on 0.9–2.4 (ca. 27 H), 2.63 (s, 1 H), 5.35–5.45 (ca. 1 H) superimposed on 5.0–5.6 (ca. 1 H).

Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80. Found: C, 75.97; H, 8.80.

Registry No.—**2** isomer A, 57346-08-4; **2** isomer B, 57346-09-5; **4**, 57346-10-8; **5**, 57346-11-9; **6a**, 57346-12-0; **6b**, 57346-13-1; **7a**, 57346-14-2; **7b**, 57346-15-3; **7c**, 57346-16-4; **7d** ½MeOH, 57346-18-6; **8**, 57346-19-7; **9a**, 57346-20-0; **9b**, 57346-21-1; **10a**, 57378-55-9; **10b**, 57346-22-2; **10c**, 57346-23-3; **10c** ½MeOH, 57427-66-4; **10d**, 17253-49-5; **11a**, 57362-17-1; **11b**, 57346-24-4; **11c**, 23163-43-1; **11d**, 23163-53-3; 2-bromo-3-dimethylaminopropene, 14326-14-8; 6-methoxytetralone, 1078-19-9; 2-ethylcyclopentane-1,3-dione, 823-36-9; 2-methylcyclopentane-1,3-dione, 765-69-5; (±)-13-ethyl-3-methoxy-11β-methylgona-2,5(10)-dien-17β-ol, 57346-25-5; (±)-13-ethyl-3-methoxy-11β-methylgona-2,5(10)-dien-17-one, 57346-26-6; (±)-13-ethyl-3-methoxy-11β-methyl-17-hydroxy-18,19-dinor-17α-pregna-2,5(10)-dien-20-yne, 53762-18-2.

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Claisen Rearrangement with Hydroxymethylpyridines and Hydroxymethylpyridones

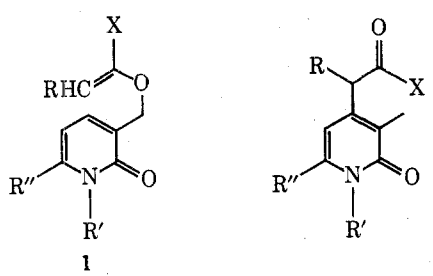
C. Richard Costin, Cary J. Morrow, and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

Received August 19, 1975

The Claisen rearrangement has been applied to 2-, 3-, and 4-hydroxymethylpyridines, using triethyl orthoacetate to generate the intermediate ketene acetals. In all three cases, the major products resulted from normal rearrangement, with the 3-hydroxymethylpyridine being the most reactive. Similar results were obtained using amide acetals in place of ortho esters. 3-Hydroxymethyl-1-methyl-2-pyridone took a different course in reaction with orthoesters, giving only thermal rearrangement to the corresponding propionates. This reaction path became minor with amide acetals and acid catalysis, normal Claisen rearrangement predominating. These rearrangements proceed more readily than with benzyl alcohols and are synthetically useful.

In the course of work directed toward the total synthesis of camptothecin, we were led to examine the Claisen rearrangement of substituted vinyl ethers prepared from 3-hydroxymethyl-2-pyridone systems, **1**. As the products of



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this reaction were found to be strongly dependent on the nature of R and X as well as on the presence or absence of acid catalysts, we decided to examine in some detail the general question of Claisen rearrangement in systems where the allylic double bond of the allyl vinyl ether is contained in a heterocyclic aromatic ring. In the extension of the Claisen rearrangement reported here, the allylic double bond is contained in a pyridine or pyridone nucleus. The method provides a convenient synthesis of alkyl-substituted pyridylacetates which are otherwise available by a rather tedious route.[1]

The Claisen rearrangement has been the subject of considerable research over six decades and has proved to be a highly versatile method in synthesis.[2] Most of this early work was concerned with the rearrangement of allyl phenyl ethers, and to date only a few, mostly unsuccessful, attempts have been made to extend the Claisen rearrangement to systems which have the allylic double bond incorporated in an aromatic ring. For example, benzyl vinyl ether was found[3] to rearrange to 3-phenylpropanal rather than *o*-tolylacetaldehyde. Similarly, α-benzyloxystyrene rearranges thermally to give β-phenylpropiophenone.[4] More recently, 5-benzyloxy-1,3-dimethyluracil was reported[5] not to undergo the Claisen rearrangement but to partially rearrange to 6-benzyl-1,3-dimethyl-5-hydroxyuracil. It is clear from these results that the thermal rearrangement of benzyl vinyl ethers does not proceed by a Claisen pathway, but may follow a free-radical scission–recombination mechanism[3] similar to that established for the thermal rearrangement of benzyl phenyl ether.[6]

Modification of the aromatic ring by substitution with electron-donating groups promotes the Claisen rearrangement. The thermal rearrangement of 3,5-dimethoxybenzyl isopropenyl ether provides 2,4-dimethoxy-6-methylphenylacetone and a minor amount of 3,5-dimethoxybenzylacetone.[7] Similarly, 3-methoxybenzyl isopropenyl ether gave a 1:1 mixture of the two corresponding ketones.[7]

In addition to the aromatic substituent effect, variations in the vinyl moiety also influence the course of the reaction. Whereas benzyl vinyl ether failed to give any Claisen product, the thermal rearrangement of benzyldiethyl orthoace-

Table I
Claisen Rearrangement of 3-Hydroxymethylpyridine and Triethyl Orthoacetate

