methyl ester are listed in Table II. In the spectrum the strong band at 5.77 μ is indicative of an unconjugated ester group. The 6.09 μ band and the band at 11.16 are characteristic of a $CH_2{=}CR_2$ double bond.[6]

TABLE II

INFRARED SPECTRUM OF METHYL 3,3,5-TRIMETHYL-5-HEXENOATE

Wave length, μ,	Intensity[a]
3.39	10
5.77	10
6.09	4
6.79–6.94	10
7.20	1
7.30	3
7.49	10
8.00–8.73	10
8.95	10
9.29	2
9.83	10
10.16	1
10.61	0
11.16	10
11.70	2
12.17	2
13.31	1

[a] Intensity scale from 0 (0–5% absorption) to 10 (95–100% absorption) in cell 0.036 mm. thick.

Hydrogenation of Ethyl 3,3,5-Trimethylhexanoate.—A mixture of 90 g. of ethyl 3,3,5-trimethylhexanoate and 10 g. of copper chromite was hydrogenated at 275° and 2500 p.s.i.g. for 24 hours. Fractionation of the product yielded 62 g. of 3,3,5-trimethylhexanol (b.p. 94.0–95.4° (18 mm.), n^{20}_{D} 1.4345, hydroxyl value, 0.655 eq./100 g., calcd. for $C_9H_{20}O$, 0.694 eq./100 g.).

Preparation of 2,3,5-Trimethylhexane.—A mixture of 37 g. of the C_9 alcohol from above, 11 g. of potassium acid sulfate, and 15 ml. of 50% sulfuric acid was distilled yielding 19 ml. of a hydrocarbon fraction boiling at 125–137°. This was hydrogenated over Raney nickel yielding 12 ml. of 2,3,5-trimethylhexane (b.p. 130–130.5°, n^{20}_{D} 1.4060, sp. gr.$^{20}/_4$ 0.7226; mol. wt. 127; C, 84.30; H 15.71; calcd. for C_9H_{20}: C, 84.28; H, 15.72, reported[7] n^{20}_{D} 1.4061; sp. gr.$^{20}/_4$ 0.7219). The infrared spectrum of the hydrocarbon corresponded to the spectrum of 2,3,5-trimethylhexane.[8]

Oxidation of 3,3,5-Trimethyl-5-hexenoic Acid with Nitric Acid.—The C_9 acid (27 g.) was added dropwise to 500 ml. of boiling 70% nitric acid and the mixture was refluxed for 4 hours. Nitric acid was distilled from the product under reduced pressure, yielding 23 g. of crystalline residue. Recrystallization from water gave 10 g. of α,α-dimethylsuccinic acid (m.p. 139°, mixed m.p. 139°; C, 49.47; H, 6.96; acidity 1.345 eq./100 g.; calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.90; acidity, 1.369 eq./100 g.).

Reaction of Mesityl Oxide with a Molten Mixture of Sodium and Potassium Hydroxides.—Two hundred seventeen grams of mesityl oxide was added at a rate of 1.5 ml. per minute to a fused mixture of 180 g. of sodium hydroxide and 220 g. of potassium hydroxide in a stainless steel vessel at 300–310°. A total of 1.45 ft.^{3} of non-condensable gas containing 96% *m* methane and 2.9 % *m* butene (mass spectrometric analysis) was formed. Material condensed in a Dry Ice cooled trap included 55 g. of a butylene fraction containing 92.4% *m* isobutene (low temperature distillation and absorption in 65% H_2SO_4) and 64 g. of a mixture of acetone, mesityl oxide and water. Distillation of this latter material yielded 23 g. of acetone (b.p. 55–60°), 14 g. of mesityl oxide (b.p. 125–129°, carbonyl value 0.97 eq./100 g., calcd. for $C_6H_{10}O$ 1.00) and 7 g. of higher boiling material. The solid in the reactor was dissolved in water, filtered, and extracted with ether. Analysis of the water layer indicated the presence of 0.38 mole of carbonates. The water layer was acidified with hydrochloric acid and extracted in a continuous extractor with ether. Distillation of the ether gave 73 g. acetic acid (b.p. 118°, eq. wt. 61, calcd. for $C_2H_4O_2$, 60).

