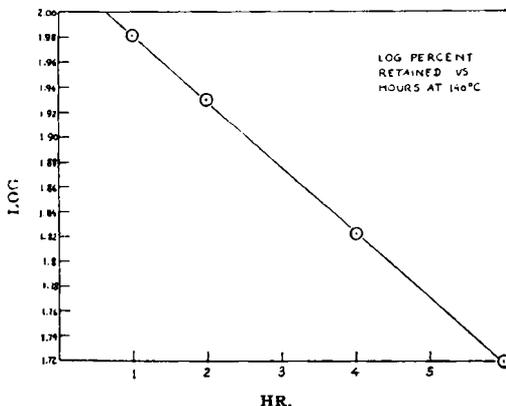


Fig. 1.—Vitamin A alcohol in Tween-Drew oil base, 500,000 units/ml., stored under nitrogen in glass bottles. Plot shows per cent potency retained as a function of hours at 140° C.

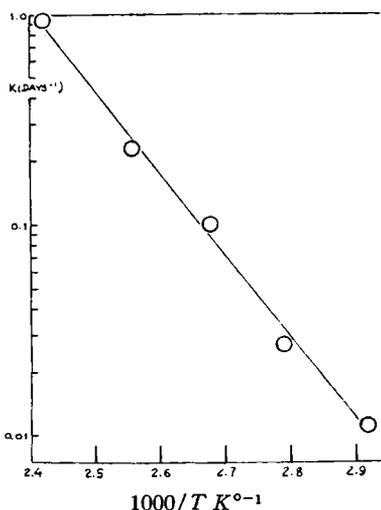


Fig. 2.—Vitamin A alcohol in Tween-Drew oil base. Plot shows pseudo first-order rate constants as a function of reciprocal absolute temperature (reciprocal °Kelvin).

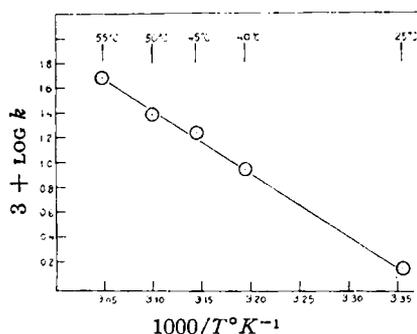


Fig. 3.—Rate constants ( $k = \text{week}^{-1}$ ) for pseudo first-order rate constants of vitamin A palmitate beadlets in dry-slugged, mannitol-base, multi-vitamin chewable tablet.  $\log k$  is plotted against reciprocal absolute temperature.

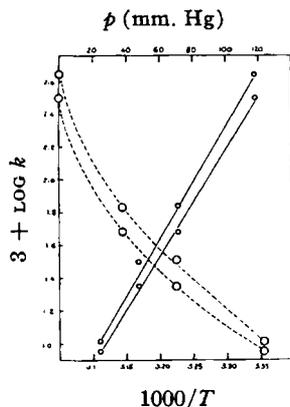


Fig. 4.—Plots of the pseudo first-order rate constant ( $k = \text{month}^{-1}$ ) for vitamin A palmitate beadlets in sugar-coated tablets. Dotted lines are regular Arrhenius plots ( $1/T$  scale); full lines are  $\log k$  vs. water vapor pressure ( $p$ -scale).

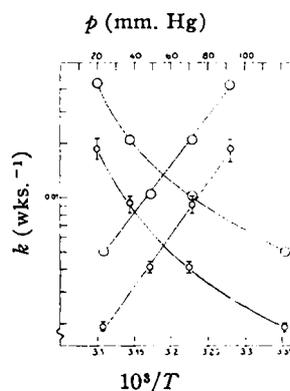


Fig. 5.—Plots of the pseudo first-order rate constants ( $k$ ) for vitamin A palmitate oil in a multivitamin drop (Tween, micelle, glycerin, water). Dotted lines are regular Arrhenius plots ( $1/T$ -scale); full lines are  $\log k$  vs. water vapor pressure ( $p$ -scale). Two different formulations (same vitamin A raw material) are shown.

tion for this. Attempts to relate (a) the absolute temperature to the water vapor pressure in the Arrhenius equation or (b) relate the water activity to the water vapor pressure lead to equations proportionalizing  $\log k$  to  $\log p$  not  $p$ .

The more deep rooted explanations to this will be the subject of subsequent publications.

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## $\beta$ -( $\alpha$ -Phenyl- $\alpha$ -3-thenylacetoxy) Ethyldimethylsulfonium Bromide as a Potential Antispasmodic

By HEINO A. LUTS\*, W. A. ZUCCARELLO†, J. F. GRATTAN‡, and W. LEWIS NOBLES

A comparative structure-activity evaluation was made to determine the potentiality of 3-methylthiophene as a possible active isoster of an agent which has demonstrated marked antispasmodic activity.

**I**N 1953, PROTIVA and Exner (1) reported on the spasmolytic activity of the sulfonium compound, thiospasmin.

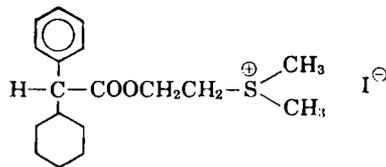
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Since that time, several structural modifications have been made. Neesby and his associates (2) in this country, utilizing the same sulfonium moiety in several model compounds, found more favorable therapeutic ratios for these derivatives. It has been suggested that a structure-activity study involving thiophene analogs should include the 3-substituted