24. **Tatsuo Moroe and Juichi Matsukura:** Synthesis of Dihydrolinalool and Isocitronellol from Levulic Acid. I.*

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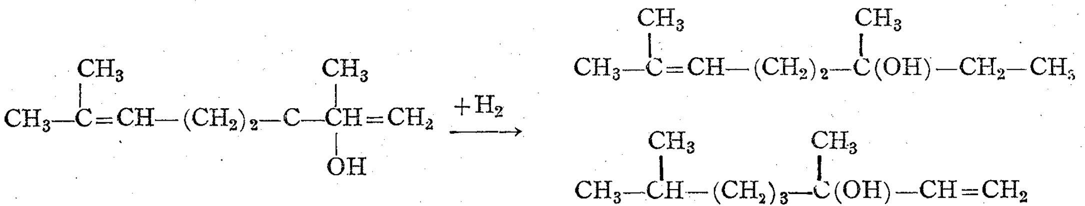
In connection with making a good use of levulic acid, a by-product of glutamic acid production in Japan, the authors attempted the preparation of synthetic perfumes, dihydrolinalool and isocitronellol, from this acid. This paper gives the results of the synthesis of the former and that of the latter was reported in the preceding paper*.

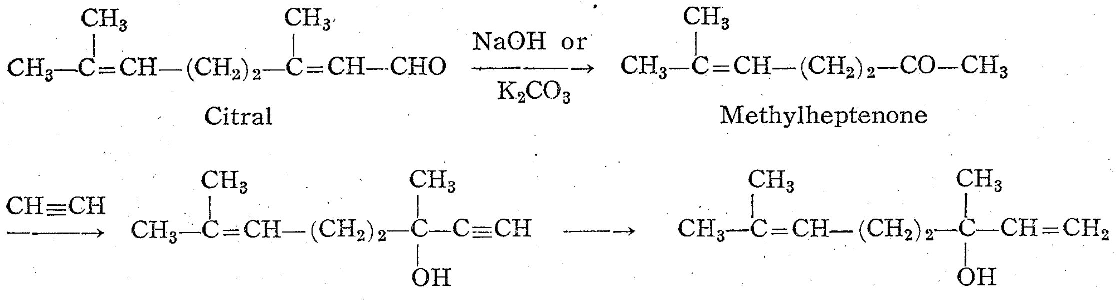
Dihydrolinalool has two isomers, (I) and (II), which are obtained through the hydrogenation of linalool, a main constituent of many essential oils. In the present experiment, dihydrolinalool (I), which had not been synthesized before, was obtained.



$$CH_3-\overset{CH_3}{\overset{|}{C}}=CH-(CH_2)_2-\underset{OH}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}-CH=CH_2 \xrightarrow{+H_2} \begin{cases} CH_3-\overset{CH_3}{\overset{|}{C}}=CH-(CH_2)_2-\overset{CH_3}{\overset{|}{C}}(OH)-CH_2-CH_3 & (I) \\ CH_3-\overset{CH_3}{\overset{|}{CH}}-(CH_2)_3-\overset{CH_3}{\overset{|}{C}}(OH)-CH=CH_2 & (II) \end{cases}$$

Linalool

Previously, Ruzicka and Farnasier[1] reported the half-synthesis of linalool from methylheptenone as follows:



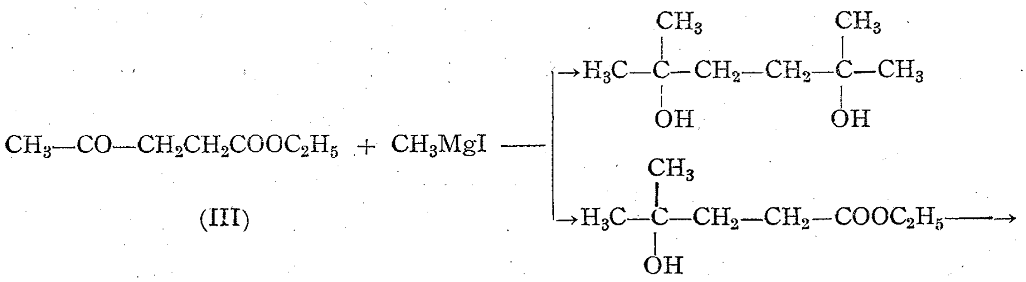
$$CH_3-\overset{CH_3}{\overset{|}{C}}=CH-(CH_2)_2-\overset{CH_3}{\overset{|}{C}}=CH-CHO \xrightarrow[K_2CO_3]{NaOH\ or} CH_3-\overset{CH_3}{\overset{|}{C}}=CH-(CH_2)_2-CO-CH_3$$

