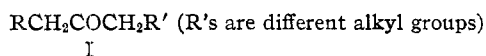


[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

Condensations of Unsymmetrical Ketones. II. Competition between Methylene Groups

BY RAYMOND P. MARIELLA AND VIRGINIA KVINGE¹

In continuing our investigations of unsymmetrical ketones² it seemed desirable to try a condensation of an ester with a ketone which did not have a methyl group competing with a methylene group, but instead possessed two differently substituted methylene groups (I).



A ketone, readily available and suitable in structure, is 3-heptanone (ethyl *n*-butyl ketone).

In past cases of methyl group *versus* methylene group, the condensation with an ester generally has proved to go one way, either at the methylene³ or at the methyl groups.⁴

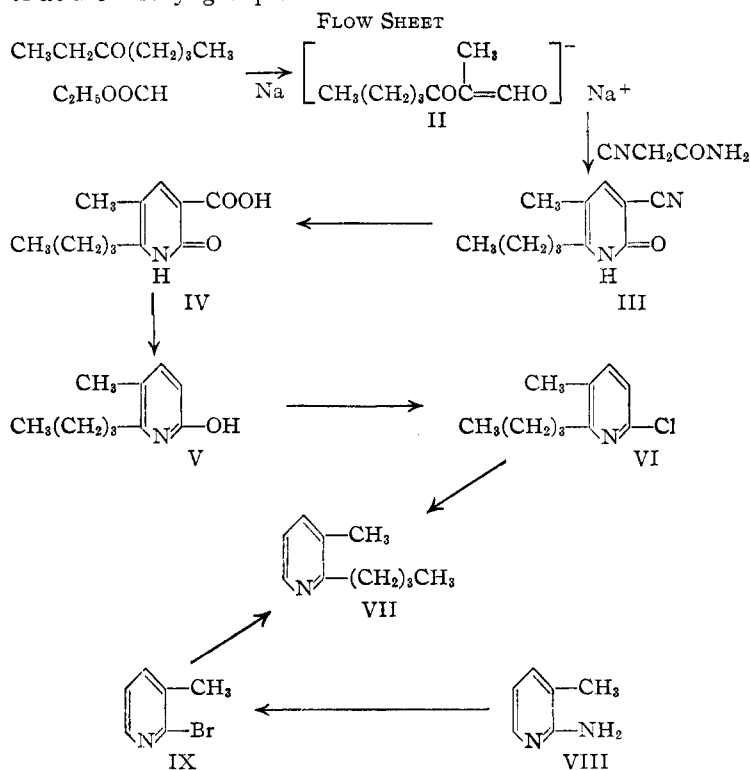


Fig. 1

(1) Present address: Northwestern University Medical School, Chicago, Illinois.

(2) For the first paper in this series, see Mariella, *THIS JOURNAL*, **69**, 2670 (1947).

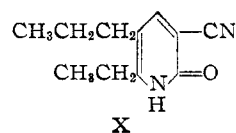
(3) (a) Tracy and Elderfield, *J. Org. Chem.*, **6**, 63 (1941); and (b) Joshi, Kaushal and Deshpande, *J. Ind. Chem. Soc.*, **18**, 479 (1941), who condensed methyl ethyl ketone with ethyl formate; *cf.* also Mariella, *ref.* (1).

(4) (a) Tracy and Elderfield, *J. Org. Chem.*, **6**, 70 (1941), who condensed methyl ethyl ketone with ethyl oxalate; (b) Harris and Wilson, *THIS JOURNAL*, **68**, 2526 (1941), who condensed methyl ethyl ketone with ethyl methoxyacetate; (c) Joshi, Kaushal and Deshpande, *ref.* 3b, who condensed methyl β -phenylethyl ketone

Some past work by Ponzio and deGaspari⁵ with 3-heptanone ketone has shown that this ketone condensed with amyl nitrite to give the two isomeric isonitroso ketones. The latter authors, however, did not state the yields of their isomeric products. These results did not seem unusual, since the competing methylene groups are substituted by somewhat similar groups (methyl and *n*-propyl). Even with this evidence of non-selective reactivity with amyl nitrite, care must be used in predicting the products of the condensation of the ketone in question with other esters, since an unsymmetrical ketone may condense differently with the various esters.^{3a,4a,4b}

In the condensation of 3-heptanone with ethyl formate the sodium salt was formed as a sticky sirupy mass which might lead one to suspect a mixture, for the sodium salts formed in the condensation of methyl ethyl and methyl isobutyl ketones, for example, with ethyl formate, were nice yellow or brown solids. The further condensation however, of this tacky sodium salt with cyanoacetamide produced only *one* isolable pyridone (III). The product was obtained in a high degree of purity after only two recrystallizations, as seen by the m. p. and analysis. Attempts to work the mother liquors to isolate any isomeric pyridone (X) were unsuccessful.

