The petroleum ether solution was then poured over a column of activated alumina (30 g.) and the azathianaphthene eluted with a solution of 25% ether-petroleum ether. This treatment removed tarry material which was difficult to remove by crystallization. The solvent was then evaporated and the residue vacuum sublimed at 60°/0.1 mm. to give 2.2 g. of product of m.p. 71.5–72.5°.

Anal. Calcd. for C_8H_7NS: C, 64.39; H, 4.73. Found: C, 64.58; H, 5.11.

The picrate was prepared and crystallized from ethanol to give a product which melted at 222–224°.

Anal. Calcd. for $C_{14}H_{10}N_4O_7S$: C, 44.45; H, 2.66. Found: C, 44.85; H, 2.96.

6-Methyl-5-azathianaphthene methiodide (VII). Compound VI was refluxed for a few minutes with excess methyl iodide and the mixture then was diluted with ether. The solid product which separated was removed by filtration and recrystallized from methanol to give a substance of m.p. 240–242°.

Anal. Calcd. for $C_9H_{10}INS$: C, 37.09; H, 3.46. Found: C, 37.18; H, 3.77.

1-Phenyl-2-[6-(5-azathianaphthenyl)]ethene methiodide (VIII). Compound VII (1.5 g.), 2 ml. of benzaldehyde, and 1 ml. of piperidine were placed in 20 ml. of methanol and refluxed for 12 hr. Cooling the mixture caused 1.03 g. of yellow solid m.p. 290–292° (decomp.) to separate. The filtrate from which the yellow solid separated was refluxed for 12 hr. more and then cooled, whereupon 0.27 g. more of the product crystallized. Recrystallization of these two fractions did not raise the melting point.

Anal. Calcd. for $C_{16}H_{14}INS$: C, 50.28; H, 3.69. Found: C, 50.97; H, 3.98.

1-Phenyl-2-[6-(5-azathianaphthenyl)]ethene (IX). Compound VIII (526 mg.) was heated at 280°/0.25 mm. which caused it to decompose and sublime. The 318 mg. of product melted at 118–120°. After recrystallization from ligroin it melted at 126–127°.

Anal. Calcd. for $C_{15}H_{11}NS$: C, 75.91; H, 4.67. Found: C, 76.08; H, 5.13.

CLAREMONT, CALIF.

[CONTRIBUTION NO. 1007 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Synthesis of Nitrogen-Containing Ketones. VII. A Study of the Acylation of 4-Picoline[1,2]

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The lateral metalation of 4-picoline cannot be effected by means of phenylmagnesium bromide, methylmagnesium iodide, or ethylmagnesium bromide. However, its reaction with phenyllithium by either the Standard Addition method (S.A.) or the Reverse Addition method (R.A.) followed by the addition of an acylating ester gives mixtures of the desired 4-picolyl ketone and the azomethine addition products, 2-phenyl-4-methylpyridine and 2,6-diphenyl-4-methylpyridine. Although the reaction of 4-picoline, *n*-butyllithium, and methyl benzoate by the S.A. method gives a mixture of 2-*n*-butyl-4-methylpyridine, A, (36%) and 4,4′-dimethyl-2,2′-dipyridyl and none of the desired 4-phenacylpyridine, B, repeating this reaction by the R.A. method gave a 15.5% yield of A and a 39.8% yield of B. Furthermore, 4-picoline may be acylated with esters in acceptable yields by using both methyllithium and sodium amide as the condensing agents.

The previous papers in this series have been concerned with the synthesis of ketones containing pyridine and quinoline rings by the side-chain acylation of 2-picoline,[4,5] 3-picoline,[6] quinaldine,[5] and certain related compounds.[2,5,7] The present report deals with the acylation of 4-picoline and certain of its derivatives.

