precipitate was deposited. A sample was recrystallized from water and identified as 5-hydroxy-6-methyl-3,4-pyridinedicarboxylic acid by its infrared absorption spectrum which was identical with that of an authentic sample.[6] The yield was 3.5 g. (18%).

Ethyl 4,5-Dicarboximido-6-methyl-2-pyridinecarboxylate (XIII).—In 25 ml. of carbitol acetate was suspended 7.0 g. (0.026 mole) of 2-carbethoxy-4,5-dicarboximido-6-methyl-3-pyridinecarboxylic acid (VIII). The mixture was heated up to the boiling point (210–215°) and the resulting solution was held under reflux for about ten minutes. About one-half of the solvent was removed by evaporation in vacuum, and the residue was taken up in 200 ml. of ethyl acetate. The solution was washed well with aqueous sodium bicarbonate solution, decolorized with carbon, dried with magnesium sulfate and evaporated to remove the ethyl acetate. Petroleum ether, 200 ml., was added, and an oily precipitate separated which soon crystallized. The yield was 4.0 g. (68%), and the yield in a duplicate experiment was 78%. The product was recrystallized from a mixture of ethyl acetate and petroleum ether and obtained as a white crystalline powder, m.p. 176–177°.

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.35; H, 4.49; N, 11.64.

Trimethyl 6-Methyl-2,4,5-pyridinetricarboxylate (XIV).—A sample of 1.0 g. of the above ethyl 4,5-dicarboximido-6-methyl-2-pyridinecarboxylate in 10 ml. of 10% sodium hydroxide solution was heated on the steam-bath for three hours. The solution was acidified with 5 ml. of 12 *N* hydrochloric acid and evaporated to dryness by heating on the steam-bath under reduced pressure. After thorough drying in air the solid was suspended in 25 ml. of methanol and treated with excess diazomethane in ether. The mixture was worked up in the usual way leaving a sirup which soon crystallized. The ester was recrystallized twice from petroleum ether and obtained as a white powder; m.p. 83–84°.

Anal. Calcd. for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.25. Found: C, 54.15; H, 5.27; N, 5.49.

When the above ester was mixed with an authentic sample of trimethyl 2-methyl-3,4,5-pyridinetricarboxylate[2] (m.p. 61–62°), the m.p. was depressed to 48–55°.

4-Amino-6-methyl-2,5-pyridinedicarboxylic Acid (XV).—To a solution of 4 g. of sodium hydroxide in 4 ml. of water was added 10 g. of chipped ice, and chlorine gas was bubbled into the mixture until the weight had increased 1.30 g. Twenty grams of chipped ice was added followed by 4.0 g. of ethyl 4,5-dicarboximido-6-methyl-2-pyridinecarboxylate. After the mixture had stood for one hour it was heated on the steam-bath for ten minutes, cooled, and acidified to *p*H 2 with hydrochloric acid. The crystalline precipitate which soon separated was collected, washed with a little water, acetone, ether and air-dried. The yield was 2.3 g. (69%). A sample recrystallized from a large volume of water melted at 270–271° dec. (uncor.).

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.30; H, 4.24; N, 14.18.

The X-ray diffraction pattern and the infrared absorption spectrum of this acid differed from those of the above 5-amino-6-methyl-2,4-pyridinedicarboxylic acid.

Dimethyl 4-Amino-6-methyl-2,5-pyridinedicarboxylate.—The dicarboxylic acid was esterified with diazomethane in the usual manner to yield the dimethyl ester, m.p. 136.5–137° from ethyl acetate–petroleum ether.

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.56; H, 5.40; N, 12.50. Found: C, 53.97; H, 5.80; N, 12.77.

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The Relative Reactivities of the Isomeric Methyl Pyridinecarboxylates in the Acylation of Certain Ketones. The Synthesis of β-Diketones Containing Pyridine Rings

BY ROBERT LEVINE AND JAMES K. SNEED[1,2]

Using sodium methoxide to effect the condensations, the relative reactivities of the three methyl pyridinecarboxylates and methyl benzoate in the Claisen acylation of acetone, acetophenone and pinacolone have been found to be methyl picolinate > isonicotinate > nicotinate and/or benzoate. An explanation for this order of reactivity is given and certain comments on the factors influencing the Claisen acylation of methyl ketones are made.

In a recent communication[3] from this Laboratory the relative reactivities of a number of aliphatic and aromatic esters, in their condensations with methyl 2-thienyl ketone, have been determined. The reactivities of these esters have been found to parallel those reported in the literature for the ammonolysis[4] and alkaline hydrolysis[5] of the same compounds.

