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The Synthesis and Photo Reaction of 7,11-Dimethyl-1,6,10-dodecatrien-3-one

Tadahiro KATO, Hideo MAEDA, Mitsuaki TSUNAKAWA, and Yoshio KITAHARA*
Department of Chemistry, Faculty of Science, Tohoku University, Sendai

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For the purpose of constructing a pinene skeleton (I), a promising intermediate for the synthesis of bergamotenes (III), the vinyl ketone (II), was synthesized from geranyl bromide (IV) by the application of Meyer's method, followed by a Grignard reaction with vinylmagnesium bromide and subsequent oxidation. The irradiation of II in absolute ether afforded an unexpected keto ether (X) in a low yield; it was characterized by means of a deuterium-exchange reaction and physical methods. No other product except X was isolated from the photoreaction mixture of II.

For the purpose of constructing a pinene skeleton (I) by the photocyclization[1] of olefinic ketone (II), we have synthesized (II) and examined its photoreaction. Compound (I) is a promising intermediate for the synthesis of bergamotenes (III), the structures of which were unequivocally confirmed by an elegant synthesis[2] from β-pinene.

Geranyl bromide (IV), easily obtainable from geraniol by treatment with phosphorous tribromide, was chosen as the starting material. The reaction of the bromide with lithium salt of 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine afforded the coupled product (V) in a 68% yield. The dihydrooxazine (V) was carefully reduced with sodium borohydride to give a fairly unstable tetrahydrooxazine derivative (VI), which, without purification, was hydrolyzed by oxalic acid to give two products, (VII) and (VIII), in 15 and 9% yields respectively.[3] The hydrolysis required the conditions of steam distillation, and the low yield of VII is due to its unstability toward acid at high temperatures. The acyclic aldehyde (VII) is fairly unstable even in a refrigerator under a nitrogen atmosphere.

The reaction of VII with vinylmagnesium bromide afforded the vinyl alcohol (IX) in a 78% yield, this substance was subsequently oxidized with active manganese dioxide to give vinyl ketone (II) in a 60% yield. Compounds (VII), (IX), and (II), especially VII and II, are fairly unstable and should be stored in a refrigerator under a nitrogen atmosphere.

The irradiation of II in absolute ether with a 100-W high-pressure mercury lamp under a nitrogen atmosphere resulted in the formation of several products, from which only a keto-ether (X) was isolated by re-

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* To whom inquiries regarding this paper should be addressed.

[1] For example, E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964).

[2] T. W. Gibson and W. F. Erman, *ibid.*, **91**, 4771 (1969).

[3] a) A. I. Meyers, A. Nabeya, H. W. Adickes, and I. R. Politzer, *ibid.*, **91**, 763 (1969). b) J. M. Fitzpatrick, G. R. Malone, I. R. Politzer, H. W. Adickes, and A. I. Meyers, *Organic Preparations and Procedures*, **1** (3), 193 (1969).

