polymerization of both materials is also similar. Therefore, isopropenyl acetate can be considered as fitting into the same general position in the series of allyl esters as allyl acetate. The reactivity of the double bond would be approximately the same, since Melville and Robb[18] have shown that there is little difference in reactivity whether substituents are on carbon 2 or 3. Primary degradative chain transfer in both compounds is comparable, the increased accessibility and decreased steric hindrance of the side methyl apparently balancing the decreased stability of the primary allylic radical as compared to the secondary allylic radical in allyl acetate.

Experimental

Materials.—The allyl esters and benzoyl peroxide were prepared and purified as described in Part II of this series.[6]

Experimental Procedure.—Polymerizations were carried out as previously described. Samples were removed for determination of unsaturation and peroxide concentration. The analytical methods employed for the allyl esters were similar to those of Bartlett and Altschul.[4] The bromate-bromide solution used was standardized against the allyl monomer under investigation. The concentration of monomer in isopropenyl acetate was determined by removal of residual monomer under vacuum at room temperature to constant weight.

Isolation of Polymer.—The polymer was isolated by removing all volatile material under vacuum at room temperature to constant weight.

Purification of Polymer for Molecular Weight Determinations.—The polymer from the polymerization of the monomer to the exhaustion of peroxide was isolated as above, dissolved in benzene, extracted with aqueous potassium carbonate, dried and isolated as described by Bartlett and Altschul.[4]

Molecular Weight Determinations.—All molecular weights were determined cryoscopically. A solution of the polymer was made up accurately by weight in benzene and transferred to the apparatus for the determination of molecular weights by freezing point depression (Eimer and Amend) utilizing a Beckmann thermometer and mechanical stirring. The values of the freezing point depressions thus obtained were in each case the result of at least two checking determinations.

Viscometric Determinations.—Viscosities were measured in benzene as solvent using a modified Ostwald pipet, in a constant temperature bath operating at 27°.

BROOKLYN 2, N. Y. RECEIVED FEBRUARY 13, 1951

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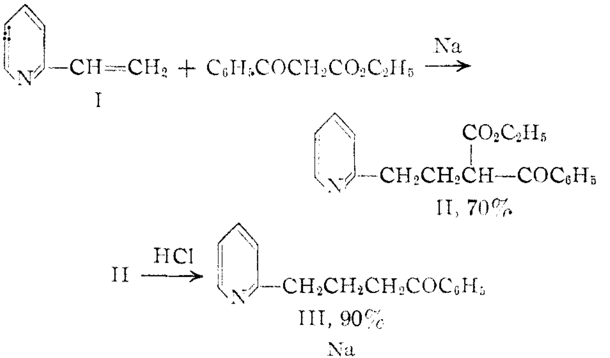
(18) H. W. Melville and J. C. Robb, *Proc. Royal Soc. (London)*, **A196**, 494 (1949); *ibid.*, **A202**, 181 (1950).

[CONTRIBUTION NO. 829 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Direct Pyridylethylation of Active Hydrogen Compounds. I. 2-Vinylpyridine with Ketones

BY ROBERT LEVINE AND MYRON H. WILT

The Michael condensation has been effected between a number of ketones and 2-vinylpyridine in the presence of sodium metal as the condensing agent. In the pyridylethylation of methyl ethyl ketone and methyl isobutyl ketone, condensation occurs at the α-methylene group of the former and the α-methyl group of the latter compound.


I

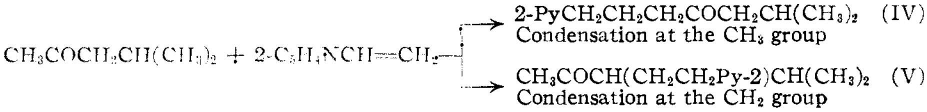
II, 70%

III, 90%

$$\mathrm{I} + CH_3COC_6H_5 \xrightarrow{Na} \mathrm{III},\ 30\%$$

While the ketones, acetone[1] and acetophenone[2] have been pyridylethylated indirectly by the reaction of the sodium derivatives of ethyl acetoacetate and ethyl benzoylacetate with 2-vinylpyridine and subjecting the condensation products to ketonic cleavage, the direct pyridylethylation of the sodium derivatives of these ketones has not been reported previously. The three equations above show how phenyl γ-(2-pyridyl)-propyl ketone may be prepared by these two routes. Since the relatively reactive ketones, phenylacetone and desoxybenzoin, have recently been condensed with 2-vinylpyridine,[3] we are reporting the results we have obtained in similar condensations with a number of other ketones.

