[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF DEPAUW UNIVERSITY]

5-Keto-7-methyljuloline and Certain Derivatives

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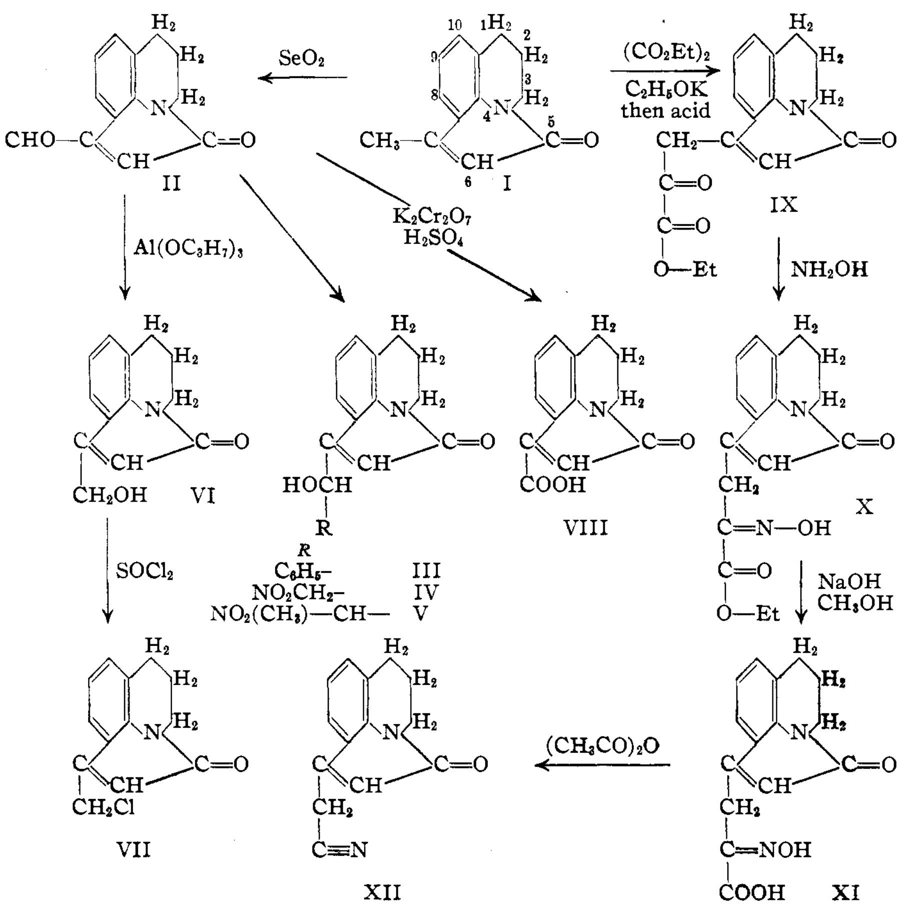
Since Reissert first prepared 5-keto-7-methyljuloline[2,3] by the action of ethyl acetoacetate on tetrahydroquinoline, no further work has been reported on this type compound. Several studies have been reported concerning the analogous compounds, N-substituted-4-methylcarbostyrils.[4,5] The use of the same techniques and ideas have been found applicable to the investigation of the chemistry of 5-keto-7-methyljuloline.

In a recent article[6] the preparation of 5-keto-7-methyljuloline and its conversion to 7-formyl-5-ketojuloline by oxidation with selenium dioxide have already been reported. The study has now been extended to the preparation of a number of derivatives of 5-ketojuloline substituted in the 7 position.

The series of reactions stem from 5-keto-7-methyljuloline (I) which is indicated in Chart I. The system of numbering is indicated for the juloline ring system.

The methyl group in the 7 position has been found to be activated in a manner similar to the 4-methyl group in N-substituted-4-methylcarbostyrils. This should be expected from the similarity in structure of the two molecules. Therefore, when I was treated with selenium dioxide in a fusion reaction, the methyl group was oxidized to the aldehyde (II) in yields of 80%. This compound, 7-formyl-5-ketojuloline, was converted to 7-(5-ketojuloline)-phenylmethanol (III) by treatment with phenylmagnesium bromide in the usual Grignard reaction. Condensation reactions between nitromethane and nitroethane with II gave the two products, α-(5-keto-7-juloline)-β-nitroethanol (IV) and α-(5-keto-7-juloline)-β-nitropropanol (V). The aldehyde was also reduced to the corresponding 5-keto-7-julolinemethanol (VI) with aluminum *i*-propoxide and this compound converted to the 5-keto-7-chloromethyljuloline (VII) with thionyl chloride. Oxidation of II with acid sodium dichromate gave 5-keto-7-juloline carboxylic acid (VIII).