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(6) Rasmussen, *Fortschritte der Chemie organischer Naturstoffe*, *V*, 331 (1948).

(7) API Project 44, Vol. 1.

(8) Serial No. 669, Naval Research Lab., API Project 44.

EMERYVILLE, CALIF. RECEIVED APRIL 17, 1951

[CONTRIBUTION NO. 815 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Synthesis of Heterocyclic Nitrogen-containing Ketones. I. Ketones Derived from 2-Picoline

BY NEWTON N. GOLDBERG, LLOYD B. BARKLEY AND ROBERT LEVINE

2-Picolyllithium, prepared from 2-picoline and phenyllithium, has been acylated in good yields with methyl benzoate, 2-furoate, 2-thiophenate, acetate, propionate and isovalerate and ethyl benzoate and isobutyrate. In addition to the 2-picolyl ketones, alkyldi-2-picolylcarbinols were isolated in those experiments in which aliphatic esters were used as the acylating reagents.

For several years, we have been interested in this Laboratory in the synthesis of heterocyclic ketones. Some of our results in the thiophene and furan series have been published[1,2,3,4] and we are at present engaged in developing methods for the preparation of heterocyclic nitrogen-containing ketones in high yields. The present paper reports our progress in the 2-picoline series.

Weiss and Hauser[5] have reviewed the literature on the use of the alkali amides for the acylation of 2-picoline, quinaldine and lepidine and have extended these syntheses considerably. 2-Picolyllithium, prepared from 2-picoline and phenyllithium, has been condensed with a number of reagents: benzoyl chloride,[6] benzoic anhydride,[6] acetic anhydride[6,7] propionic anhydride,[7] *n*-butyric anhydride,[7] acetyl chloride,[6,8] acetonitrile,[9] benzonitrile[9] and ethyl acetate.[10] In most cases low yields of ketones were obtained.

Recently, Zelinski and Benilda[11] have studied the acylation of 2-picolyllithium with ethyl benzoate, ethyl 2-furoate and ethyl 2-thiophenate. In the benzoylation of 2-picoline, these workers carried out two experiments. In the first, the following proportions of reactants were used: 0.63 mole of ethyl

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(1) Heid and Levine, *J. Org. Chem.*, **13**, 409 (1948).

(2) Levine, Heid and Farrar, THIS JOURNAL, **71**, 1207 (1950).

(3) Farrar and Levine, *ibid.*, **72**, 3695 (1950).

(4) Farrar and Levine, *ibid.*, **72**, 4433 (1950).

(5) Weiss and Hauser, *ibid.*, **71**, 2033 (1949).

(6) Kloppenburg and Wibaut, *Rec. trav. chim.*, **65**, 393 (1946).

(7) Ruigh, U. S. Patent 2,317,303, April 20, 1943.

(8) Gilman and Towle, *Rec. trav. chim.*, **69**, 428 (1950).

(9) Wibaut and DeJong, *ibid.*, **68**, 485 (1949).

(10) Beets, *ibid.*, **63**, 120 (1944).

(11) Zelinski and Benilda, THIS JOURNAL, **73**, 695 (1951).

