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# Synthesis of Methylpyridine Derivatives. XXXIV.[1] Condensation of Acetoacetamide with Ketones to form Pyridone Derivatives

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Condensation of acetoacetamide (**1**) with acetone in polyphosphoric acid (PPA) gave 4,6-dimethyl-2(1H)-pyridone (**2a**) in 32% yield. Similarly, the amide **1** was condensed with 2-butanone, 2-pentanone, 3-pentanone, cyclopentanone, cyclohexanone, cycloheptanone, acetophenone, and propiophenone to give the corresponding pyridone derivatives (**2b**—**i**) in 13—76% yields. Condensation of the amide **1** with acetylacetone and ethyl acetoacetate gave 3-acetyl-4,6-dimethyl-2(1H)-pyridone (**5**) and ethyl 4,6-dimethyl-2(1H)-pyridone-5-carboxylate (**6**), respectively. Self-condensation of the amide **1** in PPA gave 3-acetyl-4-hydroxy-6-methyl-2(1H)-pyridone (**7**).

**Keywords**——acetoacetamide; 2(1H)-pyridone derivatives; 2H-1-pyrindin-2-one; 2(1H)-quinolone; 5H-cyclohepta[*b*]pyridine; polyphosphoric acid; condensation reaction

In contrast to the vast amount of attention that has been given to the chemistry of acetoacetic esters, acetoacetamide (**1**) has languished in relative neglect. The amide **1** is readily prepared from diketene and ammonia. During the course of our studies on diketene, we have investigated potential uses of the amide **1**, and we have found that the amide **1** is useful in the synthesis of nitrogen heterocycles such as pyridine and pyrimidine.[3]

In previous papers, we have reported the synthesis of pyridone derivatives by condensation of the amide **1** with $\alpha,\beta$-unsaturated ketones or aldehydes,[4a] or $\alpha,\beta$-unsaturated esters,[4b] or $\beta$-diketones.[5] The present paper reports the condensation of the amide **1** with ketones to form 6 (and 5,6-di)-substituted 4-methyl-2(1H)-pyridones.

Hauser and Eby[6] reported that the condensation of benzoylacetamide (**3**) with acetone catalyzed by polyphosphoric acid (PPA) provides 6-methyl-4-phenyl-2(1H)-pyridone (**4**). The condensation of the amide **1** with acetylacetone catalyzed by alcoholic hydrogen chloride[7] or sodium ethoxide[5] yields 3-acetyl-4,6-dimethyl-2(1H)-pyridone (**5**). We have examined the reactions of the amide **1** with various ketones in a further investigation of the mode of condensation.

When the amide **1** and 4 equivalent amounts of acetone were heated in polyphosphoric acid (PPA), 4,6-dimethyl-2(1H)-pyridone (**2a**) was obtained in 32% yield. Under similar conditions, the amide **1** was condensed with various ketones to give the corresponding pyridone derivatives **2b**—**i** in 13—76% yields. The results are summarized in Table I.

As shown in Table I, aliphatic and alicyclic ketones generally gave better yields of the corresponding pyridones than aromatic ketones. Condensation of the amide **1** with acetone and acetophenone in the presence of *p*-toluenesulfonic acid, alcoholic hydrogen chloride, or conc. sulfuric acid as a catalyst in place of PPA did not give the corresponding pyridones **2a** and **2h**.

1) Part XXXIII: T. Kato, N. Katagiri, and A. Wagai, *Tetrahedron*, **34**, 3445 (1978).
2) Location: *Aobayama, Sendai, 980, Japan.*
3) *e. g.*, *a*) T. Kato, *Yuki Gosei Kagaku Kyokai Shi*, **32**, 632 (1974); *b*) T. Kato, N. Katagiri, and M. Daneshthalab, *Heterocycles*, **3**, 413 (1975).
4) *a*) T. Kato and M. Noda, *Chem. Pharm. Bull.*, **23**, 2193 (1975); *b*) *Idem*, *ibid.*, **22**, 2947 (1974).
5) T. Kato and M. Noda, *Chem. Pharm. Bull.*, **24**, 303 (1976).
6) C.R. Hauser and C.J. Eby, *J. Am. Chem. Soc.*, **79**, 728 (1956).
7) C. Bonsall and J. Hill, *J. Chem. Soc.* (*C*), **1967**, 1836.