Citral Methylheptenone

$$\xrightarrow{CH\equiv CH} CH_3-\overset{CH_3}{\overset{|}{C}}=CH-(CH_2)_2-\underset{OH}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}-C\equiv CH \longrightarrow CH_3-\overset{CH_3}{\overset{|}{C}}=CH-(CH_2)_2-\underset{OH}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}-CH=CH_2$$

Dehydrolinalool *dl*-Linalool

In the present attempt, dihydrolinalool (I) was prepared from levulic acid by the following scheme, via methylpentenyl bromide.



$$\underset{(III)}{CH_3-CO-CH_2CH_2COOC_2H_5} + CH_3MgI \longrightarrow \begin{cases} \rightarrow H_3C-\underset{OH}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}-CH_2-CH_2-\underset{OH}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}-CH_3 \\ \rightarrow \underset{(IV)}{H_3C-\underset{OH}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}-CH_2-CH_2-COOC_2H_5} \longrightarrow \end{cases}$$

(IV)

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* Paper read before the Annual Meeting of the Chemical Society of Japan. Part II. Tatsuo Moroe, Satohiko Hattori, Norio Ikegami: J. Pharm. Soc. Japan, 72, 1172, 1175(1952).

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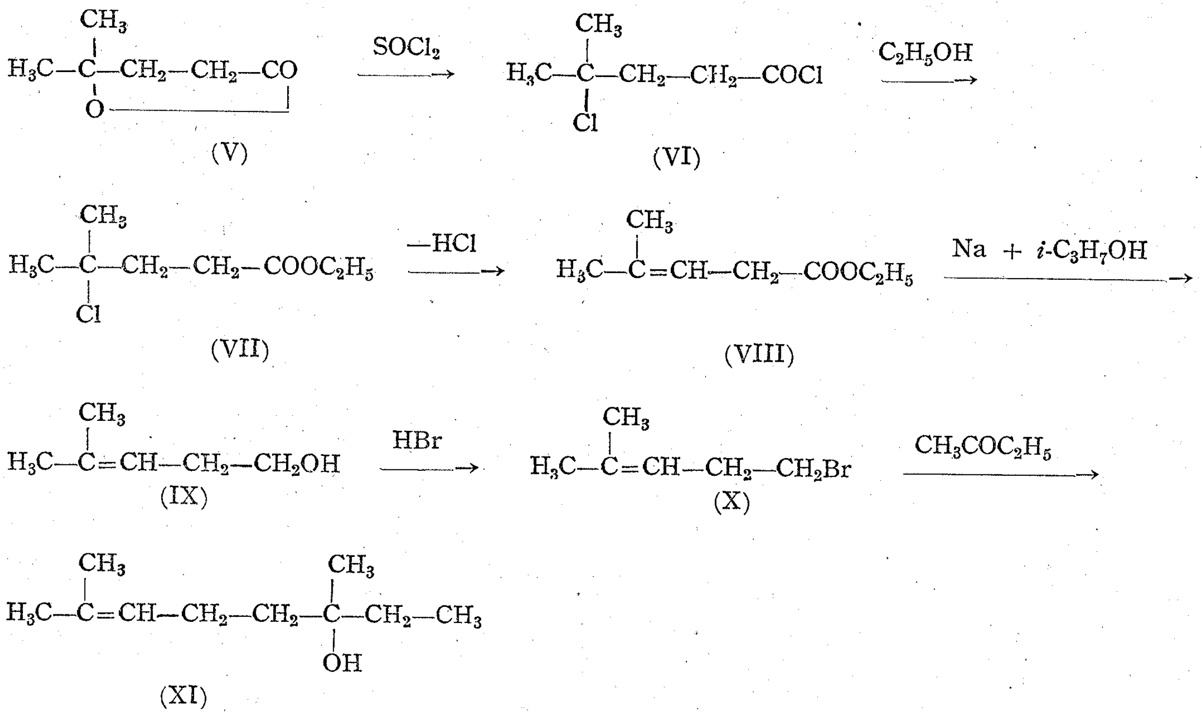
1) Helv. Chim. Acta, 2, 182(1912).



