

PYRIMIDINES

XXX.* EVALUATION OF THE REACTIVITIES OF SOME

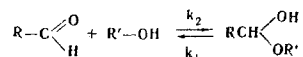
2-FORMYLPYRIMIDINES

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A comparative study was made of the addition of ethanol at the carbonyl group of some 2-formylpyrimidines and aldehydes of other series in which the carbonyl group is activated by the effect of an electron-acceptor grouping (chloral, p-nitrobenzaldehyde, and 2-formylpyridine). It is shown that 2-formylpyrimidines have high reactivities that are comparable with the reactivity of chloral.

We previously noted [2] that the carbonyl group in 2-formylpyrimidines has considerable reactivity. It seemed of interest to compare the reactivities of 2-formylpyrimidines with the reactivities of reactive aldehydes of other series. With this end in view, we studied the reaction of the aldehydes with ethanol in the absence of catalysts (Table 1). This one-step reaction is one of the simplest addition reactions at the carbonyl group. There is evidence [3,4] that in neutral media only one molecule of alcohol is added to give a hemiacetal.



Subsequent reaction of the hemiacetal with alcohol to form the acetal can be detected only in the presence of a strong acid [4].

We investigated the addition of ethanol to aldehydes by means of IR spectroscopy from the decrease in the intensity of the carbonyl absorption band.

The determination of the kinetic data for the 2-formylpyrimidines presented a number of experimental difficulties because of the ease of oxidation of the aldehydes (especially in solution) and the high sensitivity of the addition to acid catalysts.

A vibrational band at 1800 cm⁻¹ (the frequency of the vibrations of the C=O of the monomer of the acid) appears in the IR spectrum of 4,6-dimethyl-2-formylpyrimidine† in carbon tetrachloride after standing for only 0.5 h. The product was isolated in pure form and identified as 4,6-dimethylpyrimidine-2-carboxylic acid. In a comparison of the behavior of 4,6-dimethyl-2-formylpyrimidine in carbon tetrachloride, chloroform, and benzene, it was observed that oxidation proceeds most rapidly in carbon tetrachloride.

In order to reduce the possibility of the oxidation of the aldehydes to a minimum, the aldehydes were purified, the solutions were prepared under dry nitrogen, and only a freshly prepared solution of aldehyde in the appropriate solvent was used for each individual experiment.

A series of diminished absorption intensities of the carbonyl group was obtained as the reaction proceeded. The measurements were carried out until a constant, time-invariable intensity was obtained. The optical density (D) at the maximum of the analytical band was measured by the "base-line" method. The

* See [1] for communication XXIX.

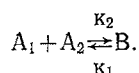
† 4,6-Dimethyl-2-formylpyrimidine was obtained via a modified method [5] which proved to be more satisfactory for this aldehyde than that in [2].

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TABLE 1. Rate Constants (k_2 and k_1) and Equilibrium Constants (K_{eq}) for the Reaction of I at 35°

Aldehyde	Solvent	Starting conc., mole/liter		K_{eq} , liter- mole ⁻¹	$k_2 \cdot 10^2$, liter- mole/sec ⁻¹	$k_1 \cdot 10^4$, sec ⁻¹
		aldehyde	alcohol			
4,6-Dimethyl-2-formyl- pyrimidine	CCl ₄	0,025	0,125	36,2	2,1	5,8
		0,025	0,125	43,6	2,2	5,0
4,6-Diphenyl-2-formyl- pyrimidine	CCl ₄	0,025	0,078	33,4	2,3	6,9
		0,025	0,078	33,0	2,6	7,9
		0,02	0,075	31,4	1,6	5,1
		0,02	0,075	30,6	1,6	5,2
Chloral	CCl ₄	0,03	0,112	198,9	1,0	0,5
		0,03	0,112	198,9	1,1	0,5
2-Formyl- pyrimidine	C ₆ H ₆	0,02	0,08	15,2	1,6	10,6
		0,02	0,08	15,2	2,1	13,8
4,6-Dimethyl-2-formyl- pyrimidine	C ₆ H ₆	0,025	0,125	14,7	2,0	13,1
		0,025	0,125	14,2	1,8	12,6
The same	CHCl ₃	0,025	0,075	6,0	0,3	5,0
		0,025	0,075	6,0	0,3	5,0
		0,025	0,125	7,0	0,2	3,0
Chloral	CHCl ₃	0,03	0,112	82,6	0,6	0,7
		0,03	0,112	74,9	0,6	0,8

aldehyde concentration at any instant was determined from the formula $c_x = c_0(D_x/D_0)$, where D_0 is the optical density of the starting aldehyde solution with a concentration of c_0 . The experimental data were treated in accordance with [6] for a second-order, reversible reaction.



The equilibrium constant (K_{eq}) was calculated from the formula

$$K_{eq} = \frac{\bar{x}}{([A_1]_0 - \bar{x})([A_2]_0 - \bar{x})},$$

where $[A_1]_0$ and $[A_2]_0$ are the initial aldehyde and ethanol concentrations, respectively, and \bar{x} is the equilibrium concentration of the hemiacetal.