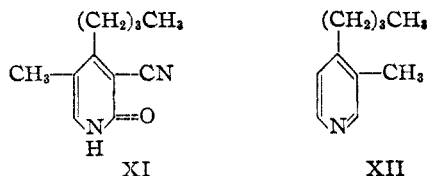
The pyridone (III) was degraded to the dialkylpyridine, 2-*n*-butyl-3-methylpyridine (Fig. 1) (steps III through VIII), but this compound was unknown, and oxidation to quinolinic acid would not be useful in identification since the isomeric pyridone (X) (which might have been formed if the initial condensation of 3-heptanone with ethyl formate had occurred at the 4 instead of the 2 position), if degraded to its corresponding dialkyl pyridine, 2-ethyl-3-*n*-propylpyridine, would also oxidize to quinolinic acid.



with ethyl formate; (d) Mariella, *ref.* 1, who condensed methyl isobutyl ketone with ethyl formate.

(5) Ponzio and deGaspari, *Gazz. chim. ital.*, **28**, II, 27 (1898).

In addition, the pyridone formed in the condensation of II with cyanoacetamide could possibly have the formula XI, and the final dialkyl pyridine could have the formula XII.



A need arose for an unequivocal synthesis of VII. Starting with 2-amino-3-methylpyridine (VIII), diazotization produced IX⁶ in a 82% yield. When IX was allowed to react with *n*-butylmagnesium bromide in refluxing butyl ether, a liquid was obtained which, although formed in poor yield, possessed the same boiling point as VII, did not contain halogen, and whose chloroplatinate did not depress the m. p. of the chloroplatinate of VII. This established the structure of the series of compounds II through VII, and proved that the initial condensation was at the 2 position.

This synthesis of an alkylated pyridine from a halopyridine appears to be a new use of the Grignard reaction and work is in progress to improve the yields.⁷

The yields in the decarboxylation of the acid (VI) to the pyridol (VII) gave poor yields in large runs, but went well (88%) in small runs. A similar experience in this type of decarboxylation has been noted before.⁸

These experiments show how markedly the difference in the two R groups in I (methyl and *n*-propyl) can cause the condensation to be selective. The effect, on the site of condensation, of changing one of the R groups in I to oxygenated groups will be reported soon.

Experimental⁹

Sodium Salt of 2-Hydroxymethylene-3-heptanone (II).—To an ice-cold stirred solution of 27 g. of sodium ribbon in one liter of absolute ether was added, dropwise over a period of one and one-half hours, a solution of 133 g. of 3-heptanone (Carbide and Carbon Company, b. p. 145.5–146.0° at 760 mm.) and 87 g. of ethyl formate.¹⁰ The reaction started very slowly and no precipitate was evident until after the first half-hour, at which time a yellow solid appeared. As the reaction progressed, the amount of solid increased and soon became a large orange mass, which adhered to the sides of the flask and stirrer, and had the consistency of heavy molasses. Stirring was continued (a powerful high-speed stirrer was used) at room temperature for one-half hour, after all the reactants had been added. The solid was separated from the liquid by

(6) Case, *THIS JOURNAL*, **68**, 2574 (1946), made this conversion in a 46% yield. The method used in the present work was adapted from "Organic Syntheses," Vol. XXVI, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 16.

(7) Apparently the temperature and solvent are very important since isobutylmagnesium bromide and 2-bromopyridine in refluxing ethyl ether gave no 2-isobutylpyridine.

(8) Mariella, Peterson and Ferris, *THIS JOURNAL*, **70**, 1494 (1948).

(9) Microanalyses by Misses Hines, Guy and Hobbs.

(10) Purified according to "Org. Syn.," Coll. Vol. II, 2nd ed., p. 180.

decantation and the viscous material dried in a vacuum at 100°, 100 g. Additional tacky material (15 g.) was also obtained from the ether solution which stood in the ice-box overnight, total yield 60%.

6-*n*-Butyl-3-cyano-5-methyl-2(1)-pyridone (III).—To a solution of 100 g. of sodium salt (II) and 100 g. of cyanoacetamide in 450 cc. of water was added the piperidine acetate catalyst (made from 12 cc. of glacial acetic acid in 15 cc. of water with addition of piperidine till basic), and the solution refluxed three hours. At the end of the heating a light oily layer appeared, which solidified on cooling and was filtered off. The brown solid was digested with dilute acetic acid, filtered and dried, 58 g., 50% yield. This material was treated with Norit in alcohol followed by several recrystallizations from ethyl alcohol and finally came out of solution as white plates, m. p. 196–197°.

Anal. Calcd. for C₁₁H₁₄N₂O: C, 69.45; H, 7.42; N, 14.7. Found: C, 69.70; H, 7.39; N, 14.7.