In the present paper, we report the results of the acylation of acetone, acetophenone and pinacolone with the three isomeric methyl pyridinecarboxylates and methyl benzoate. These reactions were carried out in refluxing anhydrous ether using one equivalent each of sodium methoxide and ester and two equivalents of ketone. The following equations, which show the preparation of picolinoylacetone, illustrate the method used.

$$CH_3COCH_3 + OCH_3^- \longrightarrow (CH_2COCH_3)^- + CH_3OH \quad (1)$$
$$\text{I}$$

$$2\text{-}C_5H_4NCO_2CH_3 + \text{I} \longrightarrow 2\text{-}C_5H_4NCOCH_2COCH_3 + OCH_3^- \quad (2)$$
$$\text{II}$$

$$\text{II} + OCH_3^- \longrightarrow (2\text{-}C_5H_4COCHCOCH_3)^- + CH_3OH \quad (3)$$

The results of our study are found in Table I. It may be seen that with the three ketones, the order of reactivity of the esters is methyl picolinate > isonicotinate > nicotinate and/or benzoate. Since the rate-controlling step in these condensations is probably the condensation of the ketone anion with the polarized form of the ester molecule (equation 2), that ester which has the most electrophilic carbonyl carbon atom should condense most readily with ketone anions. Consideration of the following resonance forms of methyl picolinate are of help in explaining the results. Form C represents the structure of the ester which is important in condensations with ketone anions (nucleophilic reagents). Also activating the carbonyl carbon atom of the ester is form A, which involves nuclear reso-

(1) This paper is based on a portion of the thesis presented by James K. Sneed to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree.

(2) The Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, Del.

(3) Sneed and Levine, THIS JOURNAL, **72**, 5219 (1950).

(4) Gordon, Miller and Day, *ibid.*, **70**, 1946 (1948).

(5) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., pp. 121, 211, 212.

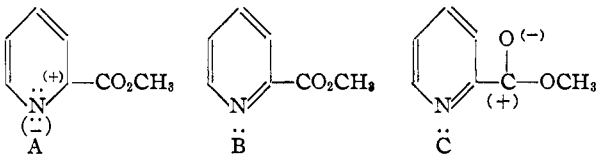
TABLE I

AROMATIC AND HETEROCYCLIC β-DIKETONES

Ester, methyl	Ketone	β-Diketone, yield, %	B.p., °C.	Mm.	M.p., °C.
Picolinate	Acetone	81, 76[a]	114–118	4.6	49–50[d]
Isonicotinate		51, 56[a]	118–120	5	66.5–67[e]
Nicotinate		34	132–134	5	82.5–83.5[f]
Benzoate		37			59–60[g]
Picolinate	Acetophenone	73	184–190	3	87–87.5[h]
Isonicotinate		45, 55[a]			84.5–85.5[i]
Nicotinate		30	177–180	1	121–121.5[d]
Benzoate		30, 27[a]			77–78[j]
Picolinate	Pinacolone	74	134–136	5[k]	
Isonicotinate		27	138–140	5[l]	
Nicotinate		5.6[c], 59.5[b]	135–136	5	43.5–44.5[f,m]
Benzoate		0.3[c], 69[b]	165–165.5	25[n]	

[a] Six-hour reaction time; in all runs reaction time was two hours. [b] Sodium amide used as base; in all other runs sodium methoxide was used. [c] Isolated as the copper salt. [d] See ref. 6. [e] Tscherne, *Monatsh.*, **22**, 615 (1901). [f] See ref. 16. [g] See ref. 12. [h] *Anal.* Calcd. for $C_{14}H_{11}O_2N$: C, 74.65; H, 4.92. Found: C, 74.71; H, 4.85. Picrate, m.p. 169–170.5°. *Anal.* Calcd. for $C_{20}H_{14}O_9N_4$: N, 12.33. Found: N, 12.04. [i] *Anal.* Calcd. for $C_{14}H_{11}O_2N$: C, 74.65; H, 4.92. Found: C, 74.82; H, 4.57. Picrate, m.p. 207–208°. *Anal.* Calcd. for $C_{20}H_{14}O_9N_4$: N, 12.33. Found: N, 12.13. [j] Arndt and Eistert, *Ber.*, **69**, 2384 (1936). [k] *Anal.* Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37. Found: C, 70.02; H, 7.54; does not form a picrate. [l] *Anal.* Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37. Found: C, 70.55; H, 7.10. Picrate, m.p. 191.5–192.5°. *Anal.* Calcd. for $C_{18}H_{13}O_9N_4$: N, 12.90. Found: N, 12.87. [m] Gives a green copper salt, m.p. 277.5–278.5°. [n] See ref. 17; gives green copper salt, m.p. 203–204°.

nance and which may make an important contribution to the structure of the ester due to the electronegativity of the nitrogen atom. Similar