A survey of the literature indicated that a general method for the synthesis of ketones of the type, $4\text{-}C_5H_4NCH_2COR$ (I), has apparently not been devised. In the aromatic series (I, R = aryl) the following results have been reported. Chichibabin[8] obtained 4-phenacylpyridine, II (I, R = C_6H_5), in unreported yield by the reaction of sodium amide, 4-picoline, and benzonitrile followed by hydrolysis of the resulting ketimine. Although only a low yield of this ketone was also obtained by Smith *et al.*[9] from the reaction of 4-picoline, phenyllithium, and benzonitrile, these workers obtained fair to good yields of II and related ketones by applying, in the 4-picoline series, the multi-stage method developed by Scheuing and Winterhalder[10] for the synthesis of aryl 2-picolyl ketones. This route involves the following steps: $4\text{-}C_5H_4NCH_3 + ArCHO \rightarrow 4\text{-}C_5H_4NCH{=}CHAr \rightarrow 4\text{-}C_5H_4NCHBrCHBrAr \rightarrow 4\text{-}C_5H_4NC{\equiv}CAr \rightarrow 4\text{-}C_5H_4NCH_2COAr$

(1) This work was performed under Contract No. AT(30-1)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.

(2) For paper VI in this series, see C. Osuch and R. Levine, *J. Org. Chem.*, **21**, 1099 (1956).

(3) This paper is based on part of the thesis presented by Carl Osuch to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree; present address: Monsanto Chemical Co., St. Louis, Mo.

(4) N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Am. Chem. Soc.*, **73**, 4301 (1951).

(5) N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **74**, 5217 (1952).

(6) A. D. Miller, C. Osuch, N. N. Goldberg, and R. Levine, *J. Am. Chem. Soc.*, **78**, 674 (1956).

(7) N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **77**, 3647 (1955).

(8) A. E. Chichibabin, *Rec. trav. chim.*, **57**, 582 (1938).

(9) J. M. Smith, H. W. Stewart, B. Roth, and E. H. Northey, *J. Am. Chem. Soc.*, **70**, 3997 (1948).

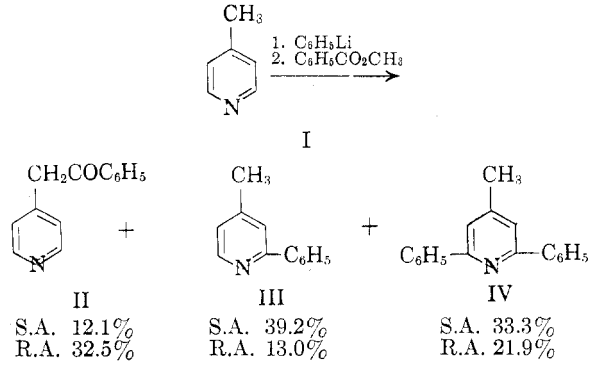
(10) G. Scheuing and L. Winterhalder, *Ann.*, **473**, 126 (1929); German Patent **594,849**, March 22, 1934 [*Chem. Abstr.*, **28**, 4542 (1934)].

Previous attempts to prepare alkyl 4-pyridyl ketones (I, R = alkyl) have also met with only moderate success. Although Burger and Ullyot[11] obtained none of the desired 4-acetonylpyridine (I, R = CH_3) from the reaction of 4-picoline, phenyllithium, and acetyl chloride or acetonitrile, this ketone was subsequently obtained in 50% yield by Burger *et al.*[12] by the interaction of the difficultly accessible 4-pyridylacetic acid with acetic anhydride and sodium acetate. During the course of the present investigation, Hey and Wibaut[13] published a report in which they claim to have obtained a 34% yield of this ketone by the reaction of ethyl acetate with 4-picolyllithium, which was prepared by the slow *addition of phenyllithium to 4-picoline* (*Reverse Addition Method*) rather than by *adding the tar base to the organolithium compound* (*Standard Addition Method*).

Based on our previous success in the 2-picoline series,[2,4,5,7] it appeared reasonable to expect that 4-picoline could also be acylated with a variety of esters provided that it could first be metalated at its side chain. Therefore, attempts were made to metalate this tar base by treating it with several Grignard reagents, organolithium compounds, and sodium amide.