Concentration of the mother liquors in several similar runs produced 1–2 g. of crude III, which, although its m. p. varied over a range of 190–240°, always hydrolyzed by concentrated hydrochloric acid to give IV, m. p. 210–212°, which did not depress the m. p. of a sample of IV (see below).

6-*n*-Butyl-5-methyl-2(1)-pyridone-3-carboxylic Acid (IV).—A solution of 14 g. of cyanopyridone (III) in 150 cc. of concentrated hydrochloric acid was refluxed for five hours. The solution was poured on to ice and then filtered, washed with ice-cold water, and dried, 7.7 g., 50% yield. The solid was fairly soluble in water and alcohol. Several recrystallizations from water gave a white powder, m. p. 211–213°. The compound gave a negative ferric chloride test.

Anal. Calcd. for C₁₁H₁₆NO₃: N, 6.7. Found: N, 7.0.

6-*n*-Butyl-5-methyl-2-pyridol (V).—In a test-tube equipped with a cold finger was put 3.2 g. of pyridone acid (IV), and the contents heated to 340° in a copper block for one-half hour. When the carbon dioxide evolution had ceased, the black, residual, crystalline mass was vacuum-sublimed at 185–190° and 0.3 mm., and 2.2 g. of small white needles were obtained (88% yield). Much lower yields resulted in bigger runs; for example, when 9 g. of acid were used only 2 g. of pyridol was obtained. The solid was very soluble in alcohol. A sample which was resublimed melted at 88–90°. The compound gave a positive ferric chloride test (red) in alcohol.

Anal. Calcd. for C₁₀H₁₆NO: N, 8.4. Found: N, 8.1.

2-*n*-Butyl-3-methyl-6-chloropyridine (VI).—To a refluxing solution of 3.3 g. of pyridol (V) in 20 cc. of phosphorus oxychloride were added 20 g. of phosphorus pentachloride in small portions, over a period of one-half hour. The temperature of the bath was then raised to 170° and maintained for an hour. The oxychloride was removed under reduced pressure, and the residue made basic with potassium hydroxide. Steam distillation of the mixture produced a heavy colorless liquid. This was extracted with ether, the solution then dried and the ether removed. The pure liquid boiled at 119.5–120.5° at 8 mm., *n*_D²⁰ 1.5180, 2.0 g. (55% yield). The liquid colored slowly on standing.

Anal. Calcd. for C₁₀H₁₄ClN: N, 7.6. Found: N, 7.2.

2-*n*-Butyl-3-methylpyridine (VII).—To a solution of 1.76 g. of chloropyridine (VI) in 100 cc. of absolute alcohol were added in order: a solution of 0.70 g. of palladium chloride in 2 cc. of concentrated hydrochloric acid, 5 cc. of 15% alcoholic hydrogen chloride and 1.5 g. of activated carbon.¹¹ The mixture was shaken with hydrogen at twenty pounds pressure and the reaction was complete in five minutes. The mixture was filtered and the filtrate evaporated until an oil (residual hydrochloride)

(11) Perez-Medina, Mariella and McElvain, *THIS JOURNAL*, **69**, 2574 (1947).

remained. An excess of strong potassium hydroxide was added to this residue, and the immiscible free pyridine base taken up in ether. The ether solution was dried, and the ether removed. Distillation gave 1.1 g. (77% yield) of a colorless liquid, b. p. 205–207° (756 mm.), n_D^{20} 1.4950.

The chloroplatinate came down readily and quickly as small orange needles, m. p. 183–185°.

Anal. Calcd. for $C_{20}H_{32}Cl_6N_2Pt$: Pt, 27.6. Found: Pt, 28.0.

The picrate came down very slowly from an alcohol solution, m. p. 64–65°.

Anal. Calcd. for $C_{16}H_{18}N_4O_7$: N, 14.8. Found: N, 14.5.

It was not possible to isolate the chloroaurate in a pure form. The product first formed as a liquid which did not appear to be stable. A solid was finally obtained, but this product decomposed slowly upon being heated, with liberation of free gold, m. p. 160–173°. All attempts at purification produced a yellow solid which visibly contained some free gold.