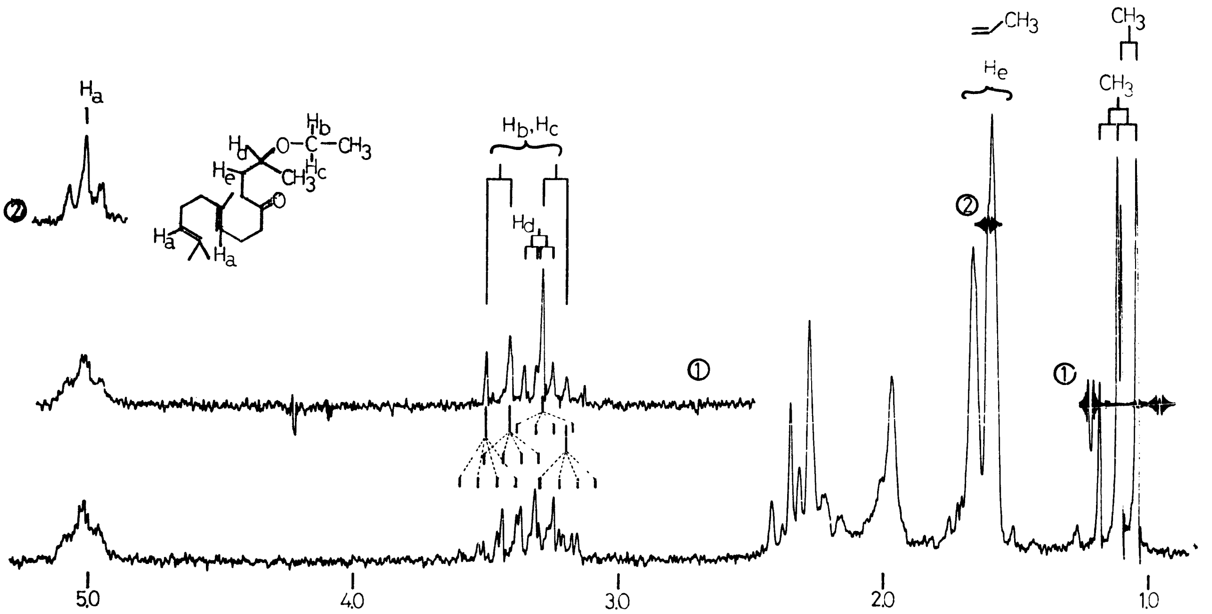


Fig. 1. 100 Mc NMR spectrum of keto ether (X) in CCl_4 plus 10% C_6D_6.

peated column chromatography in a 2% yield.

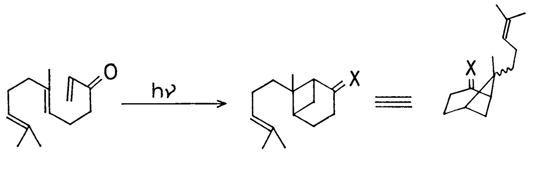
The gross structure of X was determined on the basis of the following evidence. The active hydrogens of X were replaced by deuterium under alkaline conditions[4] to give the deuterated keto ether. A comparison of the mass spectra of the original and the deuterated keto ether showed that X contained four replaceable hydrogens.

The 100-Mc NMR spectrum[5] of X in CCl_4 plus 10% C_6D_6 (Fig. 1) shows, in addition to two olefinic protons (Ha) at 5.01 and three olefinic methyl groups near 1.60 ppm, complex multiplets between 3.08 and 3.60 due to Hb, Hc, and Hd, a doublet and a triplet of the primary and secondary methyl groups respectively.

The irradiation of both the secondary and primary methyl groups (Fig. 1, ①) causes the multiplets between 3.20 and 3.50 ppm to appear as a pair of doublets centered at 3.45 and 3.24 ppm due to Hb and Hc, and a doublet of doublet at 3.31 (Hd). Simultaneous irradiation at 3.17 and 3.51 converts the triplet and doublet at 1.07 and 1.10 of the primary and secondary methyl groups to sharp singlets and at the same time affects the signals near 1.6 due to the He proton, which appears overlapping with three olefinic methyl groups. Irradiation at 1.60 ppm not only changes the broad multiplet at 5.01 due to olefinic protons (Ha) to a broad triplet (Fig. 1, ②), but also disturbs the multiplets near 3.2 ppm. These decoupling results are best explained in terms of a $-CH_2CH(CH_3)OCH_2CH_3$ grouping and an acyclic geranyl moiety which remains unchanged during the photoreaction.

Although a pinene skeleton could not be constructed by photocyclization, as has been expected at the outset of our study, it was found that the vinyl group of the vinyl ketone (II) is reactive toward ethyl ether under photoirradiation. This reaction may be general, as has been reported[6] recently in the case of conjugated cyclopentenones.

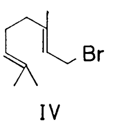
The chemical shifts and coupling modes of Hb, Hc,



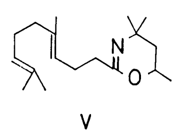
II

I X = O

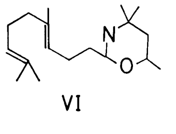
III X = CH_2



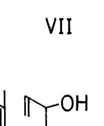
IV



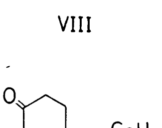
V



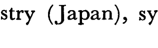
VI



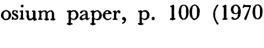
VII



VIII



IX



X

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[4] B. Nolin and R. N. Jones, *Can. J. Chem.*, **30**, 727 (1952).

[5] NMR spectra were measured with Varian T-60 and H-100 spectrometers in carbon tetrachloride if otherwise stated. The Chemical shifts were expressed with ppm from an internal standard of tetramethylsilane.

[6] Z. Yoshida, M. Kimura, and I. Tabuse, Symposium of Photochemistry (Japan), symposium paper, p. 100 (1970).

and Hd in X are of interest since they indicate that Hb and Hc are magnetically non-equivalent and that the free rotation near the ether linkage of X is restricted. This may be due to a reason similar to that reported in the case of ethyl isobutyl ether,[7] where the methylene of the ethyl group appaers as an AB of the ABX_3 system.