CHART I



A Claisen type condensation was accomplished when I was treated with diethyl oxalate in the presence of potassium ethoxide and subsequently acidified. The resulting product was ethyl 7-(5-ketojuloline)-pyruvate (IX). This compound with hydroxylamine hydrochloride gave the corresponding oximino ester (X) and the oximino acid (XI) was obtained when X was treated with an alcoholic 2 *N* sodium hydroxide solution. 5-Keto-7-julolineacetonitrile (XII) was formed when

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(1) Department of Chemistry, Purdue University, Lafayette, Indiana.

(2) Reissert, *Ber.*, **24**, 841 (1891).

(3) Reissert, *ibid.*, **25**, 108 (1892).

(4) Kaslow and Cook, THIS JOURNAL, **67**, 1969 (1945).

(5) Cook and Stamper, *ibid.*, **69**, 1467 (1947).

(6) Cook, Sears and Dock, *Proc. Indiana Acad. Sci.*, **58**, 145 (1948).

XI was treated with acetic anhydride. Attempted saponification of IX with 5% sodium hydroxide cleaved it to the original 5-keto-7-methyljuloline.

Experimental[7]

The necessary starting materials, 5-keto-7-methyljuloline (I), 7-formyl-5-ketojuloline (II) and selenium dioxide were all prepared as previously described.[6]

7-(5-Ketojuloline)-phenylmethanol (III).—To the Grignard reagent prepared from 0.96 g. of magnesium turnings and 6.5 g. of bromobenzene dissolved in 25 ml. of anhydrous ether was added dropwise a solution of 5 g. (0.024 mole) of II in 120 ml. of anhydrous benzene. After refluxing for one hour, the mixture was poured into 50 ml. of a 10% sulfuric acid solution containing 25 g. of ice. The mixture was stirred well and the benzene–ether layer separated and evaporated to dryness. The residue was recrystallized from benzene–petroleum ether (b. p. 60–65°) giving light tan crystals which melted at 143–145°. The yield was 1.35 g. or 43%. Recrystallization several times from alcohol–water solution gave a white product melting at 151–153°.

Anal. Calcd. for $C_{19}H_{17}O_2N$: N, 4.81. Found: N, 4.98.

α-(5-Keto-7-juloline)-β-nitroethanol (IV).—Two grams of 7-formyl-5-ketojuloline (0.0094 mole) was dissolved in 30 ml. of absolute ethyl alcohol and to the cool solution was added 6 ml. of nitromethane and 14 drops of diethylamine. The solution was allowed to stand for three days and at the end of this time was evaporated to about one-half its volume. With the addition of a little water, the product crystallized. The weight of the crude material was 2.3 g. (93%). One gram of the crude product was recrystallized from a solution of 40 ml. of alcohol and 50 ml. of acetone. The melting point of this product was 189–191° (dec.).

Anal. Calcd. for $C_{14}H_{14}O_4N_2$: N, 10.22. Found: N, 10.18.

α-(5-Keto-7-juloline)-β-nitropropanol (V).—In a manner analogous to the preceding preparation, 2 g. of II (0.0094 mole) was treated with 6 ml. of nitroethane in 30 ml. of absolute alcohol. After standing for three days the solution was evaporated to about one-half of its volume. A crude precipitate formed which was recrystallized from benzene–petroleum ether. The crystallized product weighed 2.6 g. (99%). With a second recrystallization the product melted at 167–169°.

Anal. Calcd. for $C_{15}H_{16}O_4N_2$: N, 9.72. Found: N, 9.62.

5-Keto-7-julolinemethanol (VI).—Four grams of II (0.0188 mole) and 1.5 g. of aluminum isopropoxide were suspended in 75 ml. of isopropyl alcohol (99%) and heated on a steam-bath for four hours until the distillate gave a negative test with the 2,4-dinitrophenylhydrazine reagent. The isopropyl alcohol was then removed and the residue poured into 75 ml. of water and 25 ml. of concd. hydrochloric acid. The solution was heated to boiling, about 0.5 g. of Norite added, and filtered while hot. Pale yellow crystals formed on cooling which weighed 2.8 g. (69%). Upon recrystallization from an alcohol–water solution, white crystals formed which had a melting point of 179–181°.

Anal. Calcd. for $C_{13}H_{13}NO_2$: N, 6.51. Found: N, 6.41.

5-Keto-7-chloromethyljuloline (VII).—Two grams of VI (0.0093 mole) and 5 g. of thionyl chloride were dissolved in 100 ml. of anhydrous benzene and refluxed for seven hours. The excess thionyl chloride and benzene was removed by distillation and the solid residue was dissolved in about 25 ml. of alcohol. Upon cooling and with the addition of a few ml. of water, tan plates formed which melted at 128–130°. The yield was 1 g. (46%). The sample was recrystallized from alcohol and melted at 127–128°.