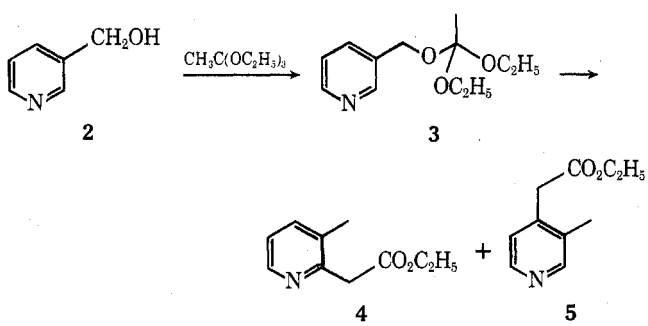
1, mol	$CH_3C(OEt)_3$, mol	Acid catalyst, mol %	Solvent	Reaction time, hr, temp, °C	Yield,[a] %	Ratio 4:5
1	8	$CH_3CH_2CO_2H$, 1		20, 190	42	61:39
1	8	$CH_3CH_2CO_2H$, 110		3, 195	48[c]	56:44
1	8	TsOH, 1		3, 190[b]	20	50:50
1	8	$CH_3CH_2CO_2H$, 1	*o*-Dichlorobenzene	48, 180	32	57:43

[a] All yields were determined by GC using hexadecane as internal standard, unless noted otherwise. [b] Continued heating at 190° (15 hr) caused extensive tar formation. [c] Isolated yield.

tate gave a low yield of ethyl *o*-tolylacetate.[8] Similarly, treatment of dibenzyl bromoacetal with potassium *tert*-butoxide proceeded via a ketene acetal intermediate to give benzyl *o*-tolylacetate.[8] A more dramatic effect has been noted in the thermolysis of an α-aminovinyl benzyl ether.[9] This reagent, prepared in situ by the use of the acetal of *N,N*-dimethylacetamide and benzyl alcohol, was rearranged to give *N,N*-dimethyl-*o*-tolylacetamide.

Results

Examination of rearrangement in the pyridine series was begun with treatment of 3-hydroxymethylpyridine (**2**) with triethyl orthoacetate and a catalytic amount of propionic acid under the conditions (140°, 15 hr) recently described.[10] These conditions failed to give Claisen rearrangement products but instead gave **3** resulting from 3-hydroxymethylpyridine exchange with the orthoacetate. Under similar conditions, benzyl alcohol reacts in the same manner giving benzyldiethyl orthoacetate. However, it has been reported[8] that at 200° benzyldiethyl orthoacetate rearranges to give a low yield of ethyl *o*-tolylacetate. Similar observations have been noted for the reaction of simple allylic alcohols and triethyl orthoacetate.[11] These reports suggest that higher temperatures might be necessary to effect the Claisen rearrangement in the pyridine series, and therefore a mixture of **2**, triethyl orthoacetate, and propionic acid was heated at 195°. A 48% yield of **4** and **5** in a ratio of 56:44 was obtained. Several additional reactions

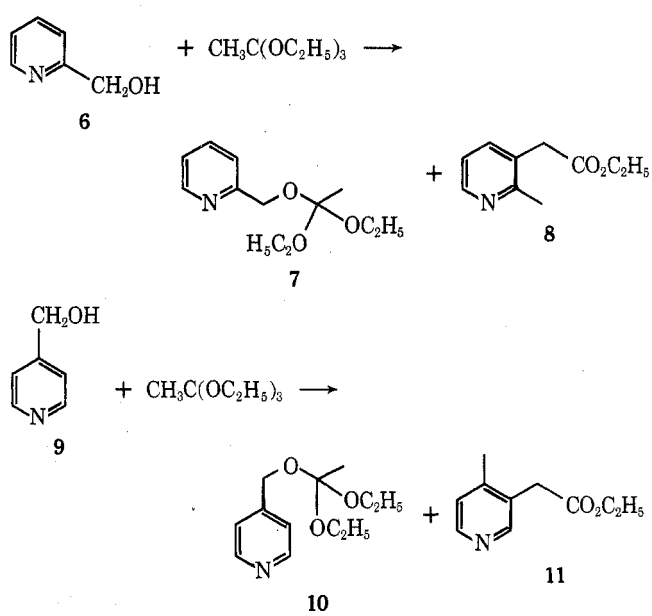


were conducted in an effort to increase the yield of **4** and **5**. The results are shown in Table I.

In each reaction the desired products, **4** and **5**, were accompanied by several minor products, whose identity has not been established. It was determined, however, that ethyl β-(3-pyridyl)propionate, an expected by-product resulting from 1,4 rearrangement, was not formed.

As shown in Table I, varying the amount of propionic acid (1 to 110 mol %) had no noticeable effect on the ratio or yield of **4** and **5**. However, when an excess of propionic acid was employed an additional unidentified by-product was formed. From these data we conclude that the preferred procedure for effecting the Claisen rearrangement in the 3-pyridyl system is heating **2** in triethyl orthoacetate containing 1 mol % of propionic acid at 195°.

Under these conditions 2- and 4-hydroxymethylpyridine also gave rise to rearranged products, but the reactivity was distinctly lower than in the 3-hydroxymethylpyridine case. Thus treatment of 2-hydroxymethylpyridine (**6**) with 8 mol of triethyl orthoacetate containing 1 mol % of propionic acid at 190° for 18 hr yielded, as the major products, the mixed ortho ester **7** (28%) and the pyridylacetate **8** (29%). Similar treatment of 4-hydroxymethylpyridine (**9**) afforded ortho ester **10** and pyridylacetate **11** in 62 and 22% yield, respectively.



