was continued until there was no further increase in product.[14] The products were isolated by distillation through a 6-in. Vigreaux column.

Method B.—The procedure of method A was varied by use of a Vycor flask, omission of the acetone, and use of a 360-W G.E. UA-3 ultraviolet lamp for irradiation. The ester was distilled in a stirred boiling point still.[16]

Method C.—The reaction is the same as in method B, but run neat.

3-Propylthiofuran.—Dibutyl phthalate (25 ml) containing 0.05 g of 2-naphthalenesulfonic acid monohydrate was placed in a flask equipped with a thermometer, dropping funnel, and a short Vigreaux still head, attached to a receiver under slightly reduced pressure (300–400 mm). The flask was heated and stirred magnetically, while 38 g of tetrahydro-2,5-dimethoxy-3-propyl-thiofuran was added, dropwise, during a 1.5-hr period. No significant reaction was observed until a reaction temperature of 285–295° was reached. The distillate was dissolved in benzene, washed with water, and distilled through a 6-in. packed column to give 14.7 g of pale yellow oil: bp 80–82° (28 mm); $n^{25}D$ 1.4993. The nmr spectrum indicated an approximate 65:35 mixture of 3- and 2-propylthiofuran.

Anal. Calcd for $C_7H_{10}OS$: C, 59.1; H, 7.1; S, 22.5. Found: C, 59.1; H, 6.9; S, 22.6.

(16) E. S. Perry, "Technique of Organic Chemistry," Vol. IV, Interscience Publishers, Inc., New York, N. Y., 1951, p 511.

Reactions of Furyl Thioethers with Maleic Anhydride (Adducts 7 and 9).—A solution of equimolar amounts of the furyl thioether and maleic anhydride in ether was used (see Table III for conditions). The products crystallized in analytically pure form.

Phthalic Anhydrides (8).—A solution of 0.10 mol of the thioether and 0.11 mol of maleic anhydride in 150 ml of benzene containing 0.1 g oxalic acid was used (see Table III for conditions). Disappearance of the thioether was followed by vpc. The products were isolated by filtration and recrystallized from toluene–ligroin (bp 100–115°); 3-methylthiophthalic anhydride was recrystallized from 2-butanone.

# Mechanism of the Prins Reaction. Kinetics and Product Composition in Acetic Acid

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Received October 9, 1967

The Prins reaction of formaldehyde with anethole in acetic acid, to give *trans*-4-anisyl-5-methyl-1,3-dioxane and the equilibrium mixture of *erythro*- and *threo*-1-anisyl-5-methyl-1,3-diacetoxypropanes obeys the kinetic law, $-d[\text{anethole}]/dt = [\text{anethole}]\{k_1[CH_2O]/(K + [CH_2O])\}$. It is postulated that formaldehyde and anethole are in rapid equilibrium with a molecular complex (dissociation constant $K = 1.8$), which is converted in a rate-determining step (rate constant $k_1 = 24.3 \times 10^{-4}$ sec^{-1}) into an intramolecularly stabilized carbonium ion. Throughout a range of formaldehyde concentrations in which the order in formaldehyde of the rate-determining process decreases from first to zero order, the product ratio shows that the dioxane-forming process remains strictly one order in formaldehyde greater than the diacetate-forming process. The stabilized carbonium ion is therefore presumed to react stereospecifically with formaldehyde to yield the dioxane product and to open to a second carbonium ion which reacts with acetic acid and/or acetate ion to produce finally the two diacetate products.