TABLE I

KETONES AND CARBINOLS FROM THE ACYLATION OF 2-PICOLYLLITHIUM WITH ESTERS

Ester, methyl	2-Picolyl ketone	Yield, %	B.p., °C.	B.p., Mm.	Alkyldi-2-picolylcarbinol	Yield, %	B.p., °C.	B.p., Mm.
Benzoate[a]	Benzoyl[b,r]	80.2 61[c]	145–153	2[d]	......	..	....	
			M. 52.5–54	[d,s]				
Benzoate	Benzoyl[b,r]	81.8	145–153	2[d]	....	..	....	
			M. 52.5–54	[d,s]				
2-Fuorate	2-Furoyl[e,r]	57.8	150–160	5	....	..	....	
			M. 49.5–51	[f,s]				
2-Thenoate	2-Thenoyl[g,r]	73.5	177–178	6[h]	....	..	....	
Acetate	Acetyl[i,r]	36.3	74–75	1.5	Methyl[k,r]	28.1	154–156	1.9
			102–102.5	10.3[j]				
Propionate	Propionyl[l,r]	50	99–103	5	Ethyl[m,r]	21.9	162.5–164	1.7
Isobutyrate[a]	Isobutyryl[n,r]	60.5	79–85	2	Isopropyl[o,r]	15.8	168–172	2.2
Isovalerate	Isovaleryl[p,r]	67	114–117	6	Isobutyl[q,r]	8.5	168–171	2

[a] Ethyl ester; in all other cases, methyl esters were used. [b] Phenylhydrazone, m.p. 84–85°; *Anal.* Calcd. for $C_{19}H_{17}N_3$: N, 14.62. Found: N, 14.39. The ketone gave a light brown copper salt, m.p. 167–169.5°, from 95% ethanol. [c] A 1:1:1 mole ratio of phenyllithium, 2-picoline and ester used. [d] See ref. 6. [e] *Anal.* Calcd. for $C_{11}H_9NO_2$: C, 70.57; H, 4.85; N, 7.48. Found: C, 70.51; H, 4.70; N, 7.38. Phenylhydrazone, m.p. 114–115°; *Anal.* Calcd. for $C_{17}H_{15}N_3O$: N, 15.16. Found: N, 15.21. The ketone gave a green brown copper salt, m.p. 165–168°, from 95% ethanol. [f] See ref. 11. [g] *Anal.* Calcd. for $C_{11}H_9ONS$: C, 65.00; H, 4.46; N, 6.89. Found: C, 65.07; H, 4.06; N, 6.71. Phenylhydrazone, m.p. 105–106°; *Anal.* Calcd. for $C_{17}H_{15}N_3S$: N, 14.32. Found: N, 14.18. The ketone gave a brown copper salt, m.p. 158.5–161°, from 95% ethanol. [h] Although Zelinski and Benilda (see ref. 11) reported this compound with a melting point, 28.5–29.5°, we have not been able to crystallize it. [i] Picrate, m.p. 140–141°, see ref. 10. Green brown copper salt, m.p. 155–158°, from 95% ethanol. [j] See ref. 7. [k] *Anal.* Calcd. for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.07; N, 12.27. Found: C, 73.73; H, 6.83; N, 12.05. Dipicrate, m. p. 213–214°, see ref. 10. [l] *Anal.* Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.25; H, 7.45; N, 9.42. Picrate, m.p. 144.2–145.5°. *Anal.* Calcd. for $C_{15}H_{14}N_4O_8$: N, 14.81. Found: N, 14.94. The ketone gave a dark green copper salt, m.p. 93–95°, from 95% ethanol. [m] *Anal.* Calcd. for $C_{16}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.62; H, 7.40; N, 11.72. Dipicrate, m.p. 193.5–195°. *Anal.* Calcd. for $C_{27}H_{24}N_8O_{15}$: N, 16.00. Found: N, 15.85. [n] *Anal.* Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.32; H, 7.83; N, 8.56. Picrate, m.p. 144.5–145.2°. *Anal.* Calcd. for $C_{16}H_{16}N_4O_8$: N, 14.28. Found: N, 14.24. The ketone gave a brown black copper salt, m.p. 110–112.5° from petroleum ether, b.p. 60–70°. *Anal.* Calcd. for $C_{20}H_{24}N_2O_2Cu$: N, 7.22. Found: N, 7.33. [o] *Anal.* Calcd. for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 75.13; H, 7.42; N, 10.75. Dipicrate, m.p. 182–184°. *Anal.* Calcd. for $C_{28}H_{26}N_8O_{15}$: N, 15.68. Found: N, 15.85. [p] *Anal.* Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.64; H, 8.38; N, 8.10. Picrate, m.p. 103–103.8°. *Anal.* Calcd. for $C_{17}H_{18}N_4O_8$: N, 13.79. Found: N, 14.03. The ketone gave a brown copper salt, m.p. 113–116°, from 95% ethanol; 2,4-dinitrophenylhydrazone, m.p. 114.6–115.6°. *Anal.* Calcd. for $C_{17}H_{19}N_5O_4$: N, 19.60. Found: N, 19.56. [q] *Anal.* Calcd. for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.91; H, 8.05; N, 10.11. Dipicrate, m.p. 172.5–173.3°. *Anal.* Calcd. for $C_{29}H_{28}N_8O_{15}$: N, 15.38. Found: N, 15.57. [r] All the ketones and carbinols gave a blue-green color with alcoholic iron(III) chloride. [s] Recrystallized from petroleum ether, b.p. 60–70°.