Most of our condensations have been effected by the interaction of two equivalents of ketone, one equivalent of 2-vinylpyridine and a small amount of sodium metal. The yields and other pertinent data on the compounds we have prepared are found in Table I. It may be seen that acetone has been pyridylethylated in negligible yield. Instead, it has been self-condensed to give a mixture of mesityl oxide and isophorone. The other ketones have been mono-2-pyridylethylated in fair to good yields. Furthermore, it may be seen that in the experiments with methyl ethyl ketone and methyl isobutyl ketone, the respective dehydrated ketols were also formed. In several of the runs, after the monopyridylethylated derivatives were distilled from the reaction mixtures, higher boiling nitrogenous materials were isolated, which probably consist of condensation products of one molecule of the ketone(s) with more than one molecule of vinylpyridine. From the pinacolone run, both mono- and di-2-pyridylethylated products have been iso-



$$CH_3COCH_2CH(CH_3)_2 + 2\text{-}C_5H_4NCH{=}CH_2 \begin{cases} \rightarrow 2\text{-}PyCH_2CH_2CH_2COCH_2CH(CH_3)_2 \quad \text{(IV)} \\ \quad \text{Condensation at the } CH_3 \text{ group} \\ \rightarrow CH_3COCH(CH_2CH_2Py\text{-}2)CH(CH_3)_2 \quad \text{(V)} \\ \quad \text{Condensation at the } CH_2 \text{ group} \end{cases}$$

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(1) Doering and Weil, THIS JOURNAL, **69**, 2461 (1947).

(2) Boekelheide and Agnello, *ibid.*, **72**, 5005 (1950).

(3) Boekelheide and Mason, *ibid.*, **73**, 2356 (1951).

TABLE I

PYRIDYLETHYLATION OF CERTAIN KETONES

Ketone	Moles of reactants Ketone	V.P.[a]	Na	Reaction time, hrs.	Yield, %[b]	B.p., °C.	Mm.	d^{25}_4	n^{20}_D	Analyses, % Products Formula	Nitrogen Calcd.	Nitrogen Found	Semicarbazones Formula	Nitrogen Calcd.	Nitrogen Found	M.p., °C.
Acetone	0.40	0.40	[c]	4	1–2[d]					[e]						
Acetophenone	1.0	.50	.10[f]	4[g]	29.2	178	3		1.5725	[h]						
Acetophenone	1.0	.50[i]	.10	6	21.5	78 (m.p.)				[j]						
p-Methylacetophenone	1.0	.50	.10	6	30.7	187–189	2	1.0723	1.5685	$C_{16}H_{17}NO$	5.86	5.81	$C_{17}H_{20}N_4O$	18.91	18.80	166–167
p-Phenylacetophenone	1.0	.50	.10	6	17.9	84.5–85.5 (m.p.)				$C_{21}H_{19}NO$	4.65	4.57	$C_{22}H_{22}N_4O$	15.64	15.70	223–223.5
Methyl β-naphthyl	1.0	.50	.10	6	25.5	44 (m.p.)				$C_{19}H_{17}NO$	5.09	5.09	$C_{20}H_{20}N_4O$	16.86	16.72	185–186
Methyl α-naphthyl	2.0	1.0	.20	6	19.6	232–235	2		1.6240		5.09	5.15	$C_{20}H_{20}N_4O$	16.86	16.86	183–184
2-Acetylthiophene	2.0	1.0	.20	6	19.8	183–184	2	1.1768	1.5977	$C_{13}H_{13}NOS$	6.06	5.90	$C_{14}H_{16}N_4OS$	19.43	19.55	167–168
2-Acetylfuran	2.0	1.0	.20	6	0[k]											
Propiophenone	2.0	1.0	.20	6	81.2	174–176	2	1.0712	1.5615	$C_{16}H_{17}NO$	5.86	5.98	$C_{22}H_{21}N_5O_4$[l]	16.71	17.05	130–131
Pinacolone	0.3	0.3	.03	6	19.7[m]	124–126	2	0.9828	1.4953	$C_{13}H_{19}NO$	6.82	6.82	$C_{14}H_{22}N_4O$	21.36	21.48	153–154
Cyclohexanone	1.0	.50	.10	3.5	39.8	142–144	1–1.5	1.0513	1.5271	$C_{13}H_{17}NO$	6.89	6.88	$C_{14}H_{20}N_4O$	21.53	21.38	165
Diethyl	2.0	1.0	.20	6	53.4	142–144	6	0.9862	1.4980	$C_{12}H_{17}NO$	7.32	7.41	$C_{17}H_{21}N_5O_4$[l]	18.87	18.95	103–104
Methyl ethyl	1.5	0.75	.15	6	28.0[n]	101–102	1	.9982	1.5012	$C_{11}H_{15}NO$	7.91	7.86	$C_{12}H_{18}N_4O$	23.91	23.75	153–154
Methyl isobutyl	1.0	.50	.10	4	32.5[o]	138	2	.9664	1.4950	$C_{13}H_{19}NO$	6.82	6.80	$C_{14}H_{22}N_4O$	21.36	21.32	65–66