The Prins reaction of anethole (1) with formaldehyde in refluxing acetic acid yields *trans*-4-anisyl-5-methyl-1,3-dioxane and a mixture of the *erythro* and *threo* forms of 1-anisyl-2-methyl-1,3-diacetoxypropane.[2,3]
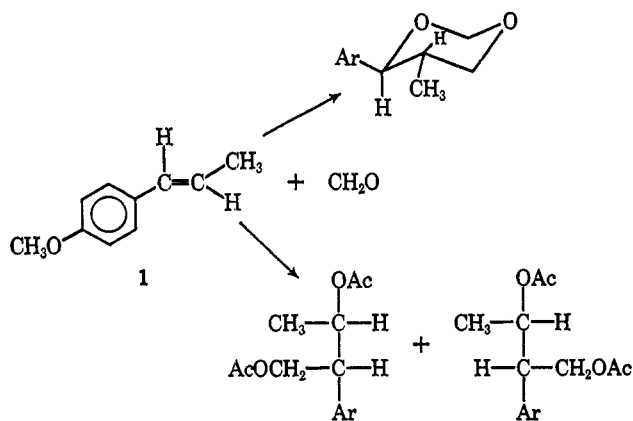
The dioxane is thus formed in a highly stereoselective process, whereas the diacetates are not.[4] This information was used by Smissman, Schnettler, and Portoghese[3] to formulate structures for some possible intermediate species in the reaction. The present paper reports studies of the kinetics and ratios of products formed in the Prins reaction in acetic acid at 125° and a mechanism consistent with the experiments.

Results

Kinetics.—The disappearance of anethole, followed spectrophotometrically at 259 mμ, is first order in anethole under conditions of excess formaldehyde (at least 40-fold in all cases) to at least 95% reaction. The first-order rate constants so obtained are given for

(1) To whom inquiries concerning this paper should be addressed.

(2) P. S. Portoghese and E. E. Smissman, *J. Org. Chem.*, **27**, 719 (1962).

(3) E. E. Smissman, R. A. Schnettler, and P. S. Portoghese, *ibid.*, **30**, 797 (1965).
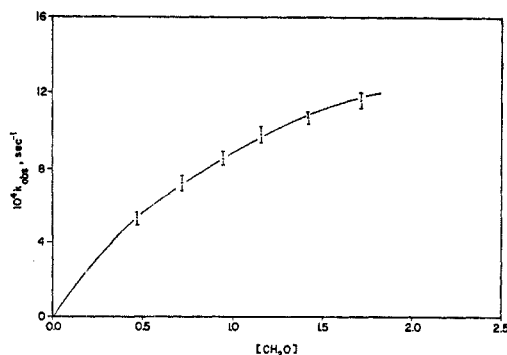
Figure 1.—Observed rate constants *vs.* formaldehyde concentration for the Prins reaction of 0.01 M anethole in acetic acid at 125°.

TABLE I
OBSERVED AND CALCULATED RATE CONSTANTS FOR THE PRINS
REACTION OF 0.01 M ANETHOLE IN ACETIC ACID AT 125°

[CH$_2$O], M	$10^4 k_{obsd}$, sec^{-1}	$10^4 k_{calcd}$,[a] sec^{-1}
0.475	5.0 ± 0.2	5.0
0.714	7.0 ± 0.3	6.9
0.952	8.5 ± 0.3	8.4
1.188	9.8 ± 0.4	9.6
1.425	10.9 ± 0.4	10.7
1.925	12.3 ± 0.5	12.5

[a] Calculated from eq 1b with $k_1 = 24.3 \times 10^{-4}$ sec^{-1} and $K = 1.8$ M. Rounded to nearest tenth.

various formaldehyde concentrations in Table I. A plot of k_{obsd} against stoichiometric formaldehyde concentration (Figure 1) shows an approximate first-order dependence on stoichiometric formaldehyde at low concentrations but falls off toward zero order in stoichiometric formaldehyde as the concentration of this reagent is increased. Such behavior is suggestive of a rate law such as eq 1a where [S]$_0$ refers to the stoichiometric concentration of anethole. The molecular significance of k_1 and K will be defined later. Ex-

$$-d[S]_0/dt = \left\{ \frac{k_1[CH_2O]}{K + [CH_2O]} \right\} [S]_0 = k_{obsd}[S]_0 \quad (1a)$$

$$k_{obsd} = k_1[CH_2O]/(K + [CH_2O]) \quad (1b)$$

traction and inversion of k_{obsd} leads to eq 2, predicting a linear dependence of $1/k_{obsd}$ on $1/[CH_2O]$. This

$$(1/k_{obsd}) = (1/k_1) + (K/k_1)(1/[CH_2O]) \quad (2)$$

dependence is demonstrated in Figure 2, from the intercept of which we find $k_1 = 24.3 \times 10^{-4}$ sec^{-1} and from the slope, $K = 1.8$ M. The solid line of Figure 1 is a plot of eq 1b, computed using these constants; calculated values of k_{obsd} are compared with experiment in Table I.