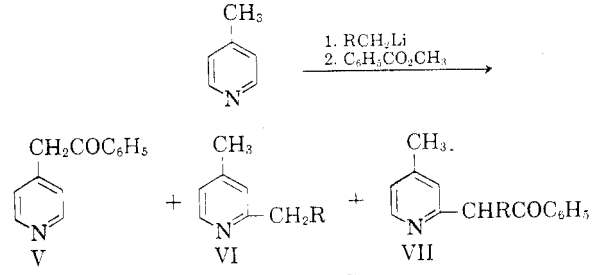
We first attempted the acylation of 4-picoline with methyl benzoate using ether solutions of phenylmagnesium bromide, methylmagnesium iodide, and ethylmagnesium bromide as the condensing agents. None of the desired 4-phenacylpyridine was obtained. Instead, the following neutral materials were isolated: triphenylcarbinol (58.8%); a mixture of dimethylphenylcarbinol and α-methylstyrene; and diethylphenylcarbinol (86.6%), respectively.[14]

We next investigated the acylation of 4-picoline with methyl benzoate using phenyllithium as the metalating agent and employing both the Standard Addition (S.A.) and the Reverse Addition (R.A.) methods. Both of these procedures gave mixtures of 4-phenacylpyridine, II, and the azomethine addition products, 2-phenyl-4-methylpyridine, III, and 2,6-diphenyl-4-methylpyridine, IV. Apparently, as shown in the accompanying scheme, the use of the R.A. method greatly decreases the extent of azomethine addition and increases the extent of lateral metalation.



Because of the above results and the claim by Hey and Wibaut[13] that the reaction of phenyllithium with 4-picoline and ethyl acetate by the R.A. method gave a 34% yield of 4-acetonylpyridine, V, (I, R = CH_3) and apparently none of the azomethine addition products, we reinvestigated the acetylation of 4-picoline by the R.A. method. In contrast with the previously reported[13] results we obtained a mixture of 4-acetonylpyridine, V, (22%) and 2-phenyl-4-methylpyridine, III, (6%).[15]

We next attempted to effect the lateral metalation of 4-picoline by means of the aliphatic organolithium compounds, *n*-butyllithium and methyllithium. Theoretically, some or all of the following products might be formed by the addition of an acylating ester such as methyl benzoate to these reaction mixtures: (*1*) the desired ketone, 4-phenacylpyridine, II, (by lateral metalation of 4-picoline followed by acylation): (*2*) the azomethine addition products, VI, and (*3*) the ketones, VII, (from VI by lateral metalation at the substituent in the 2-position of the pyridine ring followed by acylation[16]).



When 4-picoline was added to *n*-butyllithium (S.A.) followed by the addition of methyl benzoate,

(11) A. Burger and G. E. Ullyot, *J. Org. Chem.*, **12**, 342 (1947).

(12) A. Burger, J. R. Rector, and A. C. Schmalz, *J. Am. Chem. Soc.*, **74**, 3175 (1952).

(13) J. W. Hey and J. P. Wibaut, *Rec. trav. chim.*, **72**, 522 (1953).

(14) During the addition of the 4-picoline to the Grignard reagents, white precipitates are formed. These precipitates, which appear to be complexes between the Grignard reagents and 4-picoline, then probably react with the ester to give the observed products. These observations parallel those of B. Oddo [*Gazz. chim. ital.*, **37**, 356 (1907)], who found that pyridine reacts with methylmagnesium iodide and phenylmagnesium bromide to form ether-insoluble complexes, which on treatment with benzaldehyde give methylphenylcarbinol and diphenylcarbinol, respectively.

(15) Since, in our hands, the mixture of III and V could not be separated by distillation, it was converted to a mixture of picrates, which was separated into its components by fractional crystallization. Therefore, it seems possible that Hey and Wibaut[13] had a mixture of III and V.

(16) Another possible product would be an isomer of VII, which might conceivably be formed by the lateral metalation of VI at its 4-methyl group followed by acylation. However, the formation of this isomer is unlikely since the preferred reaction between an organolithium compound and a 2,4-dialkylpyridine appears to be at the 2-position of the pyridine ring (see ref. 7).

none of the desired 4-phenacylpyridine was isolated. However, there was obtained a mixture of 36% of 2-*n*-butyl-4-methylpyridine (VI, R = *n*-C_3H_7),[17] a small amount of 4,4′-dimethyl-2,2′-dipyridyl,[18] and an unidentified, viscous, high-boiling nitrogenous oil.[19] When this reaction was repeated, except that the R.A. method was used, a mixture of 15.5% of 2-*n*-butyl-4-methylpyridine and 39.8% of 4-phenacylpyridine was obtained.

