Some Displacement Reactions of Neopentyl Type Bromide Derived from Thujopsene[1]

Masaaki Ito, Kazuo Abe, Hitoshi Takeshita,* and Mitsuyoshi Yatagai*
Department of Industrial Chemistry, Kitami Institute of Technology, Kitami, Hokkaido
* *Department of Chemistry, Tohoku University, Sendai*

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The reaction of thujopsene with gaseous hydrogen bromide at low temperature affords a 48% yield of neopentyl type bromide. The reactivity of the homoallyl bromide was inspected. First, the neopentyl type bromide was derived to a diethyl widdryl malonate in order to demonstrate the reaction which indicates the involvement of homoallylcyclopropylcarbinyl ion system. The malonate was converted to a carboxylic acid and then to isomeric lactone. To demonstrate the reaction which suggests the retention of carbon frame work in the reaction, the reaction of the neopentyl bromide was extended to Grignard reaction. The Grignard reagent reacted with cyclohexanone gave a tertiary alcohol, whereas a dimeric hydrocarbon was also obtained through the Wurtz type condensation. The tertiary alcohol was converted to a dehydrated hydrocarbon and then a glycol.

It is known that reactions of thujopsene I with several acids cause skeletal rearrangements to give a variety of types of compounds according to conditions. Treatment of I with oxalic acid in alcoholic solution gave widdrol II, widdryl ether III,[2] β-chamigrene IV, cuparene V, and hydrocarbons,[3] while, the reaction of I or II with mineral acid afforded the epimeric pair of the neopentyl type chlorides VI and VII by hydrochloric acid[4] and alcohols VIII and IX by sulfuric acid.[3] We thought it worthwhile to extend this reaction with hydrobromic acid to obtain more reactive bromo derivatives which could be employed in some displacement reactions. I was reacted with gaseous hydrogen bromide at low temperature giving a neopentyl type bromide, but no isomeric pair of this type. Evidence for this will be described.

Treatment of thujopsene obtained from Thujopsis dolabrata Sieb. et Zucc. with anhydrous hydrogen bromide yielded the bromide X in 48% after purification by fractional distillation. Among other products, "the hydrocarbon II" XI[3] was obtained as a second major product. The IR spectrum of X showed C–Br stretching frequency at 670 cm^{-1}. Gas-liquid chromatography revealed I to be a single compound, and the data of elemental analysis gives the molecular formula $C_{15}H_{25}Br$. NMR spectrum of X showed very similar features to that of VI, *i.e.*, four methyl singlets at 1.02 (3 Me) and 1.15 ppm, a vinyl hydrogen at 5.08 (singlet), and signal ascribed to a methylene hydrogens at 3.18 ppm (2H singlet) suggesting the structure shown.

The reactivity of the homoallyl bromide system of X was inspected. First, we examined the displacement with diethyl sodiomalonate, typical carbanion. Product XII isolated was not a diethyl malonate derivative expected from simple substitution, but skeletal rearrangement accompanying its formation. The gas-liquid chromatogram of XII showed it to be a single compound and saponification equivalent of XII showed it to be a diester $C_{15}H_{25}CH(COOC_2H_5)_2$. The NMR spectrum of XII showed, beside ethoxyl groups, (1.27 (6H) and 4.08 (4H)), 1.07 (3 Me, overlapping singlet), 1.00 (Me, singlet), 5.47 (1H, d, d, J=10.5, 6.0 Hz), and 3.20 (1H, s). Since the splitting pattern of the above olefinic proton signal accords with that of II,[5] XII must possess the widdryl skelton, and therefore its structure was deduced as diethyl widdryl malonate. Alkaline hydrolysis of XII gave a carboxylic acid XIII which, upon treatment with sulfuric acid in alcohol, afforded an isomeric lactone XIV in good yield. The carbonyl stretching frequency of XIV (1720 cm^{-1}), the lactonic ring, was free from a strain.

The rearrangement clearly indicates the involvement of homoallyl-cyclopropylcarbinyl ion system. Thus, the geometrical requirement for these interconversion leads to the α-orientation for the malonate moiety.