Product Ratios.—As noted above, the products of the Prins reaction under these conditions are *trans*-4-anisyl-5-methyl-1,3-dioxane and an equilibrium mixture of the *erythro* and *threo* forms of 1-anisyl-2-methyl-1,3-diacetoxypropane. The ratio of the former ("*m*-dioxane") to the latter ("diacetates") was determined by vapor phase chromatographic analysis as a function of formaldehyde concentration. The ratios, given in Table II and plotted in Figure 3, are proportional to formaldehyde concentration (eq 3).

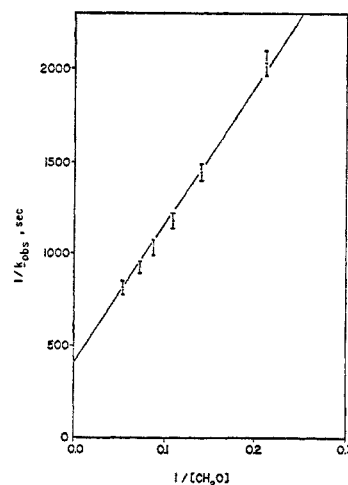$$[m\text{-dioxane}]/[\text{diacetates}] = 0.63 \, [CH_2O] \quad (3)$$

Figure 2.—Graphical test of equation 1b for the Prins reaction of 0.01 M anethole in acetic acid at 125°.
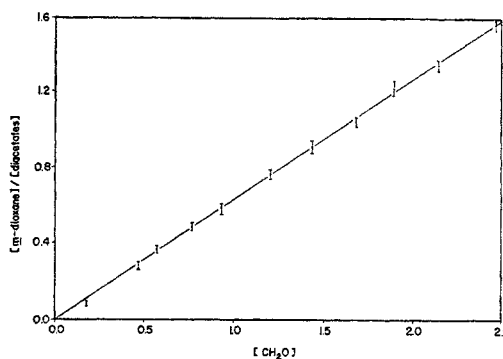

Figure 3.—Product ratio [*m*-dioxane]/[diacetates] *vs.* formaldehyde concentration for the Prins reaction of 0.01 M anethole in acetic acid at 125°.

TABLE II
PRODUCT RATIO AS A FUNCTION OF FORMALDEHYDE
CONCENTRATION IN THE PRINS REACTION OF 0.01 M ANETHOLE
IN ACETIC ACID AT 125°

[CH$_2$O], M	[*m*-dioxane]/[diacetates]
0.177	0.077 ± 0.003
0.477	0.290 ± 0.013
0.569	0.353 ± 0.015
0.761	0.460 ± 0.009
0.934	0.588 ± 0.016
1.207	0.753 ± 0.012
1.433	0.904 ± 0.070
1.673	1.036 ± 0.020
1.891	1.210 ± 0.083
2.136	1.333 ± 0.011
2.470	1.570 ± 0.030

Discussion

Kinetics and Rate-Determining Step.—A rate law of the form of eq 1 is consistent with two kinds of mechanism: (i) complexation of formaldehyde and olefin, followed by a slow reaction of the complex {at low formaldehyde, the reactants are largely in the uncomplexed form, [CH$_2$O] $\ll K$ and $k_{obsd} \approx (k_1/K)$ [CH$_2$O]; at high formaldehyde, the olefin becomes entirely complexed, [CH$_2$O] $\gg K$ and $k_{obsd} \approx k_1$}; (ii) conversion of the olefin, in a reaction not involving formaldehyde, into an activated form, which then reacts with formaldehyde (at low formaldehyde, the latter step is rate determining and the reaction ex-