A B C

Some resonance forms of methyl picolinate

activating structures may also be written for methyl isonicotinate, but the effect of nuclear resonance should probably be less than with the isomeric methyl picolinate due to the greater distance of separation between the nitrogen atom and the carbonyl group. Thus, as has been found, the carbonyl group of methyl picolinate should react more readily with nucleophilic reagents (*e.g.*, ketone anions) than that of methyl isonicotinate. In methyl nicotinate the activating effect of nuclear resonance due to the nitrogen atom should be at a minimum and, as has been found, this ester should be of about the same reactivity as methyl benzoate. It may also be seen (Table I) that increasing the reaction times from two to six hours in several of the runs did not have a great effect on the yields of the β-diketones. It is also noteworthy that the relatively unreactive ketone, pinacolone, gave a good yield of condensation product with methyl picolinate (74%); a poor yield with methyl isonicotinate (27%) and negligible yields with methyl nicotinate (5.6%) and methyl benzoate (0.3%).

The data obtained in the present study, when supplemented with those which are available from the literature, shed light on the factors influencing the Claisen acylation of methyl ketones. Thus, acetone,[6,7,8] acetophenone[8,9] and pinacolone[7] have been condensed with such reactive esters as methyl (or ethyl) picolinate, dimethyl (or diethyl) oxalate and ethyl trifluoroacetate in high yields using the weak bases sodium methoxide or ethoxide under mild conditions. With somewhat less reactive esters such as ethyl acetate, benzoate and nicotinate, these ketones[10,11] may be condensed in high yields using the strong base, sodium amide, and in only fair to good yields if sodium ethoxide is used as the condensing agent unless the reactions are carried out under "forced conditions."[9] With unreactive esters such as the higher aliphatic or alicyclic esters such as ethyl hexahydrobenzoate,[11,12] these ketones may be condensed satisfactorily only in the presence of strong bases such as sodium amide.

Thus, it appears that there are two factors which influence the Claisen acylation of methyl ketones: (1) the electrophilic character of the carbonyl carbon atom of the acylating ester, and (2) the concentration of ketone anion. If the carbonyl carbon atom of the ester is highly electrophilic, a high concentration of ketone anion is not required to effect the reaction and weak bases such as the alkali alkoxides may be employed as condensing agents. However, if the carbonyl carbon atom of the ester is not highly electrophilic, a high concentration of ketone anion is required for satisfactory condensation and strong bases such as sodium amide must be used as condensing agents.

Since the acylations referred to above in references 6–12 were performed under various conditions and by different workers, more support would be available for the two factors mentioned above if data were available from runs performed by the same operator. Therefore, pinacolone was acylated with the relatively unreactive esters, methyl benzoate and nicotinate using both sodium methoxide and amide as condensing agents. Pivaloylbenzoylmethane was obtained in 0.3% yield using sodium methoxide and in 68% yield using sodium amide as the condensing agent. Using the same

(6) Micko, *Monatsh.*, **17**, 442 (1896).
(7) Royals, THIS JOURNAL, **67**, 1508 (1945).
(8) Reid and Calvin, *ibid.*, **72**, 2948 (1950).
(9) Magnani and McElvain, *Org. Syntheses*, **20**, 32 (1940).
(10) Claisen and Feyerabend, *Ber.*, **38**, 693 (1905).
(11) Adams and Hauser, THIS JOURNAL, **66**, 1220 (1944).
(12) Sprague, Beckham and Adkins, *ibid.*, **56**, 2665 (1934).

bases, pivaloylnicotinoylmethane was obtained in 5.6 and 59.5% yields, respectively.

Experimental[13]

Preparation of Methyl Pyridinecarboxylates.—Since, in our hands, the procedures described in the literature for the preparation of methyl picolinate and nicotinate from the corresponding acids gave very low, non-reproducible yields, a description of our syntheses follows.

(a) **Methyl Picolinate.**—In a 500-ml., three-neck round-bottom flask, equipped with ground-glass joints, a mercury-sealed Hershberg stirrer, a reflux condenser (drying tube) and an addition funnel (drying tube), was placed 63.5 g. (0.5 mole) of picolinic acid. To the rapidly stirred solid, 73 ml. (1.0 mole) of thionyl chloride was added dropwise over an hour period. The acid first turned green and finally dark purple. The mixture was stirred and refluxed for one hour and then allowed to stand overnight. Absolute methanol (40.5 ml., 1.0 mole) was added to the rapidly stirred mixture. Then, 71 g. (1.25 moles) of commercial 95% sodium methoxide,[14] dissolved in 300 ml. of absolute methanol was added slowly and the mixture stirred and refluxed for 30 minutes longer. The mixture was transferred to a large beaker, diluted to about 500 ml. with ether and filtered through a büchner funnel. The precipitate of sodium chloride was washed with several 100-ml. portions of ether. The filtrate, to which the washings were added, was dried over Drierite, the solvent distilled and the residue fractionated in vacuum to give 50.1–56.2 g. (73.3–82%) of methyl picolinate, b.p. 95–96° (5 mm.) and 108–109° (10 mm.).