Anal. Calcd. for $C_{13}H_{12}ONCl$: N, 6.00. Found: N, 5.95.

5-Keto-7-julolinecarboxylic Acid (VIII).—Three grams of 7-formyl-5-ketojuloline (0.014 mole) was suspended in 150 ml. of water to which was added 2.1 g. (0.007 mole) of potassium dichromate. This mixture was stirred and over a period of five minutes 7.1 ml. of concd. sulfuric acid was added. The reaction mass was heated for about twenty minutes with stirring on the steam-bath. At the end of this time the reaction solution was heated to boiling over a burner and filtered. Some tarry residue was separated. The hot filtrate was cooled in ice and the product recovered as pale yellow crystals. With evaporation of the filtrate to about one-half of the original volume, a further yield of the acid was obtained. The total weight was 0.89 g. (28%). Three-tenths of a gram of the product was recrystallized from 75 ml. of boiling water. Long pale yellow needles were obtained. The solid softened at 200° with the melting point 208–211° (dec.).

Anal. Calcd. for $C_{13}H_{11}O_3N$: N, 6.11. Found: N, 6.18.

Ethyl 7-(5-Ketojuloline)-pyruvate (IX).—Two grams (0.05 mole) of metallic potassium was dissolved in 30 ml. of absolute alcohol and the resulting solution of the potassium ethoxide cooled in ice. A solution of 4.15 g. (0.03 mole) of diethyl oxalate in 10 ml. of anhydrous ether was added to the cooled alcoholic solution and this was followed with a solution of 5 g. (0.025 mole) of 5-keto-7-methyljuloline in 100 ml. of 1:1 absolute ether and absolute alcohol. This reaction mixture was allowed to stand for 24 hours and during this time a yellow color formed in the solution. The solvent was removed under vacuum leaving a bright yellow solid. This residue, the potassium salt, was treated with 75 ml. of 6% sulfuric acid on a steam-bath for fifteen minutes. The residue turned to a light brown solid and was removed by filtration. The weight of the impure product was 5.97 g. (100%) and melted at 152–155°. One gram of the crude product was recrystallized from 20 ml. of ethyl alcohol. A pale yellow solid was recovered which melted at 166–168°. A second recrystallization gave a product melting at 168–168.5°.

Anal. Calcd. for $C_{17}H_{17}O_4N$: N, 4.68. Found: N, 5.45.

Ethyl 7-(5-Ketojuloline)-pyruvate 2,4-Dinitrophenylhydrazone.—This derivative was prepared as directed by Shriner and Fuson.[8] The product was recrystallized several times from alcohol. The compound was found to soften at 120° with melting at 129–131°.

Anal. Calcd. for $C_{23}H_{21}O_7N_5$: N, 14.6. Found: N, 14.7.

Ethyl α-Oximino-7-(5-ketojuloline)-propionate (X).—Three grams of IX (0.01 mole) and 2 g. of hydroxylamine hydrochloride (0.03 mole) were dissolved in 25 ml. of a 1:1 mixture of pyridine and absolute alcohol. This solution was refluxed for five hours and the solvent then removed under reduced pressure. The residue was washed into 75 ml. of ice water, triturated, filtered and washed several times with cold water. The weight of the crude product was 2.06 g. (70%). The melting point of this product was 206–210°. A 0.5-g. sample of the oxime was recrystallized from 15 ml. of absolute alcohol. The product was pale yellow plates, m. p. 215–218° (dec.).

Anal. Calcd. for $C_{17}H_{18}O_4N_2$: N, 8.88. Found: N, 8.66.

α-Oximino-5-keto-7-julolinepropionic Acid (XI).—One and five-tenths grams of X (0.0047 mole) was dissolved in a solution of 10 ml. of methyl alcohol and 15 ml. of 2 *N* aqueous sodium hydroxide. The reaction mixture was refluxed for one and one-half hours, then neutralized with about 5 ml. glacial acetic acid and cooled in ice water. A gray solid was obtained which melted at 179–186° (dec.). This crude product was recrystallized by reprecipitation from a dilute sodium hydroxide solution with glacial acetic

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(7) Melting points were taken on a Fischer–Johns melting block.

(8) Shriner and Fuson, "Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 143.

acid. The crystallization took place after several days standing. The purified product melted at 178–182° (dec.) and weighed 0.44 g. (34%).

Anal. Calcd. for $C_{15}H_{14}O_4N_2$: N, 9.79. Found: N, 9.34.