SCHEME I
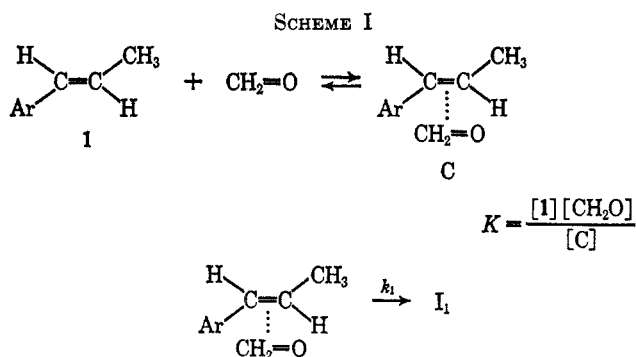
hibits a unit order in formaldehyde, while, at higher formaldehyde concentrations, its reaction with activated olefin is so rapid that activation becomes rate determining). The second possibility is difficult to formulate in reasonable chemical terms, but the first readily explains our observations. We can write the mechanism of Scheme I; we shall take up the nature of I_1 in a moment. If the rate-determining step is taken to be the k_1 step, and if the concentration of complex in terms of the stoichiometric concentration of anethole is calculated as shown (eq 4–8), we obtain the experimental rate law. Because the spectrophotometric measurements are performed at $[S]_0 < 4 \times 10^{-6} M$, it is actually $-d[S]_0/dt$ rather than $-d[1]/dt$ which is measured.

$$\frac{-d[S]_0}{dt} = k_1[C] \qquad (4)$$

$$[C] = [S]_0 - [1] \qquad (5)$$

$$[1] = K[C]/[CH_2O] \qquad (6)$$

$$[C] = [S]_0[CH_2O]/(K + [CH_2O]) \qquad (7)$$

$$-d[S]_0/dt = [S]_0 k_1[CH_2O]/(K + [CH_2O]) \qquad (8)$$

Since a product containing two formaldehyde moieties is formed throughout a formaldehyde concentration range in which the order in formaldehyde of the rate-determining process is never more than one (thus the dioxane product must obtain one of its formaldehyde units after the rate-determining step), clearly an intermediate must be formed in the rate-determining step and then be converted into the dioxane product. Furthermore the rate of this latter reaction with formaldehyde must be greater than the rate of reversion of the intermediate to the species preceding it so that intermediate formation will in fact be rate determining. Now from Figure 3, we know that the rate of diacetate formation is greater than the rate of dioxane formation at formaldehyde concentrations below 1.6 $M;$ therefore diacetate formation is also faster than reversion of the intermediate to the species preceding it. Thus it emerges that the formation of I_1 must be the rate-determining step in the reactions which lead to dioxane and diacetates both.

Intermediate Structures.—It is not generally possible to infer from kinetic data the structures of intermediate compounds. Nevertheless, the availability of some stereochemical information and the use of a reasonable degree of chemical intuition permits a few statements to be made in the present case.

Of I_1, we know it must be formed from formaldehyde and olefin, and conceivably with additional solvent

molecules as well. Furthermore we know that it eventually proceeds to a dioxane product, in which the two formaldehyde units have added *cis* to the original double bond of the olefin, and to a diacetate mixture. The differing stereochemical pathways of the two processes suggests that another intermediate I_2 intervenes. Reasonable structures for I_1 and I_2 result if we consider the k_1 step to occur as shown in eq 9.
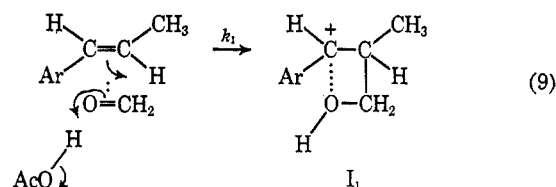