With the idea in mind that it might be possible to increase the extent of lateral metalation and decrease the extent of azomethine addition by changing the organolithium compound, the acylation of 4-picoline with both methyl benzoate and methyl acetate was attempted by the R.A. method using methyllithium as the condensing agent. From these reactions, none of the azomethine addition product was isolated and 4-phenacylpyridine and 4-acetonylpyridine were obtained in yields of 48.7% and 27.0% respectively. Since azomethine addition did not occur by the R.A. method, it was of interest to repeat these reactions by the much more convenient, less time consuming S.A. method. By this procedure, 4-phenacylpyridine (50.8%) and 4-acetonylpyridine (22.6%) as well as trace amounts of 2,4-lutidine and 4,4′-dimethyl-2,2′-dipyridyl[20] were obtained. The methyllithium-S.A. method was then used to effect three more acylations with the results listed in Table I.

Finally it was of interest to determine whether sodium amide in liquid ammonia could be used as the condensing agent. As may be seen in Table I, this base gave acceptable yields of ketones with all the esters used except methyl acetate. It should also be noted that although it was not possible to acylate 4-ethylpyridine with methyl benzoate using methyllithium as the condensing agent, an 85% yield of the desired product, α-(4-pyridyl)propiophenone was obtained by the sodium amide method.

The properties of the ketones which were prepared are found in Table II.

TABLE I

4-PICOLYL KETONES, 4-$C_5H_4NCH_2COR$, BY ACYLATING 4-PICOLINE WITH METHYL ESTERS IN THE PRESENCE OF VARIOUS CONDENSING AGENTS

R	Condensing Agent[a]	Yield, %
C_6H_5	C_6H_5Li	12.1(S.A.)[b,c]; 32.5(R.A.)[b,d]
	CH_3Li	50.8(S.A.)[b,e]; 48.7(R.A.)[b]
	n-C_4H_9Li	0.0(S.A.)[b,f]; 39.8(R.A.)[b,g]
	$NaNH_2$	73.8
4-C_5H_4N[h]	$NaNH_2$	56.0
CH_3	C_6H_5Li	22.0(R.A.)[b,i]
	CH_3Li	22.6(S.A.)[b,e]; 27.0(R.A.)[b]
	$NaNH_2$	6.3
C_2H_5	CH_3Li	54.8(S.A.)[b]
	$NaNH_2$	50.0
i-C_3H_7[j]	CH_3Li	65.6(S.A.)[b]
	$NaNH_2$	79.1
t-C_4H_9	CH_3Li	70.6(S.A.)[b]
	$NaNH_2$	63.3

[a] In all reactions a 2:2:1 molar ratio of condensing agent: 4-picoline:ester was used. [b] S.A. = Standard Addition Method, i.e., tar base was added to the organolithium compound. R.A. = Reverse Addition Method, i.e., the organolithium compound was added to the tar base. [c] A 39.2% yield of 2-phenyl-4-methylpyridine, A, and a 33.3% yield of 2,6-diphenyl-4-methylpyridine, B, were also isolated. [d] A 13.0% yield of A and a 21.9% yield of B were also isolated. [e] Traces of 2,4-lutidine, C, and 4,4′-dimethyl-2,2′-dipyridyl, D, were also isolated. [f] A 36% yield of 2-*n*-butyl-4-methylpyridine, E, and a trace of D were also isolated. [g] A 15.5% yield of E was also obtained. [h] 4-C_5H_4N = 4-pyridyl radical. [i] A 6% yield of A was also obtained. [j] Ethyl ester was used.

EXPERIMENTAL[21]

In this reaction several typical experiments are described.