5-Keto-7-julolineacetonitrile (XII).—Three-tenths gram of XI (0.001 mole) was placed in 10 ml. of acetic anhydride and heated on the steam-bath for five minutes. Carbon dioxide was evolved. The solvent was then removed under vacuum and the residue dissolved in a solution containing 15 ml. of benzene and 10 ml. of acetone. The solution was filtered and evaporated to about one-half volume. When cooled in ice, 0.1 g. of the product was recovered which melted at 194–196°. This product was not recrystallized. The yield was 50%.

Anal. Calcd. for $C_{14}H_{12}ON_2$: N, 12.50. Found: N, 12.98.

Summary

1. 7-Formyl-5-ketojuloline has been used to form a number of 5-ketojuloline derivatives with substitution in the 7 position.

2. Ethyl 7-(5-ketojuloline)-pyruvate has been prepared by the condensation of 5-keto-7-methyljuloline with diethyl oxalate and the synthesis of several compounds from the pyruvate has been described.

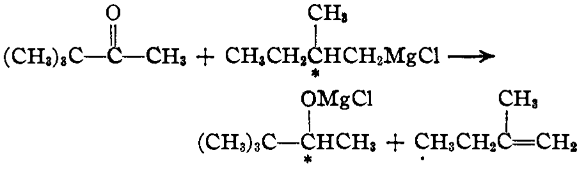
GREENCASTLE, INDIANA RECEIVED APRIL 26, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Asymmetric Reductions. II. The Action of (+)-3-Methylpentylmagnesium Chloride on Methyl *t*-Butyl Ketone

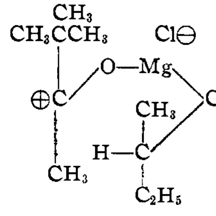
BY HARRY S. MOSHER AND EDWARD LA COMBE

It has been demonstrated that an optically active Grignard reagent can accomplish the partial asymmetric reduction of an unsymmetrical hindered ketone.[1,2] The successful cases previously reported involved a Grignard reagent with an asymmetric carbon atom in the position *beta* to the magnesium atom; for example, the reduction of methyl *t*-butyl ketone by (+)-2-methylbutylmagnesium chloride. We have proposed that the partial asymmetric reduction is a result of the steric interference of the various alkyl groups in the postulated six-membered ring transition state[2] as represented in structure A. In addition we have predicted that significant asymmetric reduction will not occur in simple cases of this type unless the asymmetric carbon atom is a member of this postulated ring. Accordingly an optically active Grignard reagent which has an asymmetric center in the *gamma* position, such as (+)-3-methylpentylmagnesium chloride, would theoretically give a transition state represented by structure B. It can be seen that the asymmetric center is not a member of the postulated ring in B. If this mechanism is assumed and the steric factors involved are considered, a study of the various possible configurations of this transition state will lead to the conclusion that no appreciable asymmetric reduction should be expected.

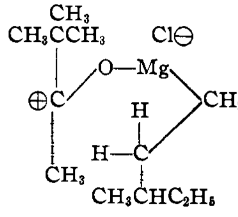


$$(CH_3)_3C-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3 + CH_3CH_2\underset{*}{\overset{\overset{\displaystyle CH_3}{|}}{C}}HCH_2MgCl \longrightarrow (CH_3)_3C-\underset{*}{\overset{\overset{\displaystyle OMgCl}{|}}{C}}HCH_3 + CH_3CH_2\overset{\overset{\displaystyle CH_3}{|}}{C}=CH_2$$

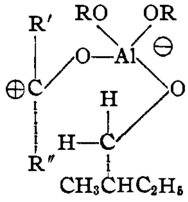
Partial



A



B



C

From a stereochemical standpoint, one would predict that the reaction would take place more readily if the transition state were as represented in either A or B, that is with the larger alkyl groups on opposite sides of the plane of the ring. But in structure B there are two hydrogen atoms on the *beta* carbon of the Grignard reagent and consequently there is an equal chance of the attack taking place on either side of the carbonyl carbon atom. The same considerations apply to the other two stereochemically less probable modes of attack in which the two larger alkyl groups are on the same side of the plane of the ring. Accordingly the formation of essentially equal amounts of the two enantiomorphic carbinols would be anticipated in a case such as B.

The reaction of (+)-3-methylpentylmagnesium chloride on methyl *t*-butyl ketone has now been studied. The amount of reduction to methyl-*t*-butylcarbinol was very small (0.2%) but there was no doubt that the carbinol formed was without significant optical activity. The success of

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(1) Vavon and Angelo, *Compt. rend.*, 224, 1435–1437 (1947).

(2) Mosher and La Combe, THIS JOURNAL, 72, 3994 (1950).