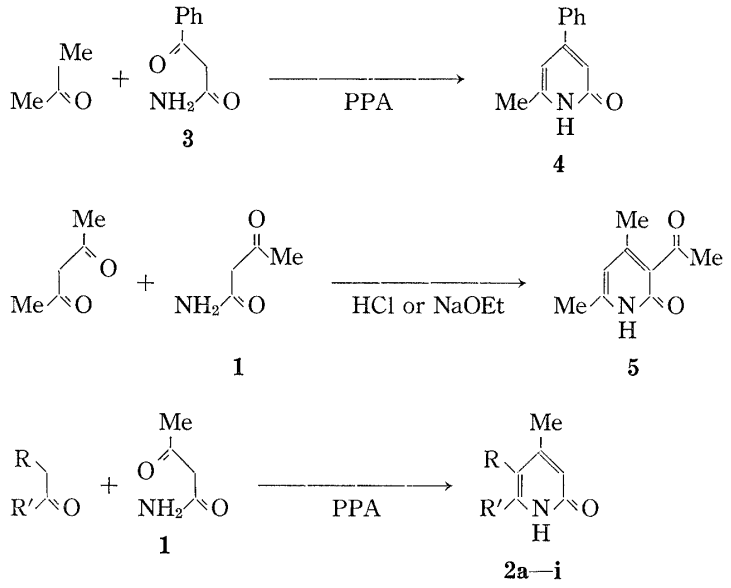



Chart 1

Table I. Condensation of Acetoacetamide (**1**) with Ketones to give **2a—i**

| | Ketone g | **1** g | PPA g | Temp °C | Time hr | No. | R | R′ | Yield % | Product Recryst. solvent[a)] | mp °C | lit. mp °C |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acetone | 5 | 2 | 10 | 100 | 2 | **2a** | H | Me | 32 | A | 176—177 | 176[b)] |
| 2-Butanone | 1.5 | 1 | 7 | 120—130 | 3 | **2b** | Me | Me | 59 | B | 248—250 | 196[c)] |
| 2-Pentanone | 1.7 | 1 | 7 | 120—130 | 3 | **2c** | Et | Me | 55 | A | 191—192 | 192[d)] |
| 3-Pentanone | 1.7 | 1 | 7 | 120—130 | 3 | **2d** | Me | Et | 76 | C | 208—209 | |
| Cyclopentanone | 1.7 | 2 | 10 | 100 | 5 | **2e** | $-(CH_2)_3-$ | | 57 | B | 238—239 | |
| Cyclohexanone | 2 | 2 | 10 | 100 | 4 | **2f** | $-(CH_2)_4-$ | | 65 | B | 248—250 | |
| Cycloheptanone | 2.2 | 1 | 7 | 120—130 | 3 | **2g** | $-(CH_2)_5-$ | | 68 | B | 250—251 | |
| Acetophenone | 4.8 | 2 | 10 | 120—125 | 2 | **2h** | H | Ph | 13 | A | 180—181 | 181—182[e)] |
| Propiophenone | 1.35 | 0.5 | 5 | 120—130 | 3 | **2i** | Me | Ph | 33 | A | 220—221 | |

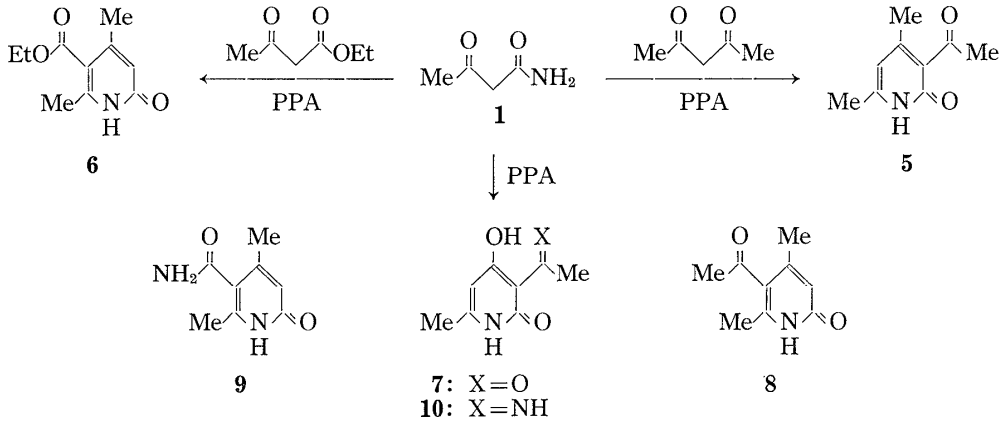
*a*) A=AcOEt; B=AcOEt−MeOH; C=acetone.
*b*) A. Nieme and H. Pechmann, *Ann.*, **261**, 190 (1891).
*c*) A. Dornow and O. Hahmann, *Arch. Pharm.*, **290**, 20 (1957). When **2b** was synthesized according to the literature, the melting point was 248—250°.
*d*) B. Witkop, *J. Am. Chem. Soc.*, **70**, 3712 (1948).
*e*) A. Sakurai and H. Midorikawa, *Bull. Chem. Soc. Jpn.*, **41**, 165 (1968).