I. *Reaction of phenylmagnesium bromide, 4-picoline and methyl benzoate.* 4-Picoline (0.2 mole, 18.6 g.), diluted with an equal volume of anhydrous ether, was added to phenylmagnesium bromide (0.2 mole in 250 ml. of anhydrous ether). During the addition of the 4-picoline a greyish-white precipitate formed. After the addition of the tar base was completed, methyl benzoate (0.1 mole, 13.6 g.), diluted with an equal volume of ether, was added at such a rate that the solvent gently refluxed. The reaction was refluxed for an additional 30 min. and was then poured onto a mixture of crushed ice and 25 ml. of concentrated hydrochloric acid. Processing the mixture in the customary fashion[2,4] gave 9.3 g. of recovered 4-picoline, b.p. 140–146°, and 15.3

(17) H. Gilman and H. S. Broadbent [*J. Am. Chem. Soc.*, 70, 2809 (1948)] have apparently prepared this compound in 13.4% yield by the reaction of 4-picoline and *n*-butyllithium at −10°. They report that its picrate melts at 88.5–90.5° while the picrate of our material melts at 98.6–99.0°. Therefore, we prepared an authentic sample of VI (R = *n*-C_3H_7) in 78.8% yield by alkylating 2,4-lutidine with *n*-propyl bromide using phenyllithium as the condensing agent [for the procedure used, see C. Osuch and R. Levine, *J. Am. Chem. Soc.*, 78, 1723 (1956)]. A mixed melting point between the picrate of the authentic sample and that obtained in the reaction of 4-picoline with *n*-butyllithium showed no depression.

(18) This compound probably arises from the nuclear metalation of 4-picoline by *n*-butyllithium to give 2-lithio-4-methylpyridine, which then undergoes azomethine addition to a second molecule of 4-picoline followed by the elimination of lithium hydride. Evidence in support of this argument was obtained by repeating this reaction in the absence of the ester and isolating 39.8% of VI (R = *n*-C_3H_7) and 0.7 g. of the dipyridyl.

(19) We have found that most ketones which have the grouping, —CHRCOR′, at the 2-position of the pyridine ring produce a blue-green color when treated with alcoholic iron (III) chloride solution. Apparently this oil does not contain an appreciable amount of α-(4-methyl-2-pyridyl)-valerophenone (VII, R = *n*-C_3H_7) since it does not give the iron (III) chloride color reaction, while an authentic sample of this ketone, which was prepared in 60% yield from the reaction of 2-*n*-butyl-4-methylpyridine, phenyllithium, and methyl benzoate, gives a positive test.

(20) That this compound probably arises from the reaction of 4-picoline and methyllithium (also see footnote 18) was shown by the fact that it was obtained in 5% yield by the interaction of these reagents in the absence of an acylating ester.

(21) The 4-picoline used in this study was supplied through the courtesy of Dr. F. E. Cislak, Reilly Tar and Chemical Corp.

TABLE II

PROPERTIES OF THE KETONES, $4\text{-}C_5H_4NCHRCOR'$

R	R'	M.P., °C.	B.P. °C.	B.P. mm.	Formula	Analysis Calcd. C	Calcd. H	Found C	Found H	M.P., °C.	Picrate Formula	Picrate Nitrogen Calcd.	Picrate Nitrogen Found
H	C_6H_5	112–113.4[a]			$C_{12}H_{10}N_2O$	72.71	5.08	72.84	5.18	167.5–168.1[b]	$C_{19}H_{14}N_4O_8$	13.14	12.97
H	$4\text{-}C_5H_4N$[c]	116–116.8[d]								[e]			
H	CH_3[f]		110–115	3–4						155–155.4[b,g]			
H	C_2H_5		86–88.5	1.0	$C_9H_{11}NO$	72.45	7.43	72.00	7.38	163.2–164[b]	$C_{15}H_{14}N_4O_8$	[h]	
H	$i\text{-}C_3H_7$		95–97	1.0	$C_{10}H_{13}NO$	73.58	8.03	73.10	7.80	121.0–121.7[b]	$C_{16}H_{16}N_4O_8$	14.28	14.07
H	$t\text{-}C_4H_9$	41.8–42.4[i]	98–102	1.0	$C_{11}H_{15}NO$	74.54	8.53	74.36	8.38	157.3–157.8[b]	$C_{17}H_{18}N_4O_8$[j]	13.79	14.26
CH_3	C_6H_5	62.4–63.0[i]			$C_{14}H_{13}NO$[k]	75.59	6.20	75.57	5.75	150.1–150.9[b,l]	$C_{20}H_{16}N_4O_8$	12.72	13.08