$$\underset{\text{(V)}}{\mathrm{H_3C{-}\overset{CH_3}{\underset{O}{C}}{-}CH_2{-}CH_2{-}CO}} \xrightarrow{\mathrm{SOCl_2}} \underset{\text{(VI)}}{\mathrm{H_3C{-}\overset{CH_3}{\underset{Cl}{C}}{-}CH_2{-}CH_2{-}COCl}} \xrightarrow{\mathrm{C_2H_5OH}}$$

$$\underset{\text{(VII)}}{\mathrm{H_3C{-}\overset{CH_3}{\underset{Cl}{C}}{-}CH_2{-}CH_2{-}COOC_2H_5}} \xrightarrow{-\mathrm{HCl}} \underset{\text{(VIII)}}{\mathrm{H_3C{-}\overset{CH_3}{C}{=}CH{-}CH_2{-}COOC_2H_5}} \xrightarrow{\mathrm{Na}\ +\ i\text{-}\mathrm{C_3H_7OH}}$$

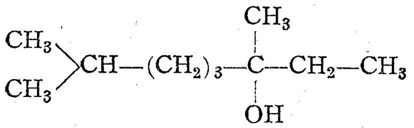
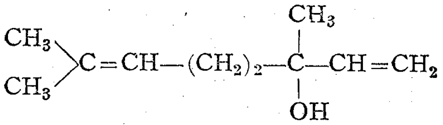
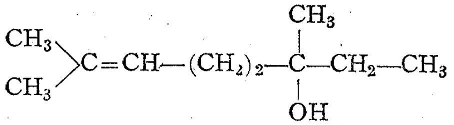
$$\underset{\text{(IX)}}{\mathrm{H_3C{-}\overset{CH_3}{C}{=}CH{-}CH_2{-}CH_2OH}} \xrightarrow{\mathrm{HBr}} \underset{\text{(X)}}{\mathrm{H_3C{-}\overset{CH_3}{C}{=}CH{-}CH_2{-}CH_2Br}} \xrightarrow{\mathrm{CH_3COC_2H_5}}$$

$$\underset{\text{(XI)}}{\mathrm{H_3C{-}\overset{CH_3}{C}{=}CH{-}CH_2{-}CH_2{-}\overset{CH_3}{\underset{OH}{C}}{-}CH_2{-}CH_3}}$$

In the Grignard reaction of ethyl levulate and methylmagnesium iodide, excess use of methylmagnesium iodide reduced the yield of the lactone (V) and resulted in the formation of a large amount of dimethyl hexanediol. Some of the hydroxy ester (IV) was already lactonized by the Grignard reaction without lactonization treatment.

The fission of the lactone ring was carried out by treatment with thionyl chloride and the crude chlorocaproyl chloride was esterified with ethanol saturated with dry hydrogen chloride. The chloroester (VII) was dehydrohalogenated through heating at a high temperature. This reaction required a somewhat long time. Methylpentenol (IX) was obtained in a good yield by the sodium reduction and converted to the bromide (X). The Grignard reaction of 4-methyl-3-pentenyl bromide and methyl ethyl ketone was carried out by the usual method.

The resulting dihydrolinalool has a linalool-like fragrance. It is assumed that the double bond is situated between C_6–C_7 carbon atoms. The physical constants of this compound is compared with synthetic linalool and tetrahydrolinalool.

dl-Tetrahydro-linalool	 $\mathrm{(CH_3)_2CH{-}(CH_2)_3{-}\overset{CH_3}{\underset{OH}{C}}{-}CH_2{-}CH_3}$	b.p$_{10}$ 86～88°	d_4^{15} 0.939	Barbier and Locquin[2)] Shiono Perfum. Co.[3)]
dl-Linalool	 $\mathrm{(CH_3)_2C{=}CH{-}(CH_2)_2{-}\overset{CH_3}{\underset{OH}{C}}{-}CH{=}CH_2}$	b.p$_{13}$ 86～88°	d_4^{15} 0.9649	Ruzicka, *et al.*[1)]
dl-Dihydro-linalool	 $\mathrm{(CH_3)_2C{=}CH{-}(CH_2)_2{-}\overset{CH_3}{\underset{OH}{C}}{-}CH_2{-}CH_3}$	b.p$_{11}$ 82～83°	n_D^{18} 1.4415 d_4^{15} 0.8687	Authors