Experimental

2-(4,8-Dimethyl-3,7-nonadienyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (V). An ether solution of *n*-butyl lithium (120 m*l*) prepared from *n*-butyl bromide (34.4 g) and lithium (4.3 g) in absolute ether (150 m*l*), was dropped, at −60°C over a one-period into an absolute tetrahydrofuran solution of 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine (18.6 g, 0.13 mol) which had been cooled to −60°C before the addition. After 2 hr stirring at −60—−70°C, geranyl bromide (31 g, 0.143 mol) in absolute tetrahydrofuran (40 m*l*) was dropped in over a 30 min period at that same temperature, after which the stirring was continued for a further 30 min. The cooling bath was removed to make the reaction mixture come to room temperature. All the above operations were carried out under a nitrogen atmosphere. The reaction mixture was then poured into ice water. The aqueous solution, after being acidified with 9N hydrochloric acid, was washed with *n*-hexane and then made alkaline by adding a 40% sodium hydroxide solution.

The alkaline solution was extracted with ether, and the ether solution was evaporated to give a residual oil. The residual oil was then purified by distillation to afford a dihydrooxazine derivative (V) (24.4 g, 68% yield); bp 95—97°C/1 mmHg. V: IR (film) 1670 cm^{-1} (ν C=N–). NMR (δ), 1.10 (sharp s, C_4–Me×2), 1.23 (d, *J*=6.2, C_6–Me), 1.63 (olefinic methyls), 4.02 (m, C_6–H), and 5.13 (olefinic protons). Mass, M$^+$ 277, Mol Wt ($C_{18}H_{31}NO$) 277.44.

Found: C, 77.49; H, 11.56; N, 4.99%. Calcd for $C_{18}H_{31}NO$: C, 77.92; N, 11.26; N, 5.05%.

2-(4,8-Dimethyl-3,7-nonadienyl)-4,4,6-trimethyl-2,3,5,6-tetrahydro-1,3-oxazine (VI). The dihydrooxazine (V) (30 g, 0.11 mol) was dissolved in 230 m*l* of a mixed solvent of tetrahydrofuran and ethanol (1: 1). The solution, after being cooled to −50°C, was carefully neutrallized with 9N hydrochloric acid to pH 7 and sodium borohydride in an aqueous solution [$NaBH_4$(4.25 g, 0.11 mol), H_2O(7 m*l*); 40% NaOH (one drop)] was gradually dropped in over a 30 min period, during which time the solution was kept neutral (pH 6—8) by the occasional addition of 9N hydrochloric acid. After the completion of the addition, the stirring was kept up for an additional hour.

The above operations were carried out at −40—−50°C. The reaction mixture was made alkaline by adding a 40% sodium hydroxide solution, and this poured into water. After extraction with ether, the ether solution was washed with a saturated sodium chloride aqueous solution and then dried over anhydrous potassium carbonate. The evaporation of the ether afforded a crude oil (VI) (30.2 g), which, due to its unstability toward heat and silica gel, was used for the next step without purification. IR (film) 3300 cm^{-1}. NMR 1.06, 1.10, and 1.13 (C_4 and C_6-methyls), 1.60 and 1.67 (olefinic methyls), 3.65 (m, C_6-H), 4.13 (t, *J*=6, C_2–H), and 5.16 (olefinic protons).

5,9-Dimethyl-4,8-decadienal (VII). A mixture of the crude tetrahydrooxazine (VI) (3.05 g), water (30 m*l*), and anhydrous oxalic acid (1.33 g) was steam-distilled under a nitrogen atmosphere, and then the distillate was extracted with ether.

From the ether solution we obtained 1.30 g of oil after an usual work-up. The crude oil was chromatographed on silica gel (20 g) by elution with a mixed solvent of benzene - cyclohexane (1: 1) to afford 544 mg of an aldehyde fraction. The aldehyde fraction was then further chromatographed on silica gel (5 g) impregnated with 5% silver nitrate. Successive elution afforded monocyclic aldehyde (VIII) (174 mg) from a benzene - cyclohexane (1:1) mixture and acyclic aldehyde (VII), (287 mg) from an ether eluent. Aldehyde (VII): IR (film) 2750, 1730, 830 cm^{-1}. NMR 1.60 and 1.63 (olefinic methyls), 5.10 (olefinic protons), and 9.80 ppm (bs, aldehyde proton). Mass M$^+$ 180, Mol wt ($C_{12}H_{20}O$) 180.28. Aldehyde (VIII): IR (film) 2750, 1730 cm^{-1}. NMR 1.00 (sharp s, Me×2), 1.60 (sharp s, olefinic methyl), and 9.83 (bs, aldehyde proton). Mass M$^+$ 180.