We extended the reaction of the neopentyl bromide X to Grignard reaction since the above mentioned homoallylcyclopropyl carbinyl ion should not be involved. The reaction with cyclohexanone was carried out in ether in the usual manner. The major product isolated by fractional distillation was found to be a tertiary alcohol XV. Its NMR spectrum revealed a sharp singlet at 5.30 ppm for an olefinic hydrogen, suggesting the retention of carbon frame work in the reaction. Four methyl signals at 0.99 (3H, s), 1.06 (3H, s), and 1.29 (6H, s) were in expected positions. When XV was passed through a silica gel column (Wako Gel Q-50), dehydrated hydrocarbon XVI was formed in nearly quantitative yield. Gas-liquid chromatogram of XVI proved it to be a single compound, whose NMR spectrum showed two singlets at 5.08 and 5.30 ppm. The singlet nature of the second olefinic hydrogen can not make the structure of XVI be regarded as XVIa, since various types of olefinic

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[1] This paper was read before 12th Symposium of Terpene, Essential Oil and Aromatics, Hamamatsu, Oct. 1968.

[2] S. Nagahama, H. Kobayashi, and S. Akiyoshi, This Bulletin, **33**, 1467 (1960).

[3] S. Ito and M. Yatagai, to be published. This part of work appared in the Abstract Papers of 14th Symposium on the Chemistry of Natural Products, p. 174, Fukuoka, Oct. 1970.

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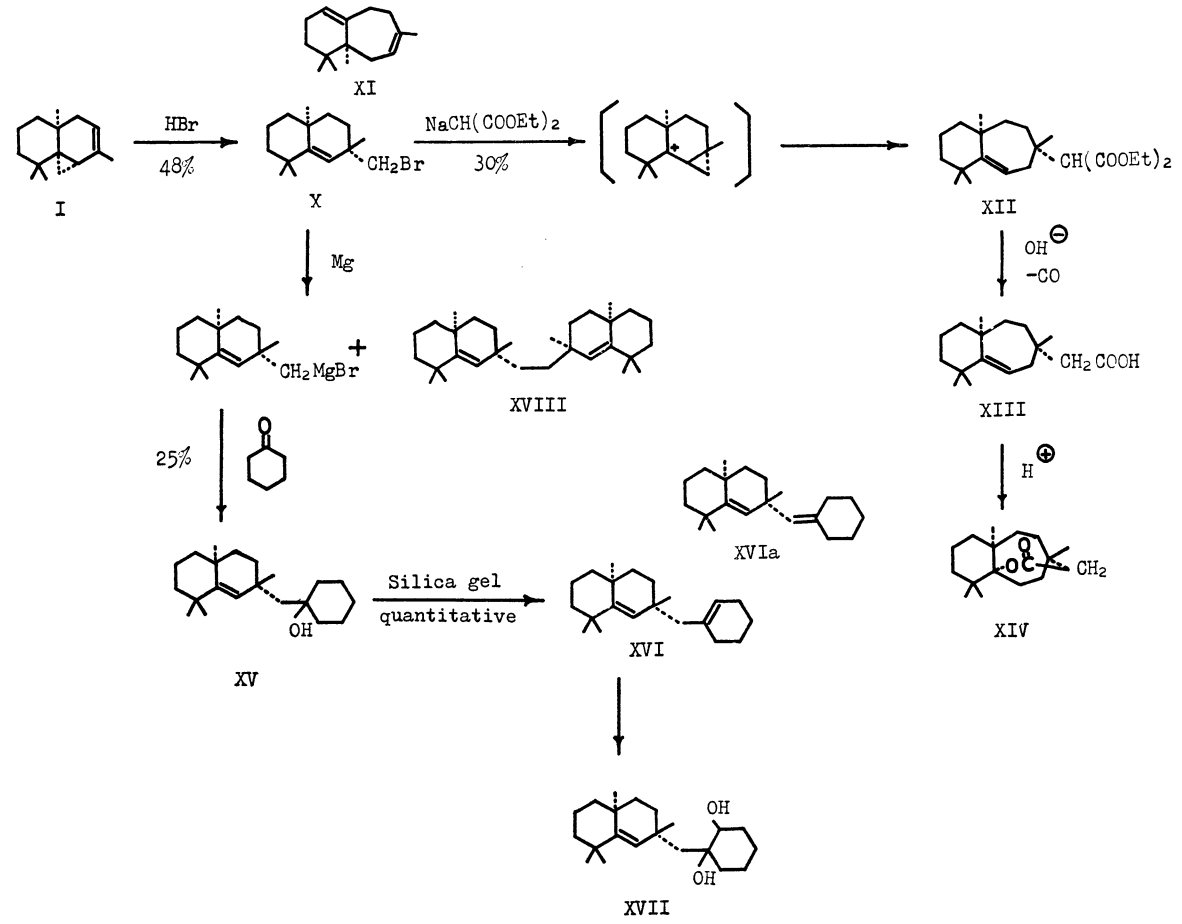
[5] S. Ito, K. Endo, H. Takeshita, T. Nozoe, and J. B. Stothers, *Chem. Ind.* (London), **1961**, 1618.