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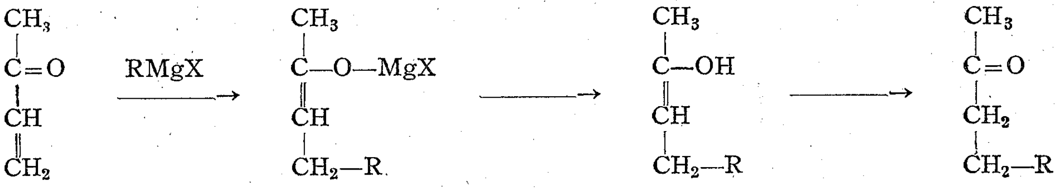
2) Barbier, Locquin: Compt. rend., 158, 1554 (1914).
3) J. Soc. Org. Synthetic Chem. Japan, 9, 90 (1951).

The attempt for the synthesis of racemic linalool by the Grignard reaction between methylpentenyl bromide and methyl vinyl ketone failed. From this reaction product a ketone, b.p$_{13}$ 70~75°, was obtained as a main product. In this reaction it seemed that the 1,4-addition of methylpentenylmagnesium bromide to methyl vinyl ketone had been effected.



The authors wish to express their thanks to the Ajinomoto Industries, Ltd., for their donation of levulic acid.

Exprimental

Ethyl Levulate (III)—Prepared according to the method of von Auwers4) from levulic acid. b.p$_{12}$ 94~96°, d_{20}^{20} 1.0156, n_D^{16} 1.4225.5)

Isocaprolactone (V)6~9)—Ethereal solution of CH_3MgI (prepared from 100 g. of Mg, 500g. of CH_3I, and 100 cc. of dry ether) was slowly added to the ethereal solution (480 g. of (III) and 2500 cc. of dry ether) under stirring for 2.5 hrs. at -5°. The reaction mixture was warmed on a water bath for 2 hrs. The magnesium compound was decomposed with water and then with 10% sulfuric acid. The ether layer was separated and the aqueous layer was extracted twice with a small amount of ether. The combined ethereal extracts was washed with 5% $NaHSO_3$ solution to remove iodine, dried over $CaCl_2$, and evaporated. The residual oil was lactonized with 60% H_2SO_4 and the crude lactone was purified by fractional distillation. It boiled at 88~96°/10 mm., d_4^{26} 1.0015, n_D^{26} 1.4245. Yield, 207 g. (53.4%).

Ethyl α-Chloroisocaproate (VII)—161 g. (1.4 moles) of (V) was dissolved in a mixture of 1000 cc. dried benzene and 500 g. (4.2 moles) of freshly distilled $SOCl_2$, and the solution was heated on a water bath for 4 hrs. After the reaction was completed, 500 cc. of benzene was removed by evaporation and 1000 cc. of ethanol saturated with dry HCl was added to the residual substance. The mixture was heated on a water bath under reflux for 20 min. and the mixture of ethanol and benzene was distilled off. 213 g. of pure chloroester was obtained through fractional distillation. b.p$_{10}$ 79~86°, d_4^{17} 1.0083, n_D^{25} 1.4295. Yield, 213 g. (84.5%).

Ethyl 4-Methyl-3-hexenoate (VIII)—213 g. of (VII) was heated on a sand bath at 160~220° for 40 hrs. After the generation of hydrogen chloride gas ceased, the black oily substance was purified through fractional distillation. b.p$_{20}$ 70~86°, d_4^{17} 0.9192, n_D^{17} 1.4296.10) Yield, 150 g. (77.2%).

4-Methyl-3-pentenol (IX)—142 g. (1 mole) of (VIII) was dissolved in 1400 cc. of absolute isopropanol and the solution was refluxed on an oil bath at 85~100°, under the cautious addition of 142 g. (6 atoms) of metallic sodium. The mixture was heated in an oil bath at 120~130° for 2 hrs. until sodium dissolved. Then the reaction mixture was decomposed with water and extracted with ether. After the removal of the solvent, oily substance was obtained. The crude methylpentenol was distilled in vacuum. b.p. 155~160°, d_{20}^{20} 0.9605. n_D^{20} 1.4425. Yield, 50 g. (50%).

25 g. of 4-methyl-3-pentenoic acid was recovered from the alkaline solution. It boiled at 81~85°/10 mm.