As previously noted,[9] the amide acetal reagent has proved superior to ortho esters for effecting Claisen rearrangement in benzylic systems. Applying this method to 3-hydroxymethylpyridine, however, gave results comparable to those observed when the ortho ester method was employed. Treatment of 3-hydroxymethylpyridine (**2**) with a mixture of *N,N*-dimethylacetamide diethyl acetal (**12**) and 1-ethoxy-1-dimethylaminoethylene (**13**) in refluxing *o*-dichlorobenzene for 18 hr afforded a 44% yield of **14** and **15** in a ratio of 65:35.

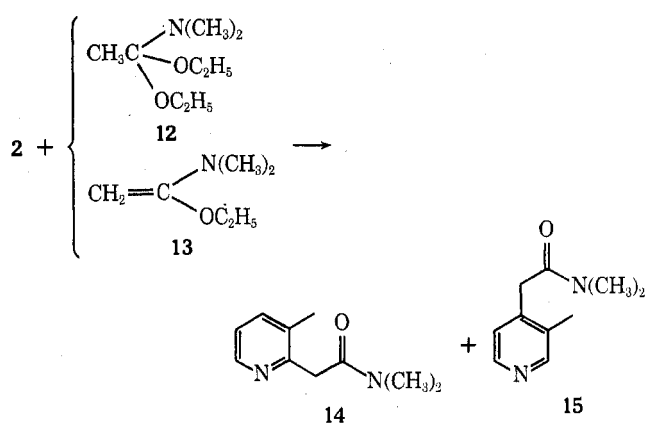
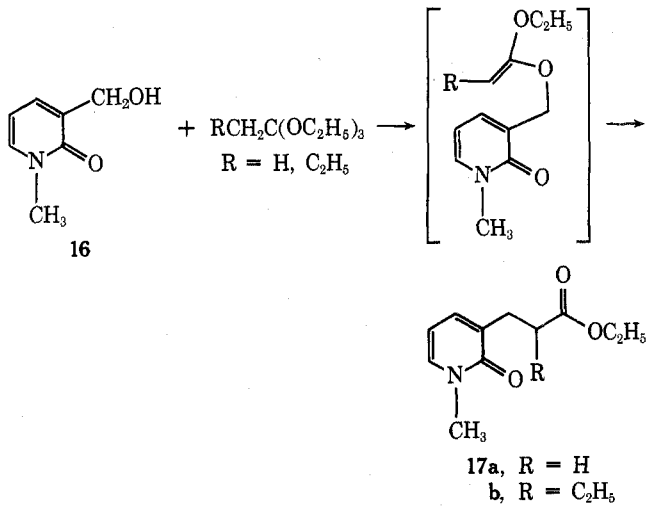


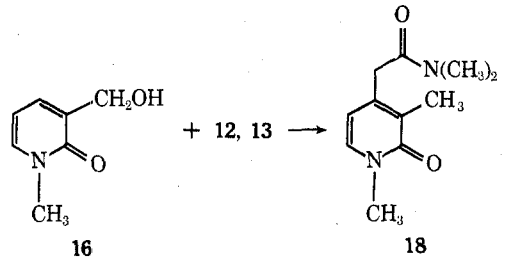
Table II
Claisen Rearrangement of 3-Hydroxymethyl-1-methyl-2-pyridone (16) with *N,N*-Dimethylbutyramide Diethyl Acetal (19)

Expt	16, mmol	19, mmol[a]	Solvent,[b] ml	Temp, °C	Time, hr	H^+ catalyst[c]	Ratio 20:21	Remarks
1	3.0	4.5	DCB, 6	Reflux ~183	42		36:64	
2	1.0	6.0		145–150	17.5	6 mol %	62.5:37.5	Loss of peaks at 5 and 6.5 min first observed
3	2.0	3.0	DCB, 6	130 160	19 24		38:62	Added 12, 13 in 2 ml of DCB at 130°
4	1.0	6.0		RT[f] Reflux	20 3	6.7 mol %	75:25	Predicted[e] ratio 80:20 at beginning of reflux
5	0.5	3.0	DCB, 3	Reflux ~183	20		41:59	
6	0.5	3.0	DCB, 3	140–150	24	2.5 μl 6.7 mol %	86:14[d]	Predicted[e] ratio 79:21 at 18.5 hr
7	0.5	3.0		RT	768	2.5 μl 6.7 mol %	88:12	

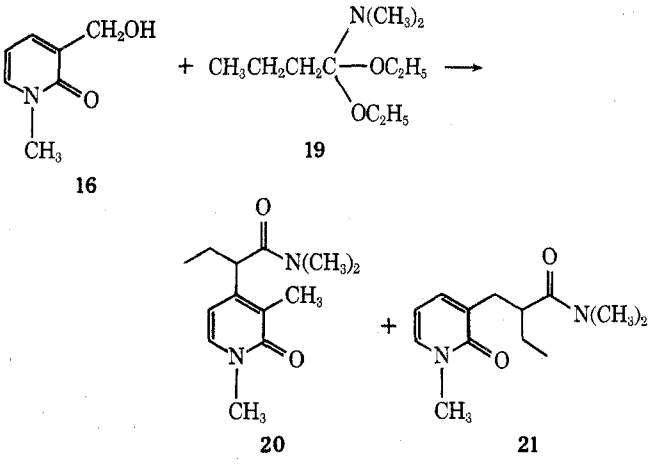
[a] Reported as if all 19. [b] DCB = *o*-dichlorobenzene. [c] Propionic acid was used in all reactions for which a catalyst is reported. [d] Failed to go to completion (~90% complete). [e] Prediction based on GC ratio of 22 to 23. [f] Room temperature.