(b) **Methyl Nicotinate.**—In a 500-ml., two-neck, round-bottom flask equipped with ground glass joints and fitted with a reflux condenser and dropping funnel (drying tubes) were placed 100 g. (0.813 mole) of nicotinic acid and 250 ml. of absolute methanol. From the dropping funnel 125 ml. (2.23 moles) of concentrated sulfuric acid was added dropwise over an hour period. When the addition of the sulfuric acid was complete, the nicotinic acid had dissolved. The solution was refluxed for two hours, cooled to room temperature, poured onto 1000 g. of ice and made alkaline by the careful addition of 270 g. (2.55 moles) of solid sodium carbonate. The mixture was extracted with several portions of ether and the combined extracts dried over Drierite. The solvent was removed and the residue distilled in vacuum to give 76.4 g. (68.9%) of methyl picolinate, b.p. 108–109° (21 mm.).

Using a similar procedure, methyl isonicotinate, b.p. 103–104° (21 mm.) and 76–77° (5 mm.), was prepared in 74–83% yield.

General Procedure for the Acylation of Ketones with Methyl Pyridinecarboxylates Using Sodium Methoxide.—In a 1000-ml. flask equipped as described above for the preparation of methyl picolinate, were placed 0.25 mole (14.5 g.) of 95% sodium methoxide[14] and 250 ml. of anhydrous ether. To this well stirred reaction mixture were added in succession 0.25 mole of ester and 0.5 mole of ketone, each diluted with 125 ml. of anhydrous ether. The reaction mixture was stirred and refluxed for the reaction times indicated in the footnotes of Table I and the reactions then stopped by the addition of 0.25 mole (15.0 g.) of glacial acetic acid. This was followed by sufficient water (*ca.* 100 ml.) to dissolve the sodium acetate which had formed. The mixture was then transferred to a separatory funnel and the aqueous phase extracted with ether until the extracts no longer gave an enol test with alcoholic iron(III) chloride solution. The combined ethereal phases were dried over Drierite, the solvent and unreacted ketone and ester removed, and the β-diketones isolated from the residues by vacuum distillation or crystallization.

Acylation of Pinacolone with Methyl Nicotinate and Benzoate in the Presence of Sodium Amide (a) Pivaloylnicotinoylmethane.—To an ethereal suspension of 0.4 mole of sodium amide[15] was added an ethereal solution of 0.2 mole (20.0 g.) of pinacolone. The reaction mixture was stirred and refluxed for 20 minutes and then an ethereal solution of 0.25 mole (34.3 g.) of methyl nicotinate was added and the mixture stirred and refluxed for two hours. Then sufficient water was added to dissolve the solid present and the aqueous phase extracted with two 100-ml. portions of ether. The aqueous phase was neutralized by the addition of 0.4 mole (24.0 g.) of glacial acetic acid and extracted with ether until the extracts no longer gave a positive test with alcoholic iron(III) chloride solution. The combined ether phases were dried over Drierite, the solvent removed and the residue distilled in vacuum to give 24.4 g. (59.5%) of pivaloylnicotinoylmethane, b.p. 135–136° (5 mm.); m.p. 43.5–44.5°.[16] its green copper salt melted at 277.5–278.5°.

Anal. Calcd. for $C_{24}H_{28}O_4N_2Cu$: C, 61.06; H, 5.98. Found: C, 60.72; H, 5.63.

(b) **Pivaloylbenzoylmethane.**—From 0.5 mole of sodium amide,[15] 0.25 mole (25.0 g.) of pinacolone and 0.31 mole (42.2 g.) of methyl benzoate and employing the copper salt method[15] for isolating the β-diketone, there was obtained 28.5 g. (69.0%) of pivaloylbenzoylmethane, b.p. 165–166.5° (25 mm.).[17] Its green copper salt melted at 203–204°.

Anal. Calcd. for $C_{26}H_{30}O_4Cu$: C, 66.43; H, 6.43. Found: C, 66.11; H, 6.12.

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(13) All analyses were performed by Mr. George Stragand of the Microanalytical Laboratory of the University of Pittsburgh.

(14) Purchased from the Mathieson Chemical Corporation, Niagara Falls, N. Y.

(15) Harris and Levine, THIS JOURNAL, **70**, 3360 (1948).

(16) Kuick and Adkins, *ibid.*, **57**, 143 (1935).

(17) Vorlaender and Kalkow, *Ber.*, **30**, 2268 (1897).