4-Methyl-3-pentenyl Bromide (X)—A calculated amount of dry hydrogen bromide gas (from tetralin and bromine) was saturated in (IX) at -5° to 0° and then the reaction mixture was boiled on a sand bath for 10 hrs. The crude bromide was washed with dil. Na_2CO_3 solution and purified through vacuum distillation. b.p. 145~149°, Yield, 59 g. (72.3%).

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4) Ber., 144, 3537.
5) Ber., 50, 1367.
6) D. T. Jones : J. Chem. Soc., 85, 1691 (1904).
7) Vanino Bd. II, 166.
8) Cason, Adams : J. Am. Chem. Soc., 66, 1764 (1944).
9) C. L. Lese : J. Chem. Soc., 1950 2725.
10) J. Chem. Soc., 85, 1693 (1904).
11) Van Aerde : Chem. Zentr., I, 832 (1909) ; Klawikordow : *Ibid.*, II, 363 (1911).

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Dihydrolinalool (XI)—15 g. (ca. 0.2 mole) of methyl ethyl ketone and 50 cc. of ether were added dropwise to the Grignard reagent (prepared from 21.5 g. (0.13 mole) of (X), 5 g. (ca. 0.2 mole) of Mg, and 20 cc. of dry ether) under vigorous stirring at −5° to 0°. The reaction product was treated by the usual method. b.p$_{11}$ 82∼83°, d_4^{14} 0.8687, n_D^{19} 1.4415. Yield, 11.5 g. (56%). *Anal.* Calcd. for $C_{10}H_{20}O$: C, 76.92; H, 12.8. Found: C, 76.94; H, 12.87.

Grignard Reaction of Methyl Vinyl Ketone and (X)—From 33 g. (0.2 mole) of (X), 7.5 g. (ca. 0.3 mole) of metallic magnesium, and 21 g. (0.3 mole) of methyl vinyl ketone (prepared according to Hagemeyer12) and others13∼17) under the same conditions as described above) 20 g. of a colorless liquid with a characteristic odor was obtained. It boiled at 70∼75°/13 mm. 2,4-Dinitrophenylhydrazone, m.p. 192∼194°. Doenigé's reagent gave no reaction. Further examination of this compound was not carried out.

Summary

Dihydrolinalool was synthesized from levulic acid and its yield was 12% of the theory.

(Received February 6, 1954)

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12) J. Am. Chem. Soc., 71, 119 (1949).
13) Oda: Synth. Chemistry (Japan) 203.
14) Morgan, Holmes: J. Chem. Soc., 1932, 2669.
15) While, Howard: J. Am. Chem. Soc., 65, 25 (1943).
16) Wingfood: C. A. 38, 2349 (1944).
17) de Fen Macquillin: J. Am. Chem. Soc., 59, 53 (1937).

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25. Tadashi Sasaki: Synthesis of Nitrofuroic and Nitrofurylacrylic Hydrazides and their Derivates.*

(*Institute of Scientific Research for Practical Life, Medical Faculty, University of Kyoto***)

An extensive study has been undertaken to find new antituberculous compounds having the structure of an acid hydrazide or its derivatives since the discovery of isonicotinic hydrazide1). Several different methods have been used on the syntheses of furoic hydrazide2), but there is no report pertaining to the preparation of the acid hydrazides having an antibacterial nitrofuryl radical. For this reason, a synthesis of nitrofuroic and nitrofurylacrylic hydrazides was attempted.

Nitrofuroic hydrazide was easily obtained by mixing methyl or ethyl nitrofuroate with hydrazine hydrate under cooling and by using ethanol or methanol as an additional solvent3). The reaction was spontaneous and exothermic. Diacylhydrazine, however,

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* Presented before the Annual Meeting of the Institute for Chemical Research of Kyoto University, October, 1952.

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1) H. L. Yale, *et al.*: J. Am. Chem. Soc., 75, 1933 (1953); Am. Rev. Tuberc., 65, 357 (1952); 67, 354 (1953).
2) Org. Reactions, 3, 435 (1946).
3) Furoic, methylfuroic, and bromofuroic hydrazides had already been prepared from their esters by heating without any solvent (cf. footnote 2). This fact shows that the reaction condition varies according to the individual reactivity and the introduction of a strong negative nitro radical strengthens the activity of the ester in this reaction.