The Reaction of Isobutylmagnesium Bromide with 2-Bromopyridine.—Isobutylmagnesium bromide was prepared from 6 g. of magnesium and 31.5 g. of isobutyl bromide (b. p. 88.5–89.0) in 125 cc. of ether. To this refluxing solution was added, slowly over a period of one hour, 31.5 g. of 2-bromopyridine.¹² The solution turned brown and by the end of the addition contained a dark insoluble material. The mixture was refluxed an additional half-hour, and then acidified with dilute hydrochloric acid (vigorous reaction). The mixture was made slightly basic with potassium hydroxide and filtered through glass wool. The clear ether solution was dried and the ether removed. Fractional distillation of the residual red liquid gave 7 g., b. p. 120–130°, and 3 g. of unreacted 2-bromopyridine, b. p. 190–195°; there was a 5-g. residue. No 2-isobutylpyridine was isolated.¹³

2-Bromo-3-methylpyridine (IX).—To a 2-liter flask equipped with a low temperature thermometer and an efficient stirrer were added 230 cc. of 48% hydrobromic acid, the contents cooled to –10°, and 50 g. of 2-amino-3-methylpyridine (VIII) (Reilly Tar and Chemical Company) added. The temperature was kept below 0° as 70 cc. of bromine were added over a period of one and one-half hours. The contents of the flask became viscous, as a voluminous red solid came out of solution. A solu-

tion of 80 g. of sodium nitrite in 150 cc. of water was added slowly over a period of two hours. Stirring was continued for an additional one-half hour, and a solution of 175 g. of sodium hydroxide in 250 cc. of water added, keeping the temperature below 20°. The opaque suspension was extracted four times with 250-cc. portions of ether. The combined ether extracts were dried, the ether removed, leaving a red liquid. Vacuum distillation gave 64 g. (82% yield) of colorless liquid, b. p. 76–77°¹⁴ at 7 mm., d_4^{20} 1.544, n_D^{20} 1.5680. The liquid turned yellow very slowly.

The Reaction of *n*-Butylmagnesium Bromide with 2-Bromo-3-methylpyridine.—A solution of *n*-butylmagnesium bromide was prepared from 2.7 g. of magnesium metal, 15 g. of *n*-butyl bromide (b. p. 100.0–100.8°) in 250 cc. of dibutyl ether (freshly distilled over sodium metal). To this refluxing solution were added 19 g. of 2-bromo-3-methylpyridine (IX), over a period of one hour. Refluxing was continued for another hour. There was a considerable amount of an orange tar on the sides of the flask. A saturated ammonium chloride solution was added till no more reaction was observed. The layers were separated, the ether layers washed with potassium hydroxide, and dried. Removal of the ether gave 5 cc. of a dark liquid. Distillation at atmospheric pressure gave 0.65 g. (4% yield) of colorless liquid, b. p. 205–207°, and 2.0 g. of pale yellow liquid, b. p. 212–225°. The former gave a negative Beilstein test, and formed a chloroplatinate very easily, which had a m. p. 185°. The mixed m. p. with the chloroplatinate of 2-*n*-butyl-3-methylpyridine (see above) was 183–185°. The higher boiling material give a positive Beilstein test, and probably was a mixture of some unreacted 2-bromo-3-methylpyridine and some 2-*n*-butyl-3-methylpyridine.

Summary

1. The reaction of ethyl formate with ethyl *n*-butyl ketone occurs at the methylene of the ethyl group.

2. The condensation product of cyanoacetamide with the sodium salt of 2-hydroxymethylene-3-heptanone was degraded to 2-*n*-butyl-3-methylpyridine.

3. Under the proper condition, an alkyl group can replace an α -bromo group in the pyridine series, by use of the Grignard reagent.

(14) Case, ref. 6, reported a b. p. 218–219°.

(12) "Organic Syntheses," Vol. XXVI, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 16.

(13) Cf. Mariella, ref. 1, who reported the b. p. of 2-isobutylpyridine to be 177–179°.

EVANSTON, ILLINOIS

RECEIVED APRIL 26, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Action of Sulfuric Acid on an Optically Active Hydrocarbon¹

BY ROBERT L. BURWELL, JR., AND GEORGE S. GORDON, III²

A simple optically active hydrocarbon is very resistant to inversion of configuration. von Weber³ reported that *d*-3-methylhexane was decomposed slowly at 400° but that the recovered hydrocarbon was unracemized. Petroleum fractions which boil above about 280° possess optical activity⁴

(1) Presented before the Division of Physical and Inorganic Chemistry of the American Chemical Society at the Chicago meeting, April 21, 1948.

(2) Standard Oil Company (Indiana) Fellow, 1946–1948.

(3) von Weber, *Z. physik. Chem.*, **179A**, 295 (1937).

(4) Fenske, Carnahan, Breston, Caser and Reacorla, *Ind. Eng. Chem.*, **34**, 688 (1942).

which survives distillation, the use of the hydrocarbons as lubricating oil in a motor vehicle and, presumably, storage for several millenia.

Racemization of a simple hydrocarbon has not been reported. Thermal racemization of certain terpenes has been claimed and seems to have been established for the case of α -pinene⁵ although the process is complicated by the simultaneous occurrence of faster isomerization reactions.

In view of the reactivity of alkanes containing a

(5) Savich and Goldblatt, *THIS JOURNAL*, **67**, 2027 (1945); Fugitt and Hawkins, *ibid.*, **69**, 319 (1947).