I_1 is thus visualized as an internally stabilized carbonium ion; such internal stabilization is particularly favored in media of low nucleophilicity such as acetic acid. Ion I_1 would be expected to open occasionally to the unstabilized form I_2 (eq 10). The stereochemical results
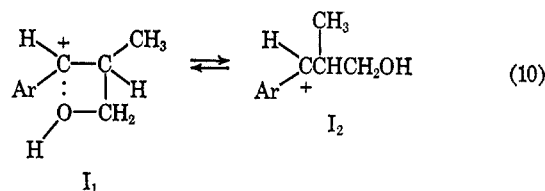
can now be explained by assuming that the stabilized ion I_1 is more selective than I_2 and reacts preferentially with the "amphoteric" nucleophile–electrophile formaldehyde *via* a transition state such as T_1. The more
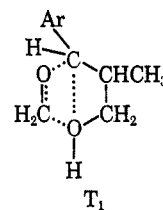

reactive ion I_2 reacts with the solvent acetic acid to yield the two diacetates (after esterification of the initially formed monoacetate). The reaction of I_1 with formaldehyde could occur with concerted loss of the hydroxyl proton to give the dioxane product immediately, or with predominant nucleophilic attack by formaldehyde to yield an ion I_3, which would then proceed to product, or possibly with prior addition of I_1 to formaldehyde (perhaps acid catalyzed by the carbonium center) to yield I_4, a structure originally suggested by Smissman, Schnettler, and Portoghese.[2]
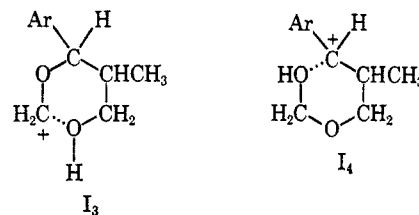
Conclusions

The kinetics, stereochemical results, and product compositions for the Prins reaction in acetic acid at 125° can be accounted for by the mechanism in Scheme II.

SCHEME II

erythro and *threo*
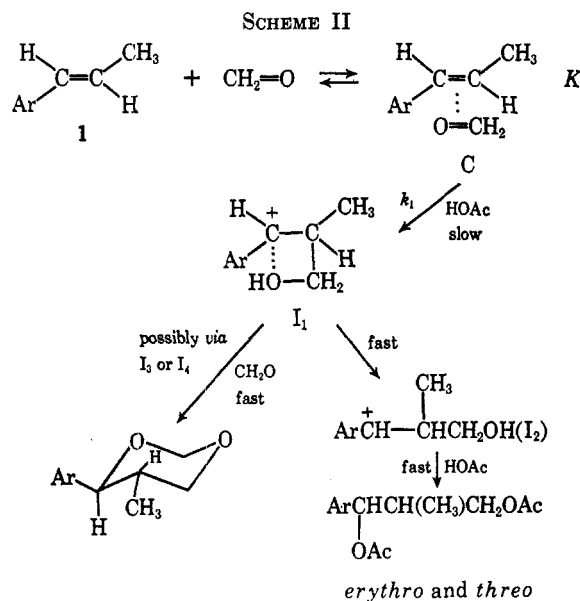
It would be desirable to obtain spectroscopic evidence for the complex C and this problem is presently under study.

Experimental Section

Materials.—Anethole (Matheson Coleman and Bell reagent) was redistilled and the fraction boiling at 52–54° (0.2 mm)[6] was used for all determinations. Glacial acetic acid (Fisher reagent) and paraformaldehyde (Matheson Coleman and Bell "95% formaldehyde") were used as received. The 95% formaldehyde assay, assumed to be correct, was confirmed by the successful extrapolation of plots of formaldehyde concentration *vs.* both observed rate constants and product ratios to zero formaldehyde concentration. Cyclohexane used for spectrophotometric determinations was Matheson Coleman and Bell Spectroquality reagent material.