The dependences of $\log(\bar{x}' - x)/(\bar{x} - x)$ on time (x is the instantaneous hemiacetal concentration and $\bar{x}' = [(K_{eq}([A_1]_0 + [A_2]_0) + 1)/K_{eq}] - \bar{x}$) are presented in Fig. 1. The experimental points all fit well on straight lines, which attests to the fact that the reactions are second-order. The second-order rate constant in each case was determined from the slope of the appropriate line. The rate constant for the reverse reaction (k_1) was calculated from the formula $k_1 = k_2/K_{eq}$. The k_1 , k_2 , and K_{eq} values for the reaction of the appropriate aldehydes with ethanol in various solvents are presented in Table 1.

The rate and equilibrium constants presented are approximate since, because of the difficult accessibility of especially pure compounds, the number of experiments in each series was small (two to three), and the effect of the reagent concentration on the rate constant was not investigated to a sufficient degree.

TABLE 2. Vibrational Frequencies of the C=O Group in Chloroform

Aldehyde	2-Formyl- pyrimidine	4,6-Dimeth- yl-2-formyl- pyrimidine	4,6-Diphenyl- 2-formyl- pyrimidine	2-Formyl- pyridine	p-Nitrobenz- aldehyde	Benz- aldehyde
ν C=O*, cm ⁻¹	1738	1732	1730	1717 †	1717 †	1705 †

*The IR spectra were obtained with a UR-20 spectrometer for solution concentrations of 1% and a layer thickness of 0.4 mm. (The accuracy of the measurements was ± 1 cm⁻¹.)

† These values are from [11].

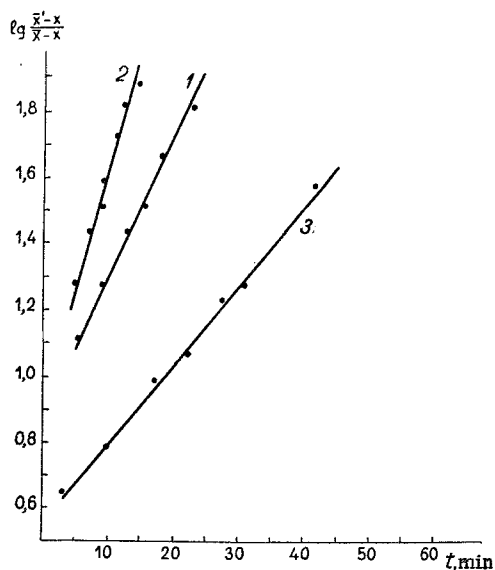


Fig. 1. Dependence of $\log [(\bar{x}' - x) / (\bar{x} - x)]$ on the time required for the addition of ethanol in carbon tetrachloride at 35°: 1) to 4,6-diphenyl-2-formylpyrimidine; 2) to 4,6-dimethyl-2-formylpyrimidine; 3) to chloral.

the carbonyl group with the aromatic ring, which stabilizes the aldehyde molecule in comparison with the hemiacetal, predominates over the inductive effect of the electron-acceptor grouping, which destabilizes the aldehyde in comparison with the hemiacetal [8]. For simple addition reactions at the carbonyl group, a high rate of conversion corresponds to a more complete conversion, and vice versa [9]. All of these results are evidence that the effect of the pyrimidine ring on the aldehyde C=O group results in considerable activation of the latter.

It is known that the frequency of the valence vibrations of the C=O bond in the IR spectra of carbonyl compounds decreases (a decrease in the double-bond character) with an increase in the electron-donor capacity of the group bonded to the carbonyl group. In this connection, it is interesting to compare the frequencies of the C=O vibrations for the aldehydes under consideration. As seen from Table 2, $\nu_{C=O}$ decreases in the order 2-formylpyrimidine > 4,6-diphenyl-2-formylpyrimidine > 4,6-dimethyl-2-formylpyrimidine > 2-formylpyridine, p-nitrobenzaldehyde > benzaldehyde. It is apparent that the electron-acceptor effect of the grouping bonded to the carbonyl group decreases in the same order. Thus, the data on the vibrational frequencies of the C=O bond indicate that the pyrimidine ring in the ground state has increased electron-acceptor capacity; this is in agreement with data on the reactivities of 2-formylpyrimidines.

EXPERIMENTAL

Analytical grade carbon tetrachloride was dried over freshly calcined potassium carbonate and distilled. The chloroform was freed from alcohol by washing with water and was then dried over calcium chloride for 24 h (chloroform decomposes when it is allowed to stand over the drying agent for many days) and distilled over calcined potassium carbonate. The benzene was dried with calcium chloride and distilled over sodium metal.