Not surprisingly, the reaction of 3-hydroxymethyl-1-methyl-2-pyridone (16) with ortho esters and amide acetals gave results quite different from those just described for reactions of pyridinemethanols. Treatment of 16 with triethyl orthoacetate under the conditions described in the literature[10] (propionic acid catalyst, 140°) failed to give any product arising from Claisen rearrangement. Instead, the only stable product was found to be ethyl 1-methyl-2(1*H*)-oxo-3-pyridinepropionate (17a). When the reaction was repeated using 16 and triethyl orthobutyrate the product formed was ethyl α-ethyl-β-[1-methyl-2(1*H*)oxo-3-pyridine]propionate (17b). In view of these results, we again tried to capitalize on the reported[9] reactivity of amide acetals with benzyl alcohol to give Claisen rearranged products. Treatment of 16 with the acetamide diethyl acetal mixture 12, 13 under the conditions described indeed did provide the desired Claisen rearranged product 18 in 82% yield. No amide product analogous to 17 was obtained.





The successful application of this method to 16 encouraged additional experiments in this area. In an analogous reaction, 16 was treated with *N,N*-dimethylbutyramide diethyl acetal (19). In this case, however, a mixture of amides 20 and 21 was obtained in a ratio of 36:64, respectively (Table II, expt 1). From these experiments it is apparent that the products of such a reaction are strongly influenced by substitution on the amide acetal.



As our interest lay in the formation of Claisen rearranged product 20, further experiments were directed toward changing the 20:21 ratio in favor of 20. When the reaction was carried out in excess butyramide acetal with 6 mol % of propionic acid a reversal of the product distribution was observed giving 20 and 21 in a ratio of 63:37 (Table II, expt 2). The cause of this sudden change in the product ratio was not obvious as several factors had been changed from the initial experiment. To further determine which variables affect the product ratio a series of reactions was performed with systematic variation of the solvent, ratio of reactants, temperature, and presence of acid catalyst. The results are summarized in Table II, expt 3–7.

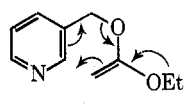
These results clearly show that the single factor most strongly favoring the formation of 20 is the presence of the acid catalyst (expt 2, 4, 6, 7). Variations in temperature influenced only the ratio of products but not the yield, while the presence of a solvent and the reactant ratios appear to have a minimal effect on the product ratio.

The explanation for this unexpected acid influence on the course of the reaction is not known. However, it appears that the formation of 20 and 21 occurs via two distinct intermediates, 22 and 23, respectively, clearly distin-

guishable by GC. The interchange between these intermediates appears slow, while their formation from starting material seems rapid. By assuming that the larger peak at 6.5-min retention time is a precursor **22** of **20** and the smaller peak at 5-min retention time is a precursor **23** of **21**, in the acid-catalyzed reactions one can predict with reasonable accuracy the final ratio of **20:21** several hours before the reaction is complete. Examples of these predictions are given under "Remarks" in expt 4 and 6, Table II. In expt 2, 6, and 7 the predicted fraction of **20** was low indicating that extended reaction times favored this product. This may be ascribed to a slow conversion of **23** to **22**, a suggestion supported by the high ratio **20:21** found in expt 7.

Discussion

The mechanism of the Claisen rearrangement of benzyl vinyl ethers has not been clearly established; however, it appears that electron enrichment of the aromatic ring promotes the rearrangement of benzyl isopropenyl ether.[7] It is interesting that the pyridyl systems undergo rearrangement more readily than the corresponding benzylic compounds, since the π-electron density of pyridine is less than that of benzene. Perhaps one explanation is that the more electron-deficient pyridine ring promotes migration of the electron-rich ketene acetal moiety, facilitating the rearrangement as shown in **24**.



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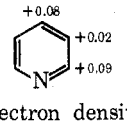
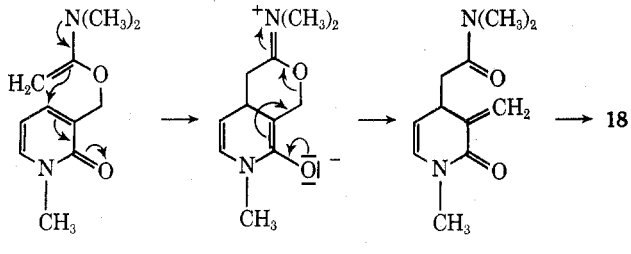


π-electron densities

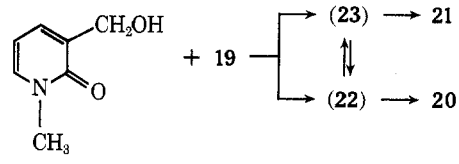
In addition this hypothesis helps explain the fact that the rearrangement is more facile in the 3-pyridyl system than in the 2- and 4-pyridyl systems. Molecular orbital calculations[12] show that the π-electron density at positions 2 and 4 of the pyridine ring is less than at position 3; therefore, migration of the electron-rich ketene acetal moiety to the 2 and 4 positions would be comparatively more favorable.

Another observation difficult to explain is the apparent 1,4 rearrangement of the ketene acetals formed from **16** and ortho esters. This is no doubt an example of the well-known thermal rearrangement of enol ethers to carbonyl compounds.[2a] Unfortunately the mechanism of this reaction is poorly understood and there is evidence for both radical and nonradical routes. The purely thermal reactions studied have been found second order in the enol ether, but none of these studies have provided a truly appropriate analogy for the present case.

Without some explanation for the formation of the 1,4-rearranged products found in the ortho ester reactions of **16**, it can certainly not be clearly determined why the amide acetal reactions with **16** lead to formation of Claisen products. One suggestion[9] is that the resonance stabilization of the carbonyl function by the dimethylamino group helps to favor product formation. Another possibility is that the enamine intermediate is providing a source of electrons and thereby promoting the rearrangement. In this regard, the observed rearrangement may be considered as Michael addition of an enamine to an α,β-unsaturated amide followed in a second step by cleavage of the weakened ether bond. The first step would be facilitated by the presence of an acid to protonate the pyridone. The inability of a ketene acetal of **16** to undergo this Michael addition step would preclude the formation of Claisen rearranged products in these cases but does not explain why the 1,4 rearrangement occurs.