[a] V.P. means 2-vinylpyridine. [b] Yield of pyridylethylated product based on vinylpyridine. [c] Five grams of 38% Triton B used as catalyst; sodium amide, sodium, and boron fluoride were ineffective catalysts; with sodium ethoxide, a 46% yield of 2-(2-pyridylethyl) ethyl ether, b.p. 95–97° at 16 mm. was obtained, picrate m.p. 106° (see Doering and Weil, ref. 1). [d] Isolated as picrate, m.p. 111–112° (see ref. 1); mesityl oxide, b.p. 126°, 2,4-dinitrophenylhydrazone, m.p. 203° (Campbell, *Analyst*, **61**, 393 (1936)) and isophorone semicarbazone, m.p. 189–190° (Crossley and Gilling, *J. Chem. Soc.*, **95**, 24 (1909)) were isolated in considerable amounts from all the runs with acetone. [e] Picrate, m.p. 111–112°; semicarbazone, m.p. 115°; mixed m.ps. of each with an authentic sample showed no depression (see ref. 1). [f] Sodium amide was also an effective condensing agent; Triton B was not. [g] In a one-hour reaction time, the yield was 16.6%. [h] Picrate, m.p. 134°; semicarbazone, m.p. 163–164°; mixed m.ps. of each with an authentic sample showed no depression (see ref. 2). [i] 4-Vinylpyridine was used in this run. [j] Picrate, m.p. 140–141° (see ref. 3). [k] Only an intractable tar was isolated. [l] This derivative is a 2,4-dinitrophenylhydrazone. [m] There was also obtained 15.7 g. of what is believed to be a dipyridylethylated derivative, b.p. 206–208° at 2 mm.; d^{25}_4 1.0342; n^{20}_D 1.5321: *Anal.* Calcd. for $C_{20}H_{26}N_2O$: N, 9.02. Found: N, 8.88. [n] Ten grams of 3-methylhepten-3-one-5 was isolated, b.p. 162–164°; d^{25}_4 0.8504; semicarbazone, m.p. 113–114° (Bodroux and Taboury, *Compt. rend.*, **149**, 423 (1902)). [o] Twenty grams of 2,4,8-trimethylnonen-4-one-6 was isolated, b.p. 213–215° (see previous ref.); 2,4-dinitrophenylhydrazone, m.p. 125–126° (Shine and Turner, *J. Inst. Petroleum*, **36**, 73 (1950)).