benzoate, 1.4 moles of lithium, 0.71 mole of bromobenzene and 1.4 moles of 2-picoline. Under these conditions, only 0.71 mole of 2-picolyllithium is available for reaction and based on the mechanism indicated below, which is similar to that proposed by Weiss and Hauser[5] for the reactions in which the alkali amides are used as condensing agents, the theoretical yield of product in this reaction is 0.355 mole. Thus the 27% yield reported by these workers[11] is actually 49.3%. Similarly in their run in which a 1:1:1 mole ratio of ethyl benzoate, 2-picoline and phenyllithium was employed, their reported yield of 20% is actually 40%.

As an orienting experiment, we studied the acylation of 2-picoline with ethyl benzoate. In the first reaction in which molar equivalents of phenyllithium, 2-picoline and ester were used and the reaction mixture refluxed for two hours, a 58.4% yield of phenyl 2-picolyl ketone (based on the assumption that the third step indicated below occurs) was obtained. When this experiment was repeated and a 2:2:1 ratio of the reagents was used the yield of ketone was increased to 80.2%. When this second experiment was repeated without a reflux period, the yield of product was 76.2%. Using methyl benzoate in place of the ethyl ester and refluxing the reaction mixture for only one-half hour gave a 81.8% yield of a much purer product. Therefore, in all the other runs, with the exception of the one in which ethyl isobutyrate was used, methyl esters were used as acylating esters.

Our results are summarized in Table I. It may be seen that good yields of ketones were obtained with the aromatic and heterocyclic esters and with methyl isovalerate and ethyl isobutyrate. The yields of ketones using methyl acetate and methyl propionate as the acylating esters are only fair. It may also be seen that in those experiments involving the aliphatic esters, alkyldi-2-picolylcarbinols as well as the alkyl 2-picolyl ketones are obtained.

The probable course of these acylations may be represented by the equations. The 2-picoline is first converted to its lithium derivative, I, by an acid–base reaction with phenyllithium (equation 1).

$$C_6H_5Li + 2\text{-}CH_3C_5H_4N \longrightarrow C_6H_6 + \underset{I}{2LiCH_2C_5H_4N} \quad (1)$$

$$I + RCO_2R' \longrightarrow R'OLi + \underset{II}{2\text{-}RCOCH_2C_5H_4N} \quad (2)$$

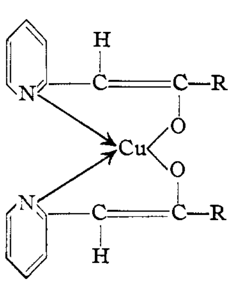
$$I + II \longrightarrow \underset{III}{(2\text{-}RCOCHC_5H_4N)Li} \text{ and } \underset{IV}{RC(OH)(CH_2C_5H_4N\text{-}2)_2} \quad (3)$$

In equation 2, I is acylated by the ester to give the ketone, II, which then reacts with I (equation 3) either at the α carbon atom to give the lithium derivative of the ketone, III, or at the carbonyl carbon atom to give the carbinol, IV.