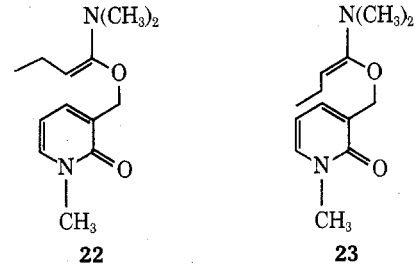


Either this mechanism or a true Claisen rearrangement is consistent with the assumption that the two peaks observed in the reaction of **16** with butyramide acetal may correspond to intermediates **22** and **23** leading to products **20** and **21**, respectively. The data suggest that the initially detected concentrations of **22** and **23** constitute a kinetically controlled distribution of the two products. As the reaction continues, the mixture of **22** and **23** slowly approaches the equilibrium concentration in which **22** is the thermodynamically stable product. Simultaneously with this interchange, **22** and **23** are being converted to **20** and **21** respectively at approximately equal rates. If product formation is more temperature dependent than the **22** $\rightleftarrows$ **23** equilibrium, the proportion of **23** converted to the more stable **22**, and hence to **20**, is increased at lower temperature, as is observed.



16

If one assumes that **22** and **23** are the trans and cis isomers of the ketene azacetal, their going to **20** and **21**, respectively, can be rationalized with molecular models



22 **23**

strictly on the basis of steric interactions in the transition state postulated for the Claisen rearrangement or the Michael addition. The trans isomer as **22** can assume either required conformation more readily than can **23** as the cis isomer. On the other hand, the cis isomer can more readily enter a bimolecular reaction in the alkenyl portion of the side chain. This is an observation of possible significance as in one case of thermal 1,4 rearrangement, product and kinetic evidence has been presented for a bimolecular reaction.[2a,13] The only data thus far presented for the relative rates of reaction of cis and trans isomers in the Claisen rearrangement are for γ-methylallyl phenyl ether, γ-phenylallyl phenyl ether, and substituted versions thereof. In every case, the data showed the trans isomer to rearrange 1.5–2 times as fast as the cis.[14]

Experimental Section[15]

Diethyl(3-pyridylmethyl) Orthoacetate (3). Procedure A. A solution of 3-hydroxymethylpyridine[16] (**2**, 316.5 mg, 2.9 mmol), triethyl orthoacetate (3.8 g, 23.5 mmol), and propionic acid (1.5 mg, 0.02 mmol) was heated at 140° in a N_2 atmosphere while ethanol was continuously removed by distillation. GC analysis [5% Chromosorb W (CW) 20M, 145°, flow rate 160 ml/min] of aliquots

taken at 3-, 6-, and 15-hr intervals were essentially identical, showing one major and three minor peaks with retention times (min) of 3.52, 2.16, 4.44, and 5.20, respectively. Compound 3.52 was isolated by preparative GC (5% CW 20M, 145°) and identified as diethyl(3-pyridylmethyl) orthoacetate (3): NMR (CCl_4) δ 1.17 (6 H, t, J = 7 Hz), 1.45 (3 H, s), 3.54 (4 H, q, J = 7 Hz), 4.59 (2 H, broad d), 7.14 (1 H, m), 7.59 (1 H, m), and 8.40 (2 H, m).

Compound 5.20 had an identical retention time with that of 3-hydroxymethylpyridine. This product was not present in the reaction mixture as determined by NMR, and was apparently formed during GC analysis. The identity of the other minor components, 2.16 and 4.44, was not established.

Ethyl 3-Methyl-2-pyridylacetate (4) and Ethyl 3-Methyl-4-pyridylacetate (5). A solution of 3.46 g (31.6 mmol) of 3-hydroxymethylpyridine, 41 g (252 mmol) of triethyl orthoacetate, and 2.58 g (35.0 mmol) of propionic acid was heated at 195° for 5.5 hr under conditions for distillative removal of ethanol in a nitrogen atmosphere. The reaction mixture was chromatographed on Woelm neutral alumina (activity III). Elution with petroleum ether removed several non-pyridine-containing products. Further elution with petroleum ether–ether (1:1) gave 3.03 g (54%) of a mixture of products. GC analysis (5% CW 20M, 145°, flow rate 160 ml/min) showed the mixture to be primarily two components with retention times (min) of 2.94 and 4.20 in a ratio of 56:44, respectively. The products were isolated by preparative gc (10% QF-1, 150°).

Compound 2.94 was assigned the structure **4:** ir (CCl_4) 1746, 1478, 1178, and 1025 cm^{-1}; NMR (CCl_4) δ 1.25 (3 H, t, J = 7 Hz), 2.29 (3 H, s), 3.74 (2 H, s), 4.12 (2 H, q, J = 7 Hz), 7.00 (1 H, m), 7.39 (1 H, m), and 8.29 (1 H, broad d); mass spectrum (70 eV) m/e (rel intensity) 179 (58), 134 (43), 133 (51), 107 (70), 106 (100), 92 (21), 79 (30), 77 (22), 65 (27), 39 (39), 29 (55).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3; N, 7.8. Found: C, 66.8; H, 7.2; N, 7.8.