[a] See reference 9. [b] Recrystallized from 95% ethanol. [c] $4\text{-}C_5H_4N$ = 4-pyridyl radical. [d] Recrystallized from 75–90° petroleum ether. [e] Attempts to prepare an analytically pure picrate or trinitrocresolate failed. [f] Reference 13 gives a b.p. of 75.5° at 0.1 mm. [g] See reference 13. [h] Calcd.: C, 47.62; H, 3.73. Found: C, 47.72; H, 3.84. [i] Recrystallized from 30–60° petroleum ether. [j] Calcd.: C, 50.25; H, 4.46. Found: C, 49.93; H, 4.38. [k] Calcd.: N, 6.63. Found: N, 6.82; obtained in 84.8% yield. [l] Darkens on standing.

g. (58.8%) of triphenylcarbinol, m.p. 161–162° alone and when mixed with an authentic sample.

II. *Reaction of phenyllithium and methyllithium with 4-picoline and methyl benzoate.* (a) *Phenyllithium and the Standard Addition (S.A.) Method.* By using the previously described procedures for the acylation of 2-picoline[4] and its homologues,[2] the interaction of phenyllithium (0.4 mole), 4-picoline (0.4 mole, 37.2 g.), and methyl benzoate (0.2 mole, 27.2 g.) gave 23.2 g. (39.2%) of 2-phenyl-4-methylpyridine, b.p. 113–114° at 2.0 mm. (picrate, m.p. 187.5–188.5°[22]); 16.4 g. (33.3%) of 2,6-diphenyl-4-methylpyridine, b.p. 188–190° at 1.5 mm.,[22] and 4.8 g. (12.1%) of 4-phenacylpyridine, m.p. 112–113.4° (lit.[9] 113–115°), picrate, m.p. 167.5–168.1°.

Anal. Calcd. for $C_{19}H_{14}N_4O_8$: N, 13.14. Found: N, 12.97.

(b) *Phenyllithium and the Reverse Addition (R.A.) Method.* Phenyllithium (0.4 mole in 400 ml. of anhydrous ether) was added to 4-picoline (0.4 mole, 37.2 g., in 250 ml. of anhydrous ether) at such a rate that the ether did not reflux (2.5 to 3 hr.). To the dark, brownish-red suspension thus obtained, methyl benzoate (0.2 mole, 27.2 g.), dissolved in 50 ml. of anhydrous ether, was added at such a rate that the solvent refluxed gently. The mixture was refluxed for an additional 30 min. and processed in the regular manner[2,4] to give 8.8 g. (13.0%) of 2-phenyl-4-methylpyridine, 12.8 g. (32.5%) of 4-phenacylpyridine, and 10.8 g. (21.9%) of 2,6-diphenyl-4-methylpyridine.

(c) *Methyllithium and the Standard Addition (S.A.) Method.* When reaction IIa was repeated, except that the phenyllithium was replaced by methyllithium (0.4 mole), there were obtained 17.4 g. of basic material (fraction A, b.p. 138.5–160°) and 20.0 g. (50.8%, b.p. 140–160° at 1.0 mm., m.p. 112.5–113.4° from 60–70° petroleum ether) of 4-phenacylpyridine. The small amount of oil, which remained in the column after the distillation of the above materials, was shown to contain some 4,4′-dimethyl-2,2′-dipyridyl since it gave a red color when treated with aqueous iron (II) sulfate solution and formed a picrate, m.p. 202–203° alone and when mixed with an authentic sample. Redistillation of fraction A gave 15.0 g. of material, b.p. 140–150° (predominantly 4-picoline) and less than one gram of residue, which was shown to contain some 2,4-lutidine since it gave a picrate, m.p. 179.5–180.5° alone and when mixed with an authentic sample.