Product-Ratio Studies.—Enough paraformaldehyde to make a final solution of 0.2 to 2.5 *M* in formaldehyde was carefully weighed into a 25-ml erlenmeyer flask and dissolved in hot acetic acid. To the cooled solution was added enough anethole to make a final solution of 0.01 *M* and additional solvent to bring to volume. The final solutions were added to clean Pyrex test tubes previously constricted at the neck. The tubes were sealed and kept at 125.0 ± 0.1° for approximately ten half-lives (from 1 to 10 hr depending on the formaldehyde concentration). After filtration of any precipitated paraformaldehyde and removal of acetic acid under reduced pressure (34–36°, 28 mm), the residue, diluted with ether, was filtered through magnesium sulfate, concentrated, and analyzed by gas–liquid partition chromatography.

All gas chromatography was performed on a Beckman Model GC-4 gas chromatograph equipped with a hydrogen-flame detector, using a 6-ft, $^1/_8$-in. stainless steel column packed with 3% SE-30 on 100–120 mesh Chromosorb G (acid washed and DMCS treated) and a helium flow rate of 40 cc/min. The temperature was programmed in each analysis from 135 to 235° at a rate of 10°/min. The major peaks, those of the *m*-dioxane and

(6) Boiling points are uncorrected.

the diacetates (the diacetates were not separable under the conditions used), were identified by comparing their relative retention times with those of authentic samples. Minor peaks, other than those of anethole, ether, or acetic acid, were shown to constitute no more than 5% of the combined products; some of these were shown to be thermal decomposition products of anethole formed during the reaction. No evidence of decomposition of products while on the column was observed. Relative instrument response of the products *m*-dioxane/diacetates was found to be 0.95 ± 0.05 on glpc analysis of a 1:1 mixture of the two. Peak areas computed from the formula $A = \frac{1}{2}bh$ were within experimental error of those obtained by the alternate method of weighing the individual peaks. Control experiments, together with previous results on product stability,[3] showed that equilibration of the dioxane with diacetates was not occurring within the reaction time periods studied.

Kinetic Studies.—For each run, and in a manner similar to that described for product-ratio determinations, a 25-ml solution of the appropriate quantity of paraformaldehyde and anethole in acetic acid was prepared. About 2 ml of the resulting solution was introduced into each of twelve 12 × 75 mm Pyrex test tubes with a constriction at the neck. The tubes were sealed and placed in a constant-temperature bath of 125.0 ± 0.1°. After 5 min the first tube was removed, plunged into ice water, and time recorded. At appropriate intervals (varying from 2 to 15 min) and finally after ten half-lives the remaining tubes were similarly treated. After warming to room temperature, a 20-μl aliquot of the contents of each tube was placed in a 5-ml volumetric flask and solution was brought to volume with spectral quality cyclohexane. Absorbance (*A*) at 259 mμ was measured using a Cary Model 14 spectrophotometer. Rate constants were obtained from semilogarithmic plots of fraction reaction $[(A_0 - A_t)/(A_0 - A_\infty)]$ *vs.* time. Data for a typical kinetic run are shown in Table III.

TABLE III

KINETIC DATA FOR REACTION OF 0.0105 *M* ANETHOLE WITH 0.9516 *M* FORMALDEHYDE IN ACETIC ACID AT 125.0 ± 0.1°

Time, min	Absorbance[a]	Fraction reaction
0.00	0.710	0.000
4.00	0.591	0.183
7.87	0.489	0.339
9.87	0.446	0.405
14.92	0.360	0.537
19.87	0.295	0.722
25.12	0.239	0.722
46.92	0.113	0.916
59.83	0.087	0.956
133.00	0.058	1.000

[a] Absorbance measured after 250-fold dilution.

Beer's law was demonstrated to hold throughout the anethole concentration range studied. Aliquots (20 μl) of standard solutions (1 × 10⁻⁴ to 1 × 10⁻² *M*) of anethole in acetic acid were diluted to 5 ml with cyclohexane and absorbance at 259 mμ was recorded. A plot of absorbance *vs.* concentration was perfectly linear passing through the origin.