Compound 4.20 was identified as **5:** ir (CCl_4) 1746, 1587, 1198, and 1039 cm^{-1}; NMR (CCl_4) δ 1.23 (3 H, t, J = 7 Hz), 2.28 (3 H, s), 3.50 (2 H, s), 4.10 (2 H, q, J = 7 Hz), 7.01 (1 H, d, J = 5 Hz), and 8.29 (2 H, m); mass spectrum (70 eV) m/e (rel intensity) 179 (79), 134 (30), 133 (30), 107 (45), 106 (100), 105 (52), 79 (22), 77 (28).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3; N, 7.8. Found: C, 66.8; H, 7.3; N, 7.9.

The identity of a minor component (ca. 6%) with a retention time of 2.60 min was not established.

Variations of the Claisen Rearrangement of Diethyl(3-pyridylmethyl) Orthoacetate. The following experiments were conducted using hexadecane as internal standard. The molar response factor for hexadecane was determined to be 0.54.

A. Catalytic Amount of Propionic Acid. A solution of 309.5 mg (2.84 mmol) of 3-hydroxymethylpyridine (**2**), 3.7 g (23 mmol) of triethyl orthoacetate, 2.3 mg (0.03 mmol) of propionic acid, and 70.7 mg (0.31 mmol) of hexadecane (internal standard) was heated at 190° in a nitrogen atmosphere while ethanol was continuously removed by distillation. Gc analysis (5% CW 20M, 145°, flow rate 160 ml/min) of the reaction mixture at 2-, 4-, and 20-hr intervals showed a mixture of **4** and **5** in a combined yield of 20, 31, and 42%, respectively.

B. Catalytic Amount of *p*-Toluenesulfonic Acid. A mixture of 218 mg (2.0 mmol) of 3-hydroxymethylpyridine (**2**), 2.5 g (15.5 mmol) of triethyl orthoacetate, 5.5 mg of *p*-toluenesulfonic acid, and 50.3 mg (0.22 mmol) of hexadecane (internal standard) was treated as in A. After 3 hr, GC analysis indicated that the yield of **4** and **5** was 20%. Continued heating at 190° (ca. 15 hr) results in considerable tar formation without any major improvement in yield.

C. *o*-Dichlorobenzene as Solvent. A mixture of 219.6 mg (2.01 mmol) of 3-hydroxymethylpyridine (**2**), 2.6 g (16 mmol) of triethyl orthoacetate, 1.5 mg (0.02 mmol) of propionic acid, and 49.2 mg (0.22 mmol) of hexadecane (internal standard) in 3 ml of *o*-dichlorobenzene was heated at reflux (bath temperature 185°) in a nitrogen atmosphere for 48 hr. GC analysis showed a 32% yield of **4** and **5** in a 57:47 ratio.

Ethyl 2-Methyl-3-pyridylacetate (8). A solution of 1.60 g (14.7 mmol) of 2-hydroxymethylpyridine (**6**),[17,18] 19.0 g (117 mmol) of triethyl orthoacetate, and 10.9 mg (0.15 mmol) of propionic acid was heated at 190° for 18 hr in a nitrogen atmosphere, while ethanol was continuously removed by distillation. Chromatography of the reaction mixture on Woelm neutral alumina (activity III), eluting with petroleum ether–ether (1:1), gave two major fractions. The faster moving fraction (0.94 g, 28%) was assigned the structure of the ortho ester **7:** NMR (CCl_4) δ 1.19 (6 H, t, J = 6 Hz), 1.53 (3 H, s), 3.59 (4 H, q, J = 6 Hz), 4.73 (2 H, d), 7.21 (1 H, m), 7.48 (2 H, m), and 8.43 (1 H, m).

GC analysis (5% CW 20M, 125°, flow rate 160 ml/min) of the other fraction (0.76 g, 29%) showed only one peak with a retention time (min) of 4.48. This product was isolated by preparative GC (5% QF-1, 150°) and identified as the pyridylacetate **8:** ir (CCl_4) 3071, 1746, 1436, 1359, 1323, 1140, and 1020 cm^{-1}; NMR (CCl_4) δ 1.21 (3 H, t, J = 6 Hz), 2.51 (3 H, s), 3.53 (2 H, s), 4.12 (2 H, q, J = 6 Hz), 7.00 (1 H, m), 7.40 (1 H, m), and 8.31 (1 H, m); mass spectrum (70 eV) m/e (rel intensity) 179 (78), 134 (26), 133 (47), 107 (71), 106 (100), 105 (43), 79 (58), 78 (18), 77 (27), 65 (50), 63 (18), 39 (67).

Benzyldiethyl Orthoacetate. A solution of 0.539 g (5.0 mmol) of benzyl alcohol, 6.50 g (40 mmol) of triethyl orthoacetate, and 15 μl (0.2 mmol) of propionic acid was refluxed in a nitrogen atmosphere for 26.5 hr. GC analysis (5% SE-30, 130°) showed one major peak with a retention time of 7.6 min. This product was isolated by preparative GC and identified as benzyldiethyl orthoacetate: ir ($CHCl_3$) 3020, 1733, 1496, 1450, 1375, 1206, 1152, 1041, 1021, 952, 926, and 684 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (6 H, t, J = 7 Hz), 1.53 (3 H, t, J = 4 Hz), 3.55 and 3.60 (4 H, two overlapping q, J = 7 Hz), 4.61 (2 H, d, J = 4 Hz), and 7.33 (6 H, broad s); mass spectrum (70 eV) m/e 179 (M − 45), 178 (M − 46), 150 (179 − 29), 149 (178 − 29), 132 (M − 92), 108 ($C_6H_5CH_2O$), 107, 105, 104, 91, 79, 77.