III. *Reaction of n-butyllithium with 4-picoline by the S.A. Method.* (a) *In the presence of methyl benzoate.* From 0.292 mole of *n*-butyllithium [prepared in 73% yield from 0.8 mole (5.6 g.) of lithium and 0.4 mole (54.8 g.) of *n*-butyl bromide], 0.292 mole (27.2 g.) of 4-picoline, and 0.146 mole (19.8 g.) of methyl benzoate there was obtained a mixture of 15.8 g. (36.3%) of 2-*n*-butyl-4-methylpyridine (b.p. 205–208°; picrate, m.p. 98.6–99.0° alone and when mixed with an authentic sample, see below), 0.1 g. of 4,4′-dimethyl-2,2′-dipyridyl (m.p. 169.5–170.3°[23] from 60–70° petroleum ether), and 10.8 g. of a viscous, nitrogenous oil (b.p. 148–180° at 1.5 mm.) from which it was not possible to isolate any pure compounds. The dipyridyl gave a bright red color when treated with aqueous iron (II) sulfate solution and formed a monopicrate, m.p. 202–203°, from 95% ethanol.

Anal. Calcd. for $C_{18}H_{15}N_5O_7$: C, 52.30; H, 3.62. Found: C, 52.33; H, 3.48.

(b) *In the absence of methyl benzoate.* From the interaction of 0.278 mole of *n*-butyllithium and 0.278 mole (25.9 g.) of 4-picoline, there was obtained 16.5 g. (39.8%) of 2-*n*-butyl-4-methylpyridine, b.p. 205–208°, and 0.7 g. of 4,4′-dimethyl-2,2′-dipyridyl, m.p. 169.6–170.4°.

IV. *Synthesis of an authentic sample of 2-n-butyl-4-methylpyridine.* The interaction of phenyllithium (0.4 mole), 2,4-lutidine (0.4 mole, 42.9 g.), and *n*-propyl bromide (0.2 mole,

(22) C. Osuch and R. Levine, *J. Am. Chem. Soc.*, **78**, 1723 (1956).

(23) F. H. Case, *J. Am. Chem. Soc.*, **68**, 2574 (1946).

24.6 g.), using the previously described procedure[22] for similar alkylations, gave 23.5 g. (78.8%) of 2-*n*-butyl-4-methylpyridine, b.p. 205–208°, which gave a picrate, m.p. 98.6–99.0° (lit. 88.5–90.5°[17]).

Anal. Calcd. for $C_{16}H_{18}N_4O_7$: N, 14.81. Found: N, 14.85.

V. *Synthesis of an authentic sample of α-(4-methyl-2-pyridyl)valerophenone.* The interaction of phenyllithium (0.2 mole), 2-*n*-butyl-4-methylpyridine (0.2 mole, 29.8 g.), and methyl benzoate (0.1 mole, 13.6 g.), using the previously described procedure for similar acylations,[2,4] gave 15.1 g. (59.7%) of α-(4-methyl-2-pyridyl)valerophenone, b.p. 168–170° at 1.5 mm.

Anal. Calcd. for $C_{17}H_{19}NO$: N, 5.53. Found: N, 6.05.

This ketone gave a dark, blue-green color with iron(III) chloride solution and gave a picrate, m.p. 109.2–109.6° (from 95% ethanol).

Anal. Calcd. for $C_{23}H_{22}N_4O_8$: N, 11.61. Found: N, 11.56.

VI. *The use of sodium amide to effect the benzoylation of 4-alkylpyridines.* (a) *4-Picoline.* Undiluted 4-picoline (0.4 mole, 37.2 g.) was added to a suspension of sodium amide [prepared from 0.4 mole (9.2 g.) of sodium in 300 ml. of anhydrous liquid ammonia] and the mixture was stirred for 15 to 20 min. To the suspension of 4-picolylsodium thus obtained, methyl benzoate (0.2 mole, 27.2 g.), dissolved in 30 ml. of anhydrous ether, was added over a period of 25 to 35 min. and stirring was continued for one more hour. The reaction was quenched by the addition of excess solid ammonium chloride and the liquid ammonia was replaced by adding ether and warming on a water bath. When the liquid ammonia had evaporated, as indicated by the refluxing of the ether, the reaction mixture was poured onto a mixture of ice and hydrochloric acid and processed in the regular fashion.[2,4] The solvent was distilled from the dried ether extracts and on cooling a semi-solid mass was obtained. This was filtered and gave 26.4 g. of 4-phenacylpyridine, m.p. 112–113.4°. The mother liquor was distilled to give 4.0 g. of 4-picoline, b.p. 140–145°, and 6.9 g. of a solid mixture of benzamide and 4-phenacylpyridine, b.p. 135–160° at 1.1 mm. This mixture was washed with several portions of cold anhydrous ether and filtered to separate the ketone from the amide. On the funnel there remained 3.6 g. of benzamide, m.p. 126.4–127.6° alone and when mixed with an authentic sample. The combined ether washings were distilled to given an additional 2.7 g. of 4-phenacylpyridine, b.p. 135–150° at 1.1 mm., m.p. 112–113.5°. The total yield of the ketone was 29.1 g. (73.8%).