Table II. Spectral and Elemental Analysis Data for Compounds **2**

| Compound No. | IR $\nu_{max}^{KBr}$ cm$^{-1}$ | | NMR ($CDCl_3$) $\delta$ | | Formula | Analysis (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Calcd | | | Found | | |
| | NH | C=O | 3-H | 4-Me | | C | H | N | C | H | N |
| **2b** | 2840 | 1655 | 6.32 | 2.16 | $C_8H_{11}NO$ | 70.04 | 8.08 | 10.21 | 70.02 | 8.09 | 9.94 |
| **2d** | 3320<br>2920 | 1640 | 6.30 | 2.15 | $C_9H_{13}NO$ | 71.49 | 8.67 | 9.26 | 71.24 | 8.60 | 9.25 |
| **2e** | 2920 | 1655 | 6.27 | 2.13 | $C_9H_{11}NO$ | 72.45 | 7.43 | 9.39 | 72.39 | 7.47 | 9.27 |
| **2f** | 2920 | 1650 | 6.30 | 2.10 | $C_{10}H_{13}NO$ | 73.59 | 8.03 | 8.59 | 73.88 | 7.93 | 8.64 |
| **2g** | 2920 | 1655 | 6.30 | 2.17 | $C_{11}H_{15}NO$ | 74.54 | 8.53 | 7.90 | 74.47 | 8.55 | 7.68 |
| **2i** | 2920 | 1650 | 6.38 | 2.20 | $C_{13}H_{13}NO$ | 78.36 | 6.58 | 7.03 | 78.33 | 6.61 | 6.80 |

The structures of the new pyridones **2d**, **2e**, **2f**, **2g**, and **2i** were established on the basis of elemental analyses and spectral data (Table II). The structures of the other pyridones were confirmed by mixed melting point determination or comparisons of spectral and physical data with those of authentic samples.

Previously, we[5] have reported that the amide **1** reacts with β-diketones such as acetylacetone in the presence of a basic catalyst such as sodium ethoxide to give the pyridone **5** in 30% yield in the cited case. When this reaction was carried out in PPA, the same pyridone **5** was obtained in 48% yield. Under similar conditions, ethyl acetoacetate condensed with the amide **1** to give ethyl 4,6-dimethyl-2(1H)-pyridone-5-carboxylate (**6**). However, the self-condensation of the amide **1** in PPA did not give 5-carbamoyl-4,6-dimethyl-2(1H)-pyridone (**9**),[8,9] but 3-acetyl-4-hydroxy-6-methyl-2(1H)-pyridone (**7**) in 8% yield. Such a self-condensation had to be considered in view of the reported formation of 3-acetimidoyl-4-hydroxy-6-methyl-2(1H)-pyridone (**10**) by the pyrolysis of acetoacetamide.[9]




**6** **1** **5**

**9** **8**

**7**: X=O
**10**: X=NH

Chart 2

During the course of investigations of diketene chemistry, we[10] reported that diketene reacted with 4-amino-3-penten-2-one to give a poor yield[11] of a pyridone derivative of mp 214—215°, to which we assigned the structure 5-acetyl-4,6-dimethyl-2(1H)-pyridone (**8**) on the basis of elemental analysis and IR spectroscopic data. However, this was found to be identical with compound **5** obtained above. Therefore, the pyridone of mp 214—215° obtained from diketene[10] is not the 5-acetylpyridone **8** but the 3-acetylpyridone **5**.

## Experimental[12]

**General Procedure for the Condensation of Acetoacetamide (1) with Ketones to form Pyridone Derivatives (2a—i)**——A mixture of the amide **1**, ketone, and polyphosphoric acid was heated with stirring. The reaction mixture was poured onto crushed ice, and neutralized with solid $NaHCO_3$. Separated crystals were collected by filtration, washed with water, and dried *in vacuo*. Recrystallization gave the product (**2a—i**) as needles. Compounds **2a**, **2b**, and **2c** were identified by mixed melting point determination and IR comparison with authentic samples. Compound **2i** was identified by comparison of its IR spectrum with that of an authentic sample. The results are summarized in Table I and II.