Ethyl β-(1-Methyl-2(1*H*)-oxo-3-pyridine)propionate (17a). A solution of 139 mg (1.0 mmol) of 1-methyl-3-hydroxymethyl-2-pyridone (**16**)[16] and 1.31 g (8.1 mmol) of triethyl orthoacetate containing a drop of propionic acid was refluxed for 3 hr in a nitrogen atmosphere. GC analysis (5% QF-1, 185°, flow rate 120 ml/min) showed two major peaks with retention times of 8.5 and 17.0 min. The products were isolated by preparative GC. Compound 8.5 was unstable and was slowly converted to a new material which has not been identified. Compound 17.0 was assigned the structure **17a:** ir ($CHCl_3$) 2950, 1706, 1640, 1586, 1547, 1430, 1391, 1358, 1332, 1310, 1281, 1200, 1176, 1150, 1092, 1030, and 870 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (3 H, t, J = 7 Hz), 2.67 and 2.76 (2 H, two overlapping d, J = 7 Hz), 3.54 (3 H, s), 4.14 (2.5 H, q, J = 7 Hz), 4.35–5.26 (0.5 H, m), 6.05 (1 H, t, J = 6 Hz), and 7.00–7.33 (2 H, m).

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.1; H, 7.2; N, 6.7. Found: C, 63.2; H, 7.1; N, 6.5.

Ethyl α-Ethyl-β-(1-methyl-2(1*H*)-oxo-3-pyridine)propionate (17b). A mixture of 278 mg (2.0 mmol) of 1-methyl-3-hydroxymethyl-2-pyridone (**16**)[16] and 2.2 g (16 mmol) of triethyl orthobutyrate[19] containing 0.992 mg (0.125 mmol) of propionic acid was heated at 150° in a nitrogen atmosphere for 8 hr and then left at 25° for 60 hr. GC analysis (5% SE-30) showed two peaks with retention times of 8.0 and 16.0 min. The first product decomposed slowly and its identity was not established. The second product (16 min) was isolated by preparative GC and assigned the structure of **17b:** ir ($CHCl_3$) 3000, 1722, 1650, 1588, 1562, 1460, 1405, 1371, 1320, 1166, 1100, 1030, and 823 cm^{-1}; NMR ($CDCl_3$) δ 0.70–3.00 [11 H total, m, including 0.95 (t, J = 7 Hz), 1.17 (t, J = 7 Hz), and 2.72 (t, J = 2 Hz)], 3.53 (3 H, s), 4.06 (2 H, q, J = 7 Hz), 6.05 (1 H, t, J = 7 Hz), and 7.17 (2 H, d, J = 7 Hz); mass spectrum (70 eV) m/e 237 (M), 222 (M − 15), 208 (M − 29), 205, 192 (M − 45), 176 (M − 61), 164 (M − 73), 163 (M − 74), 162 (M − 75), 148, 134, 123, 122 (M − $CH_3CH_2CHCO_2C_2H_5$).

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.8; H, 8.1; N, 5.9. Found: C, 65.7; H, 8.1; N, 5.9.

Reaction of 3-Hydroxymethylpyridine (2) with *N,N*-Dimethylacetamide Diethyl Acetal (12, 13). A solution of 2.36 g (21.6 mmol) of 3-hydroxymethylpyridine (**2**) and 5.51 g of a mixture[20] of *N,N*-dimethylacetamide diethyl acetal (**12**) and 1-ethoxy-1-dimethylaminoethylene (**13**) in 30 ml of *o*-dichlorobenzene was refluxed for 18 hr in a nitrogen atmosphere. Fractional distillation afforded 0.589 g at 70–105° (0.05 mm) and 1.25 g at 105–123° (0.05 mm); GC analysis (5% CW 20M, 175°, flow rate 160 ml/min) of the lower boiling fraction showed one major component (75%) with a retention time of 3.28 min. Similar analysis of the higher boiling fraction showed that it contained the 3.28 peak and another peak at 8.35 in a ratio of 53:47, respectively. The yield of 3.28 and 8.35 was 44% in a ratio of 65:35, and the products were isolated by preparative GC (5% CW 20M, 175°).

Compound 3.28 was assigned the structure of amide **14:** ir (CCl_4) 3009, 1657, 1645 (shoulder), 1437, 1378, and 1119 cm^{-1}; NMR (CCl_4) δ 2.37 (3 H, s), 3.01 (6 H, d, J = 16 Hz), 3.80 (2 H, s), 6.98 (1 H, m), 7.38 (1 H, m), and 8.27 (1 H, m); mass spectrum (70 eV) m/e (rel intensity) 178 (61), 134 (36), 107 (100), 106 (67), 72 (85).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.3; H, 7.9; N, 15.7. Found: C, 67.2; H, 7.9; N, 15.5.

Compound 8.35 was identified as amide **15:** ir (CCl_4) 3007, 1666, 1381, and 1221 cm^{-1}; NMR (CCl_4) δ 2.22 (3 H, s), 2.95 (6 H, s), 3.53 (2 H, s), 6.90 (1 H, m), and 8.27 (2 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 178 (15), 162 (47), 147 (60), 133 (22), 120 (33), 119 (91), 106 (20), 105 (100), 91 (36), 79 (24), 77 (20), 72 (36), 41 (20), 39 (16).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.3; H, 7.9; N, 15.7. Found: C, 67.2; H, 7.9; N, 15.5.