Chloral was obtained by dehydration of chloral hydrate; chloral hydrate was shaken in a separatory funnel with concentrated H_2SO_4 with several changes of acid. The chloral was then separated and distilled in the presence of a small amount of H_2SO_4 under nitrogen, with collection of the fraction with bp 97-97.5°, which was again distilled over freshly calcined calcium oxide.

4,6-Dimethyl-2-formylpyrimidine (I). A. Preparation of 2-(1,3-diphenyl-2-imidazolidinyl)-4,6-dimethylpyrimidine (Ia). A solution of 2 g (0.016 mole) of 2-cyano-4,6-dimethylpyrimidine in 50 ml of methanol was hydrogenated at room temperature in the presence of 3.4 g (0.016 mole) of dianilinoethane, 1.6 ml of glacial acetic acid, and 6.2 g of Raney nickel until 360 ml of hydrogen had been absorbed. The

The rate and equilibrium constants for the addition of alcohol to 2-formylpyrimidines and to such reactive aldehydes as chloral have a significance of one order of magnitude.

The introduction of an electron-donor methyl group into the 2-formylpyrimidine molecule does not have an appreciable effect on the reaction rate (k_2 for unsubstituted 2-formylpyrimidine and 4,6-dimethyl-2-formylpyrimidine in benzene are identical). The decrease in k_2 (for example, for 4,6-dimethyl-2-formylpyrimidine) in chloroform as compared with carbon tetrachloride can probably be explained by the inhibiting effect of the polarity of the medium on the addition at the carbonyl group (reinforcement of the nonspecific solvating action of the solvent on the carbonyl group) [7].

In addition to the aldehydes indicated in Table 1, we also investigated the reaction with alcohol of such aldehydes as p-nitrobenzaldehyde and 2-formylpyridine. It was found that these aldehydes did not react with ethanol (the intensity of the band of the C=O group of these aldehydes did not change with time) even when the aldehyde-alcohol ratio in carbon tetrachloride was 1:10. This is evidence that, in this case, the effect of conjugation of the

catalyst was filtered off and washed with ethyl acetate. The filtrate was evaporated to one third its original volume, and the resulting precipitate was filtered and dried to give 2.3 g (45%) of Ia with mp 146-148° (from ethyl acetate). Found %: C 75.85; H 6.50; N 17.11. $C_{21}H_{22}N_4$. Calculated %: C 76.33; H 6.67; N 16.98.

B. Decomposition of Ia. A solution of 2 g of Ia in 50 ml of chloroform was stirred for 5-10 min with 30 ml of 18% HCl. The initial green-yellow coloration vanished as dianilinoethane dihydrochloride precipitated. The precipitate was filtered and washed with chloroform, and the filtrate was neutralized with sodium bicarbonate. The chloroform layer was separated, and the aqueous layer was extracted with chloroform. The combined chloroform solutions were dried with $MgSO_4$, the solvent was evaporated, and the residue was recrystallized from petroleum ether (40-60°) to give 0.5 g (66%) of I with mp 89-90° (identical to the product obtained in [2]). A sample for the kinetic measurements was recrystallized twice from dry petroleum ether (40-60°) and vacuum-sublimed at 70° (15 mm).

2-Formylpyrimidine and 4,6-Diphenyl-2-formylpyrimidine. These were obtained by the method in [2].

2-Formylpyridine. This was similarly obtained [2] from 10 g (0.073 mole) of methyl picolinate and 1.73 g (0.036 mole) of lithium aluminum hydride. The yield of product with mp 76-78° (25 mm) (bp 181° [12]) was 4 g (50%).

p-Nitrobenzaldehyde. Pure grade p-nitrobenzaldehyde was recrystallized from petroleum ether (70-100°) to give material with mp 104-105°.

All of the aldehydes were stored in the dark under nitrogen over P_2O_5 at 5°. Immediately prior to use they were subjected to repurification. The purity of the aldehydes was monitored by comparison of their IR spectra with the spectra of analytical samples.

The kinetic measurements* were made with a UR-10 spectrophotometer in thermostated cuvettes made of KRS-5 with an absorbing-layer thickness of 1 mm. The measurements were made from the absorption band of the carbonyl group of the corresponding aldehyde.

The aldehyde solutions were prepared in a dry box filled with nitrogen. A freshly prepared aldehyde solution was used for each individual experiment. An aliquot of the aldehyde solution in the appropriate solvent was introduced into a reaction vessel equipped with a jacket for thermostating, and the vessel was sealed with a stopper and transferred out of the dry box. An aliquot of an alcohol solution in the same solvent was introduced into a second vessel with thermostating. Both solutions were thermostated at the reaction temperature, and they were then mixed (the zero time of the reaction) by means of rapid connection of the ground-glass joints of both reaction vessels. The reaction mixture was stirred thoroughly and transferred through a polyethylene capillary into a cuvette (one of the vessels had a glass capillary outlet). All of these operations were performed without allowing contact with the atmosphere. The reaction of the aldehyde with ethanol occurred directly in the cuvette.

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