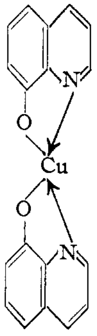
While we have not isolated any carbinol in the acylations with methyl benzoate, 2-furoate and 2-thiophenate, Kloppenburg and Wibaut[6] did obtain some phenyldi-2-picolylcarbinol from 2-picolyllithium and benzoyl chloride. These workers[6] and Gilman and Towle[8] have obtained methyldi-2-picolylcarbinol as well as methyl 2-picolyl ketone from the reaction of 2-picolyllithium with acetyl chloride.

It may be seen (Table I) that the relative amounts of alkyl 2-picolyl ketone, II, formed decreases in the order R = isopropyl, ethyl, methyl and that the relative amounts of the carbinol, IV, formed increases in the same order. Thus, while the ketone, II, is the main reaction product in the cases studied, it may be seen that the steric requirements of the ketones are probably such that the extent of carbonyl attack (to give the carbinol) decreases with an increase in the size of the radical, R.

It is of interest to note that all the ketones and carbinols prepared in this investigation give a blue-green color test with alcoholic iron(III) chloride solution, while 2-picoline does not give such a color. Also, the 2-picolyl ketones form copper chelates when treated with aqueous copper(II) acetate solution. The formation of these chelates is probably analogous to those obtained with 8-hydroxyquinoline (oxine) except that with the ketones the chelates have a six-membered ring and with oxine a five membered ring is present in the chelates. These similarities may be seen in the structures



copper chelate with 2-picolyl ketones



copper chelate with oxine

Work is now in progress in this Laboratory on the evaluation of these 2-picolyl ketones as possible organic analytical reagents and on the extension of our studies to the acylations of 4-picoline, the lutidines, lepidine, quinaldine and related tar bases with a series of esters.

Experimental[12]

General Procedure for the Acylation of 2-Picolyllithium with Esters.—Since all the runs were performed under essentially the same conditions, only one will be described in detail.

In a 1000-ml. three-necked round-bottom flask equipped with ground glass joints and fitted with a mercury-sealed stirrer, an addition funnel and a reflux condenser (protected from atmospheric moisture by a drying tube filled with Drierite), 0.4 mole of phenyllithium (from bromobenzene and lithium ribbon[13]) was prepared in 500 ml. of anhydrous ether. 2-Picoline (0.4 mole) was added to the mixture over a ten-minute period and then the solution was refluxed for 30 minutes. The conversion of the 2-picoline to 2-picolyllithium was assumed to be quantitative.

To the rapidly stirred solution of the 2-picolyllithium, 0.2 mole (23.2 g.) of methyl isovalerate, b.p. 115–116° (740 mm.), dissolved in 25 ml. of absolute ether was added over a 20-minute period so that the ether refluxed rapidly. After the ester was added, the reaction mixture was refluxed for 30 minutes longer on a water-bath. Then, 75 ml. of water was added slowly and the mixture poured onto 100 ml. of 6 *N* hydrochloric acid and 500 g. of ice. The ether phase was extracted several times with 6 *N* hydrochloric acid and the combined aqueous phases treated with 20% sodium hydroxide solution until the solution remained slightly acid. Then, solid sodium bicarbonate was added until the mixture was slightly basic. The basic mixture was extracted with ether until the extracts no longer gave a blue-green color with alcoholic iron(III) chloride. The combined ether extracts were dried over Drierite, the solvent distilled on a water-bath and the residue fractionated in vacuum. In this way, there were obtained 23.7 g. (67%) of isovaleryl 2-picolyl ketone, b.p. 114–117° at 6 mm. and 4.6 g. (8.5%) of isobutyl-di-2-picolylcarbinol, b.p. 168–171 at 2 mm. The ketone gave a brown copper salt, m.p. 113–116°, when treated with saturated aqueous copper(II) acetate solution. The pertinent analytical data for these compounds and the others prepared in this study are found in the footnotes to Table I.

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[12] All analyses were performed by Mr. George Stragand in the Microanalytical Laboratory of the University of Pittsburgh.

[13] The lithium ribbon was purchased from the Metalloy Corporation, Rand Tower, Minneapolis, Minnesota.