***N,N*-Dimethyl(1,3-dimethyl-2(1*H*)-oxo-4-pyridine)acetamide (18).** A solution of 419 mg (3.0 mmol) of 3-hydroxymethyl-1-methyl-2-pyridone (**16**)[16] and 742 mg (4.6 mmol) of a mixture[20] of **12** and **13** in 6 ml of *o*-dichlorobenzene was refluxed under nitrogen for 24 hr. The mixture was chromatographed on silica gel. Elution with chloroform removed the *o*-dichlorobenzene. Further elution with 3% methanol in chloroform afforded 515 mg (82%) of product. GC analysis (5% QF-1, 220°, flow rate 150 ml/min) showed one major peak with a retention time of 11.0 min. This compound was identified as **18:** ir ($CHCl_3$) 2941, 1623, 1578, 1387, 1235, and 1127 cm^{-1}; NMR ($CDCl_3$) δ 2.10 (3 H, s), 2.97 and 3.02 (6 H together, two s), 3.50 and 3.57 (5 H together, two s), 6.03 (1 H, d, J = 7 Hz), and 7.17 (1 H, d, J = 7 Hz); mass spectrum (70 eV) *m/e* 208 (M^+), 189, 175, 174, 161, 160, 146, 132, 128, 118.

Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.4; H, 7.7; N, 13.4. Found: C, 63.6; H, 7.9; N, 13.0.

Dimethylbutyramide Diethyl Acetal (19). Triethyloxonium tetrafluoroborate (ca. 0.2 mol) was covered with 20.71 g (0.180 mol) of *N,N*-dimethylbutyramide while stirring mechanically. The salt failed to react until the mixture was heated sufficiently to reflux the liberated ether. Reflux was continued for 1 hr and the reaction mixture formed two layers; the upper was decanted, the lower was dissolved in 50 ml of methylene chloride (distilled from P_2O_5), and the solution was placed in a dropping funnel.

To 110 g of dry ethanol was added 5.478 g (0.238 daltons) of sodium. When the sodium had dissolved, the mixture was cooled in ice and to it was added the solution in the dropping funnel over 2 hr. A precipitate formed as the addition proceeded. After standing overnight, the solid was removed by centrifugation, the supernatant was distilled at reduced pressure, and the final oily fraction [bp 60–80° (20 mm)] was redistilled at atmospheric pressure through a 25-cm platinum spiral column. A fraction boiling at 145–153° was found to contain the product mixture and 5% of unreacted dimethylbutyramide: GC (5% QF-1 on CW 80/100, 10 ft × 0.25 in., flow rate 100 ml/min, 150°) retention time 1.1 min; ethanol, 0.9 min; dimethylbutyramide, 2.5 min.

Reaction of 3-Hydroxymethyl-1-methyl-2-pyridone (16) with *N,N*-Dimethylbutyramide Diethyl Acetal–1-(*N,N*-Dimethylamino)-1-ethoxy-1-butene (19) (see Table II). The series of reactions reported in Table II was performed by the following general procedure. In a 25-ml three-neck round-bottom flask fitted with condenser, serum cap, and nitrogen atmosphere were placed the 3-hydroxymethyl-1-methyl-2-pyridone,[16] solvent, amide acetal, and catalyst if any. The mixture was then heated at the specified temperature and time. The reactions were analyzed by GC (5% QF-1, 196°, flow rate 200 ml/min) and showed two peaks with retention times of 8.0 and 13.75 min. The products were isolated by preparative GC.

Compound 8.0 was identified as **21:** ir (film) 3550, 2960, 1637, 1585, 1559, 1400, 1222, 1143, 1104, and 760 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 7 Hz), 1.13–2.00 (2 H, m), 2.57–3.43 (9 H, m, including singlets at 2.90 and 3.00), 3.54 (3 H, s), 6.05 (1 H, t, J = 7 Hz), and 7.17 (2 H, d, J = 7 Hz); mass spectrum (70 eV) *m/e* 236 (M^+), 192, 191 ($M - H - CH_3OCH_3$), 164 [$M - (CH_3)_2NCO$], 163, 162, 148, 122 [$M - (CH_3)_2NC(O)C_2H_6$].

Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.1; H, 8.5; N, 11.8. Found: C, 66.0; H, 8.5; N, 11.8.

Compound 13.75 was assigned the structure **20:** ir (film) 2963, 1632, 1594, 1385, 1229, 1150, and 785 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (3 H, s), 2.85 and 2.93 (6 H together, two singlets), 3.50 (3 H, s), 3.72 (1 H, t, J = 7 Hz), 6.16 (1 H, d, J = 7 Hz), and 7.07 (1 H, d, J = 7 Hz); mass spectrum (70 eV) *m/e* 236 (M^+), 191 ($M - H - CH_3OCH_3$), 176 (191 − CH_3), 164 [$M - CON(CH_3)_2$], 163, 162, 148.

Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.1; H, 8.5; N, 11.8. Found: C, 65.9; H, 8.5; N, 12.0.

Acknowledgments. C. R. Costin thanks the National Institutes of Health for a Postdoctoral Fellowship. Valuable experimental assistance was provided by D. S. Jones, P. D. Maestas, and R. K. Y. Ju.

Registry No.—**2,** 100-55-0; **3,** 57408-45-4; **4,** 5552-80-7; **5,** 57408-46-5; **6,** 586-98-1; **7,** 57408-47-6; **8,** 3654-30-6; **12,** 19429-85-7; **13,** 816-65-9; **14,** 57408-48-7; **15,** 57408-49-8; **16,** 36721-61-6; **17a,** 57408-50-1; **17b,** 57408-51-2; **18,** 57408-52-3; **19,** 55857-42-6; **20,** 57408-53-4; **21,** 57408-54-5; triethyl orthoacetate, 78-39-7; benzyldiethyl orthoacetate, 57408-55-6; benzyl alcohol, 100-51-6; triethyl orthobutyrate, 24964-76-9; triethyloxonium tetrafluoroborate, 368-39-8; *N,N*-dimethylbutyramide, 760-79-2.

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