Scheme 1

hydrogen of cyclohexene often appeared without clear splittings. We carried out oxidation with osmium tetraoxide to afford the glycol XVII which clearly revealed a signal at 3.87 ppm due to a presence of a carbinyl proton with adjacent methylene group. Thus, the structure of XVI is as depicted.

The remaining crystalline mass on distillation of XV was recrystallized and gave a dimeric hydrocarbon XVIII in 14% yield. Its structure was deduced from elemental analysis, osmometric molecular weight determination, and mainly from the NMR spectrum which has a sharp singlet at 5.00 (2H), 0.91 (6H), 1.05 (6H), 1.09 (6H), and 1.13 (6H) ppm respectively, indicating a symmetric structure. We tried to obtain the same hydrocarbon on simple hydrolysis of the Grignard reagent and found the formation of XVIII in a fairly high yield through the Wurtz type condensation.

Experimental

All infrared absorption spectra were measured with a Shimadzu Model IR-27G grating spectrophotometer and the NMR spectra on a varian A-60A analytical spectrometer using tetramethylsilane as an internal standard. Gas-liquid chromatographic data were measured on a Shimadzu GC-1C gaschromatograph, using helium as a carrier gas. All melting points were obtained on a Büchi micro melting point apparatus and are uncorrected. Analyses performed on a Micro-Analyser, Shimadzu.

Thujopsene. This was isolated from Cedar H oil by repeated rectification: bp 119—120°C/10 mmHg, d^{20}_{20} 0.9362, n^{20}_{D} 1.5033, $[\alpha]^{20}_{D}$ −93.68.

Neopentyl-type Bromide of Thujopsene. Into freezing thujopsene in a round bottomed 200 m*l* flask was passed dry hydrogen bromide generated by dropping bromine into a mixture of red phosphorus and water and drying with calcium bromide, until absorption reached the calculated volume. The bromides were obtained in 48% yield at reaction temperature −20°C and in 40% at 0°C. The product was then dissolved in ether, washed with water, dried over calcium bromide and distilled, a fraction 149—151°C/10 mmHg, d^{20}_{20} 1.1592, $[\alpha]^{27}_{D}$ +83 (2% CCl_4) being collected. The gas-liquid chromatogram of the fraction exhibited two peaks, partly overlapping, due to compound X (*ca.* 70%, first eluted) and compound XI (*ca.* 30%, second eluted) which was identical with the authentic sample. The IR spectrum of X showed C–Br absorption at 15 μ.

Found: C, 63.82; H, 8.90%. Calcd for $C_{15}H_{25}Br$: C, 63.16; H, 8.83%.

No attempt was made to separate these two compounds on a preparative scale. The crude product was used directly in the following reactions.

Preparation of the Diethyl Malonate Derivative starting from the Neopentyl-type Bromide of Thujopsene. To an alcoholic solution of sodium ethylate containing 1.7 g metallic sodium (0.075 mol) and 40 m*l* absolute alcohol in an ice bath was added dropwise 12 g (0.075 mol) of diethyl malonate in a

100 m*l* flask equipped with a magnetic stirrer, and then 21.4 g (0.075 mol) of bromide X dropwise. The mixture was stirred for 0.5 hr after the addition was completed and then refluxed for 22 hr. The solvent was removed on a steam bath. The reaction mixture was poured into water and extracted with ether. The ether solution was dried and the solvent removed on the steam bath with a rotary evaporator. Analytically pure material XII bp 218—219°C/10 mmHg, d_{20}^{20} 1.0363, n_{D}^{20} 1.4891. $[\alpha]_{\mathrm{D}}^{18}$ +87.4 (CCl_4), was obtained by further distillation. The yield was 30% theoretically. IR (carbon tetrachloride): $\nu_{C=O}$ 1752 cm^{-1} (S), 1726 cm^{-1} (S), $\lambda_{\max}^{\mathrm{MeOH}}$ 215 mμ.

Found: C, 72.45; H, 9.83%. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.95%.