(b) *4-Ethylpyridine.* The last reaction was repeated except that sodium amide (0.2 mole), 4-ethylpyridine (0.2 mole, 21.5 g.), and methyl benzoate (0.1 mole, 13.6 g.) were used. On processing the reaction mixture there was obtained 18.8 g. of crude product, b.p. 130–147° at 1 mm. This material, which crystallized on standing, was filtered and washed with several portions of anhydrous ether. Benzamide (0.5 g., m.p. 126.5–127.5°) remained on the funnel. The solvent was removed from the combined ether washings to give 17.9 g. (84.8%) of α-(4-pyridyl)propiophenone, m.p. 62.4–63.0° (from 30–60° petroleum ether).

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.57; H, 5.75; N, 6.82.

The ketone gave a picrate, m.p. 150.1–150.9° (from 95% ethanol).

Anal. Calcd. for $C_{20}H_{16}N_4O_8$: N, 12.72. Found: N, 13.08.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

Thiazolidine Chemistry. II. The Preparation of 2-Substituted Thiazolidine-4-carboxylic Acids[1,2]

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Twenty-two 2-substituted thiazolidine-4-carboxylic acids have been prepared by the condensation of cysteine with aliphatic and aromatic aldehydes. Attempts to synthesize similar compounds from some α,β-unsaturated aldehydes were unsuccessful. An explanation of this failure of the reaction is discussed.

In the course of an investigation directed towards the preparation of water-soluble thiazolidine salts, the scope of the reaction of cysteine with aldehydes has been extended and an attempt made to explain its limitations. Twenty-two new (L)-2-substituted thiazolidine-4-carboxylic acids,[5] listed in Table I, were prepared using the method of Schubert.[6]

The preparation of the thiazolidines from the saturated aliphatic aldehydes indicated that increasing the chain length does not hinder the reaction. All these compounds crystallize in shining white platelets and are soluble in boiling isopropyl alcohol. The melting points decrease with increasing molecular weight. This was to be expected, since the compounds change from essentially heterocyclic carboxylic acids with a small aliphatic side chain to hydrocarbons with a small heterocyclic acid at one end.

The potassium salts of 2-undecyl and 2-hexadecylthiazolidine-4-carboxylic acids were prepared. The former was found to be soluble in water at a concentration of 0.1%, but the latter was insoluble at a 0.02% concentration, at 25°. The potassium salts were unstable and slowly decomposed on aging. This is in agreement with the reported findings

(1) Previous paper in series: H. Soloway, F. Kipnis, J. Ornfelt, and P. E. Spoerri, *J. Am. Chem. Soc.*, **70**, 1667 (1948).

(2) Abstracted in part from the M.S. thesis of Irving R. Schmolka, Polytechnic Institute of Brooklyn, June 1950. Presented in part at the first Meeting in Miniature, Metropolitan Long Island Subsection of the AMERICAN CHEMICAL SOCIETY's New York Section, March 17, 1950.

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(5) Y. Kashida, *J. Pharm. Soc. Japan*, **69**, 185 (1949), has since reported No. 15 and No. 19, Table I.

(6) M. P. Schubert, *J. Biol. Chem.*, **111**, 671 (1935); **114**, 341 (1936); **121**, 539 (1937); **130**, 601 (1939).