Found: C, 79.90; H, 11.25%. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18%.

Tosyl Hydrazone of VIII. A mixture of the aldehyde (VIII) (73 mg), *p*-tosylhydrazine (100 mg), and methanol (5 m*l*) was stirred overnight at room temperature. The subsequent recrystallization of the crude hydrazone with methanol afforded a pure specimen (85 mg); mp 117°C.

Found: C, 65.26; H, 8.11; N, 8.14%. Calcd for $C_{19}H_{27}N_2O_2S$: C, 65.67; H, 7.83; N, 8.06%.

7,11-Dimethyl-1,6,10-dodecatrien-3-ol (IX). To a tetrahydrofuran solution of vinyl magnesium bromide, prepared from magnesium (200 mg), vinyl bromide (980 mg), and anhydrous tetrahydrofuran (3 m*l*), we added the aldehyde (VII) (477 mg) in anhydrous tetrahydrofuran (6 m*l*) under a nitrogen atmosphere; the reaction mixture was then stirred overnight at room temperature.

The reaction mixture, after being poured into an aqueous ammonium chloride solution, was extracted with ether. From the ether solution we obtained, after an usual work-up, crude oil; this oil was chromatographed on silica gel (16 g) with benzene to give oily vinyl alcohol (IX) (447 mg, 78%). A pure specimen of IX was obtained by rechromatography on silica gel and subsequent distillation. IR (film) 3300, 1670, 1645, 920 cm^{-1}. NMR 1.60 and 1.67 (olefinic methyls), 4.05 (m, CHOH), 5.05—6.13 (five olefinic protons). Mass M$^+$ 208, Mol wt ($C_{14}H_{24}O$) 208.33.

Found: C, 80.34; H, 11.41%. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61%.

7,11-Dimethyl-1,6,10-dodecatrien-3-one (II). A mixture of the alcohol (IX) (200 mg), active manganese dioxide (2.2 g), and carbon tetrachloride (10 m*l*) was stirred at room temperature overnight. The subsequent removal of the solid and the evaporation of the combined solvents afforded a crude oil (170 mg) which was passed through silica gel (8 g) with a mixed solvent of benzene - cyclohexane (1:1) to give pure ketone (II) (113 mg, 60%). IR (film) 1700 (W), 1680, 1615 cm^{-1}. NMR 1.60 (olefinic methyls), 5.10(b, 2H), and 5.73—6.5(–CH=CH_2 group). Mass M$^+$ 206, Mol wt ($C_{14}H_{22}O$) 206.32. UV λ_{max}^{MeOH} 324 mμ (64).

Photoreaction of Vinyl Ketone (II). Vinyl ketone (II) (173 mg) in 100 m*l* of absolute ether was irradiated under a nitrogen atmosphere for 8 hr with a 100-W high-pressure mercury lamp. Similarly, 253-, 250-, and 250 mg portions of vinyl ketone were separately irradiated under the same conditions until the starting material disappeared on thin-layer chromatography.

The above reaction mixtures were then combined and passed through 70 g of silica gel by changing the solvents successively. From cyclohexane - benzene (1:1) and benzene -

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[7] E. Bullock, E. E. Burnell, and B. Gregory, *Chem. Commun.*, **1967**, 193.

isopropylether (4: 1) we obtained 30 mg of the recovered material and 373 mg of a crude oil respectively. The latter was further chromatographed on 5% silver nitrate - silica gel (170 g) with cyclohexane - isopropyl ether (10:1) to give 54 mg of oil, which was then rechromatographed on a short silica-gel column with benzene to afford the pure photoproduct (X) (23 mg). No other product was obtained in a pure form. IR (film) 1715 cm^{-1}. NMR (Fig. 1).

Deuterium Exchange of the Photoproduct (X). The photoproduct (X) and anhydrous sodium carbonate (5 mg) were dissolved in a mixture of CH_3OD (4 m*l*) and D_2O (0.5 m*l*). After the mixture has been refluxed for an hr under a nitrogen atmosphere, the solvents were removed *in vacuo*.

The residue was successively worked up by the addition of CH_3OD (4 m*l*) and D_2O (0.5 m*l*), refluxing, and the subsequent removal of the solvents. The residue was picked up in absolute ether to obtain the deuterated product. Major fragment ions of X and its deuterated product. X: 280(M^+), 234, 191, 165, 151, 136, 121, 111, 98. deuterated X: 284(M^+), 238, 195, 194, 169, 168, 155, 136, 121, 114, 102.

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