lated and characterized. It is also of interest to note that while our method for the preparation of phenyl γ-(2-pyridyl)-propyl ketone gives only about half the yield obtained by the method of Boekelheide and Agnello,[2] our route is a more direct one and is effected in much less time. The direct 2-pyridylethylation method has the further advantage that it does not depend upon the use of β-ketoesters as starting materials, very few of which are available from commercial sources. It has also been possible to directly pyridylethylate acetophenone with 4-vinylpyridine to give phenyl γ-(4-pyridyl)-propyl ketone, which was recently prepared[3] from ethyl benzoylacetate and 4-vinylpyridine.

While there is no doubt as to the structures of the monopyridylethylated products derived from the first twelve ketones listed in Table I, it is entirely possible that the reaction of 2-vinylpyridine with the unsymmetrical ketones, methyl ethyl and methyl isobutyl ketone, could give rise to a mixture of isomeric condensation products by pyridylethylation at the α-methyl and/or the α-methylene carbon atoms. The following scheme indicates the formation of the two possible pyridine-containing derivatives from the latter ketones (Py represents the pyridine ring).

In order to determine the structure of the ketone prepared by the direct pyridylethylation procedure, an authentic sample of IV was prepared by the reaction of ethyl isovalerylacetate, which was synthesized by the carbethoxylating methyl isobutyl ketone with diethyl carbonate in the presence of sodium amide,[4] with 2-vinylpyridine and subjecting the condensation product to ketonic cleavage. The boiling points of the material prepared by these two routes were identical. Also, mixed melting points on the semicarbazones of the ketone made by these two different methods showed no depression. Therefore, it appears that the 2-pyridylethylation of methyl isobutyl ketone occurs apparently exclusively at the α-methyl carbon atom.

Since the carbethoxylation of methyl ethyl ketone with diethyl carbonate in the presence of sodium amide is known to give a mixture of isomeric β-ketoesters by acylation at the α-methyl and α-methylene carbon atoms,[4] it was desirable to defi-

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[4] Levine and Hauser, THIS JOURNAL, **66**, 1768 (1944).

nitely establish the structure of its pyridylethylated derivative. This was done by condensing ethyl α-methylacetoacetate with 2-vinylpyridine and subjecting the product to ketonic cleavage. The semicarbazone of this material and that obtained by direct pyridylethylation of the ketone were identical. These reactions are outlined in the following scheme.

$$\begin{array}{l}
CH_3COCH(CH_3)CO_2C_2H_5 + 2\text{-}C_5H_4NCH{=}CH_2 \\
\qquad\qquad\downarrow \\
CH_3COC(CH_3)(CH_2CH_2C_5H_4N\text{-}2)CO_2C_2H_5 \\
\qquad\qquad\downarrow \\
CH_3COC(H)(CH_3)(CH_2CH_2C_5H_4N\text{-}2) \\
\qquad\qquad\uparrow \\
CH_3COCH_2CH_3 + 2\text{-}C_5H_4NCH{=}CH_2
\end{array}$$

Thus, with methyl ethyl ketone pyridylethylation appears to occur exclusively at the α-methylene carbon atom.

The mechanism of the pyridylethylation of ketones in the presence of sodium is probably analogous to that proposed by Doering and Weil[1] for the condensation of β-ketoesters and malonic esters with 2-vinylpyridine in the presence of alcoholic sodium ethoxide.

Work is now in progress in this Laboratory on the extension of these studies to the direct pyridylethylation of more ketones and a large variety of other types of active hydrogen compounds with 2- and 4-vinylpyridine.