Preparation of the Lactone XIV: Starting from the Diethyl Malonate XII. 814 mg (2.24 mmol) of XII was hydrolyzed in alcohol with 751 mg (13.4 mmol) of potassium hydroxide for 2 hr. After the usual work-up 762 mg of the dicarboxylic acid was obtained and then decarboxylated 2 hr at 150°C under a pressure of 20 mmHg. The resulting residue (160 mg) was dissolved in chloroform (7 m*l*) and the solution was added to a mixture of concentrated sulfuric acid (2 m*l*) and chloroform (2 m*l*) at −5°C. The mixture was swirled in an ice bath for 5 min and then poured on ice. The product was extracted with dichloroethane; the extract was washed with potassium bicarbonate solution and dried and the solvent was removed. Preparative tlc of the reaction mixture gave 16.5 mg of pure lactone XIV. The IR spectrum showed C=O absorption at 1720 cm^{-1}.

Grignard Reaction of Bromide X with Cyclohexanone. The Grignard reagent was prepared from 27.4 g (0.075 mol) of bromide X, 2.0 g (0.083 mol) of magnesium, and 10 m*l* of absolute ether in the usual way. It was cooled and 7.4 g (0.075 mol) of cyclohexanone in absolute ether was added dropwise with stirring for over 1 hr, cooled, and poured into a mixture of ice and an aqueous ammonium chloride solution. The ether layer was separated, and the aqueous layer was washed twice with ether. The combined ether extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to leave crude oil which upon distillation at 202—203°C/10 mmHg gave 5.7 g (25%) of XV as a colorless liquid. The thin-layer chromatogram (silica gel, *n*-heptane : ethylmethyl ketone=80 : 20) showed a spot at R_f 0.89. The gas-liquid chromatogram showed a single peak. The molecular weight was determined to be 298.5 (Calcd for 304.5). IR (carbon tetrachloride): ν_{OH} 3550 cm^{-1} (S).

Found: C, 82.48; H, 11.78%. Calcd for $C_{21}H_{36}O$: C, 82.83; H, 11.12%.

The distillation residue of the reaction mixture gave a crystalline compound XVIII after recrystallization from ethyl acetate. Analytically pure material melted at 88—89°C, $[\alpha]_{\mathrm{D}}^{20}$ +69.4 (CCl_4), molecular weight: Found 408.4 (Calcd 410.7). IR (carbon tetrachloride: ν_{C-H} 2840, 2850, 2910, 2950, 3025 cm^{-1}.

Found: C, 88.02; H, 12.13%. Calcd for $C_{30}H_{50}$: C, 87.73; H, 12.27%.

The Grignard reagent prepared from 2.0 g (0.01 mol) of bromide X in the manner mentioned above was, hydrolyzed directly with a mixture of ice and an aqueous ammonium chloride solution. Crude crystalline XVIII weighed 2.4 g.

The melting point, mixed melting point and IR spectrum were identical with those of the by-product of the Grignard reaction mentioned above.

Dehydration of Tertiary Alcohol XV to Hydrocarbon XVI on a Silica-gel Column. Chromatagraphy of XV over a column of silica-gel (Wako-gel Q-50) using petroleum ether gave 2 g of XVI, n_{D}^{20} 1.5159, $[\alpha]_{\mathrm{D}}^{20}$ +101.1 (CCl_4). The gas-liquid chromatogram showed a single peak. The molecular weight was determined to be 283 (calcd 286). IR (carbon tetrachloride): ν_{C-H} 2815, 2915, 3150 cm^{-1}. NMR (CCl_4), 5.09 (1H, singlet olefinic proton), 5.30 (1H, singlet olefinic proton) ppm.

Found: C, 87.64; H, 11.90%. Calcd for $C_{21}H_{34}$: C, 88.04; H, 11.96%.

Osmium Tetraoxide Oxidation of Hydrocarbon XVI. Five hundred milligrams of XVI was oxidized in chloroform and pyridine with 550 mg of osmium tetraoxide overnight. The reaction mixture was washed with water and the reagent was removed by passage of hydrogen sulfide into the solution and filtration. Pale yellow oil obtained by evaporation of the solvent was fractionated through the silica gel column to yield 50 mg of XVII. Colorless liquid.

Found: C, 78.55; H, 11.41%. Calcd for $C_{21}H_{34}O_2$: C, 78.69; H, 11.32%.

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