**3-Acetyl-4,6-dimethyl-2(1H)-pyridone (5)**——A mixture of PPA (10 g), acetylacetone (4 g), and the amide **1** (2.0 g) was heated at 110° with stirring for 3 hr. The reaction mixture was poured onto ice and

8) Structure (**9**) was incorrectly reported by L. Claisen and K. Mayer, *Ber.*, **35**, 583 (1902).
9) T. Kato, H. Yamanaka, J. Kawamata, and T. Shibata, *Chem. Pharm. Bull.*, **16**, 1835 (1968).
10) T. Kato, H. Yamanaka, and T. Hozumi, *Yakugaku Zasshi*, **91**, 740 (1971).
11) The main product of this reaction is 3-acetyl-2,6-dimethyl-4(1H)-pyridone (E. Ziegler, I. Herbst, and Th. Kappe, *Monatsh. Chem.*, **100**, 132 (1960)).
12) IR spectra were taken with a JASCO IR-S spectrophotometer. NMR spectra were taken on a Hitachi R-20 instrument. Chemical shifts are reported on the δ scale, parts per milion downfield from tetramethylsilane as an internal standard. All melting points are uncorrected.

separated crystals were collected by filtration. Recrystallization from acetone gave 1.58 g (48%) of product **5** as needles, mp 214—215°, undepressed on admixture with an authentic sample prepared according to the literature.[5,7] Admixture of this compound (**5**) with a sample obtained from diketene[10] showed no melting point depression.

**Ethyl 4,6-Dimethyl-2(1H)-pyridone-5-carboxylate (6)**——A mixture of PPA (10 g), ethyl acetoacetate (5.2 g) and the amide **1** (2.0 g) was heated at 110° with stirring for 3 hr. The reaction mixture was poured onto ice and neutralized with 10% $Na_2CO_3$. Precipitated crystals (**6**) were filtered off and the filtrate was extracted with AcOEt. The organic layer was concentrated and the residue was chromatographed on a silica gel column. Elution with hexane–$CHCl_3$ (3: 1) gave crystals. Crystals were combined and recrystallized from acetone to afford 0.96 g (25%) of product **6** as needles, mp 138—139° (lit.[13] mp 138—139°).

**3-Acetyl-4-hydroxy-6-methyl-2(1H)-pyridone (7)**——A mixture of PPA (10 g) and the amide **1** (2.0 g) was heated at 110—120° with stirring for 2 hr. The reaction mixture was poured onto ice and extracted with AcOEt. The extract was dried over $Na_2SO_4$ and concentrated. The residue was recrystallized from acetone to afford 0.14 g (8%) of product **7** as needles, mp 258—260° (dec.), which gave an IR spectrum identical with that of an authentic sample.[14]

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13) J.N. Collie, *J. Chem. Soc.*, **71**, 299 (1897).
14) S. Seto, H. Sasaki, and K. Ogura, *Bull. Chem. Soc. Jpn.*, **39**, 281 (1966).

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# Activation of N-Hydroxy Compounds by P-O Bond Formation through Anodic Oxidation of Triphenylphosphine

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Controlled potential electrolyses of triphenylphosphine (TPP) in acetonitrile containing an excess of N-hydroxy compounds such as ketoximes, aldoximes, and hydroxamic acids were examined: subsequent treatment of the products under mild conditions gave amides, nitriles, and ureas, respectively. Electrolyses under conditions where the amounts of TPP were equal to or larger than those of the N-hydroxy compounds did not give satisfactory results.

**Keywords**——anodic oxidation; controlled potential electrolysis; triphenylphosphine; Beckmann rearrangement; phosphonium ions

Recently several investigators have reported modifications of the Beckmann rearrangement using organophosphorus compounds such as hexamethylphosphoric triamide[2] and μ-oxo-bis[tris(dimethylamino)-phosphonium]-bis-tetrafluoroborate,[3] where ketoximes are activated by P–O bond formation. In the rearrangement induced by the phosphonium ion, it is emphasized that the reaction can be effected under mild conditions.[3] The formation of alkoxyphosphonium salts in the anodic oxidation of triphenylphosphine (TPP)[4] suggested

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3) I.J. Galpin, P.E. Gordon, R. Ramage, and W.D. Thorpe, *Tetrahedron*, **32**, 2417 (1976).
4) H. Ohmori, S. Nakai, M. Sekiguchi, and M. Masui, *Chem. Pharm. Bull.*, **28**, 910 (1980).