Experimental

General Procedure for the 2-Pyridylethylation of Ketones.—A mixture of two equivalents of the appropriate ketone and one of 4- or 2-vinylpyridine was placed in a 500-ml. three-necked, round-bottom flask equipped with ground-glass joints and carrying a thermometer dipping into the mixture, a dibutyl phthalate-sealed stirrer and a reflux condenser protected from atmospheric moisture with a drying tube filled with Drierite. To the rapidly stirred mixture, 0.2 of an equivalent of small pieces of sodium metal was added rapidly. After a few minutes of stirring, a highly exothermic reaction started. If the reaction became too violent, it was checked by immersing the flask in an ice-water-bath. After the exothermic reaction subsided, the mixture was heated to and kept at its reflux temperature for the reaction times indicated in Table I. The mixture was then allowed to cool to room temperature and poured onto a mixture of ice and 1.3–1.5 equivalents of concentrated hydrochloric acid. Any acid-insoluble oil was removed and the aqueous solution extracted with several 50-ml. portions of benzene. The oil and the combined benzene extracts were dried over anhydrous sodium carbonate, the solvent distilled and the residue distilled first at atmospheric pressure and then in vacuum to give recovered ketone and neutral condensation products. The aqueous phase was then made strongly basic by the addition of 30% aqueous sodium hydroxide solution. After separating the oil which formed, the water layer was extracted with several 50-ml. portions of benzene. The oil and the benzene extracts were combined, dried over anhydrous sodium carbonate, the solvent removed and the residue fractionated in vacuum to give unreacted 2-vinylpyridine and the pyridylethylated ketones.

Preparation of Authentic Samples of Pyridylethylated Ketones.—Phenyl γ-(2-pyridyl)-propyl ketone, isobutyl γ-(2-pyridyl)-propyl ketone and methyl (α-methyl-γ-2-pyridylpropyl) ketone were prepared by the sodium-catalyzed pyridylethylation of ethyl benzoylacetate, ethyl isovalerylacetate and ethyl α-methylacetoacetate and subjecting the condensation products to ketonic cleavage by methods which have been published previously.[1,2] Mixed melting points on the semicarbazones of these compounds with samples prepared by the direct pyridylethylation of acetophenone, methyl isobutyl ketone and methyl ethyl ketone, respectively, showed no depression.

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PITTSBURGH 13, PENNSYLVANIA RECEIVED JUNE 18, 1951

[CONTRIBUTION FROM THE RESEARCH DIVISION OF ANHEUSER-BUSCH, INC., AND DEPARTMENT OF BOTANY, WASHINGTON UNIVERSITY]

Uridine as a Growth Factor for a Strain of *Streptococcus Faecalis*[1]

BY HARRISON A. HOFFMANN[2] AND PAUL L. PAVCEK

Hitherto unreported factors in yeast extract (Basamin) stimulate early growth of a strain of *Streptococcus faecalis*. The growth stimulating substances have been concentrated approximately a thousand-fold by extraction with aqueous acetone and subsequent treatment with charcoal and Superfiltrol. By means of ultraviolet spectrophotometry and paper-partition chromatography, one of the active components of the concentrate was identified as uridine. Commercial uridine and pure preparations obtained from Basamin evoke a half-maximum growth response as compared to the activity of the concentrate; however, surface-active agents such as Tween-80 and Triton A-20 act synergistically with uridine to give a growth response equivalent to that obtained from yeast extract.

A number of lactic acid bacteria grow well in a medium of known chemical composition. However, supplementation of the synthetic medium with extracts of natural substances such as yeast and liver significantly shortens the lag phase and the incubation time required for maximum growth of these organisms.

During an investigation of the nutritional requirements of lactic acid bacteria, it was observed that yeast extract (Basamin) provided a stimulation of the rate of growth of a strain of *Streptococcus faecalis*, which could not be duplicated by supplementation of the basal medium with any of a large variety of known compounds available at that time. Studies described here show that uridine is one of the factors in Basamin contributing to the early growth of the test organism, and present evidence for other factors in yeast extract which act synergistically with uridine.

Experimental

The organism used in this study is a strain of *S. faecalis*, presumably ATCC No. 8043. However, a more recent culture of the same number obtained from the American

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[1] Presented in part, before the Division of Agricultural and Food Chemistry, at the April, 1951 Meeting of the American Chemical Society at Cleveland, Ohio.

[2] From the Ph.D. dissertation of H. A. Hoffmann, 1951.