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Diterpenoids. XXV.[1] Autoxidation of Styrene Type Compounds derived from *l*-Abietic Acid

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Autoxidation is important phenomenon in the resin acid field. Styrene (III and VIII) and homostyrene (VII) compounds were autoxidized to the corresponding benzonilidene derivatives (IV and IX), which are expected to have interesting reactivity.

In the course of the conversion of *l*-abietic acid (I) to the diterpene alkaloids,[3] the styrene compound (III) was synthesized first from II. The compound (III) was so sensitive to autoxidation in air at room temperature and was converted gradually to a new compound. By gas chromatographic analysis, it was shown that (III) was converted to the new product in 82% yield after 1 week and in almost 100% yield after 5 weeks. This phenomenon was repressed when the air was replaced by nitrogen gas. The oily product was purified by column chromatography to obtain (IV) as crystalline product, mp 148—150.5°.

Analysis of its mass spectrum shows that two protons of the starting compound (III) were replaced by one oxygen atom, suggesting the occurence of autoxidation at a methylene group to give a carbonyl group. The carbonyl group must be ascribed to a dienone type by comparison of its infrared (IR) absorption at 1665 cm^{-1} with that of benzilic carbonyl group (mean value, 1690 cm^{-1}).

Nuclear magnetic resonance (NMR) absorptions due to benzene protons are divided into two parts, 2.4—2.8 τ (C_{11}-, C_{12}-, and C_{13}-H) and 1.8—2.1 τ (C_{14}-H). In general, the analogous compound having a C_7-carbonyl group shows a signal due to C_{14}-H which is shifted to a lower field by paramagnetic anisotropy or electrical effect of the carbonyl group.

The structure (IV)[4] has been further confirmed by chemical evidence. i) The compound (IV) was hydrogenolysed (10% Pd-C, EtOH) to give the deoxo ester (V), which was identical with the hydrogenation product of the starting styrene compound (III). Thus, the skeleton is not altered during autoxidation (III→IV). ii) The deoxo ester (V) was oxidized (CrO_3–AcOH–H_2O) to the 7-oxo compound (IV). The compound (VI) was treated with selenium dioxide to regenerate the starting material (IV). iii) The compound (IV) was also obtained from III by chromic acid oxidation.

Next, this type of autoxidation was also applied to VII and VIII synthesized from *l*-abietic acid (I).[3] The oxidation in air was completed in 40 days. Even during the course of the reaction, no peaks other than those of the starting material (VII or VIII) and the end-product (IX) could be observed by gas–liquid chromatography (GLC). Also the IR spect-

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[1] Part XXIV: A. Tahara and T. Ohsawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 483 (1973). All melting points were measured on Kofler block and were not corrected. NMR spectra were usually measured at 60 MHz in $CDCl_3$ *vs.* Me_4Si as internal standard. Gas–liquid chromatography was carried out under the condition: 1.5% OV-17 on Shimalite-W, 80—100 mesh, 4 mm × 2 m.

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[3] A. Tahara, K. Hirao, and Y. Hamazaki, *Tetrahedron*, **21**, 2133 (1965); *idem*, *Chem. Ind.*, **1965**, 850; *idem*, *Chem. Pharm. Bull.* (Tokyo), **15**, 1785 (1967); A. Tahara and K. Hirao, *Tetrahedron Letters*, **1966**, 1453; *idem*, *Chem. Pharm. Bull.* (Tokyo), **15**, **1934** (**1967**).

[4] The name "benzonilidene" should be suitable for this phenyl–vinyl ketone system following the common usage of "acetonilidene" for methyl–vinyl ketone system.

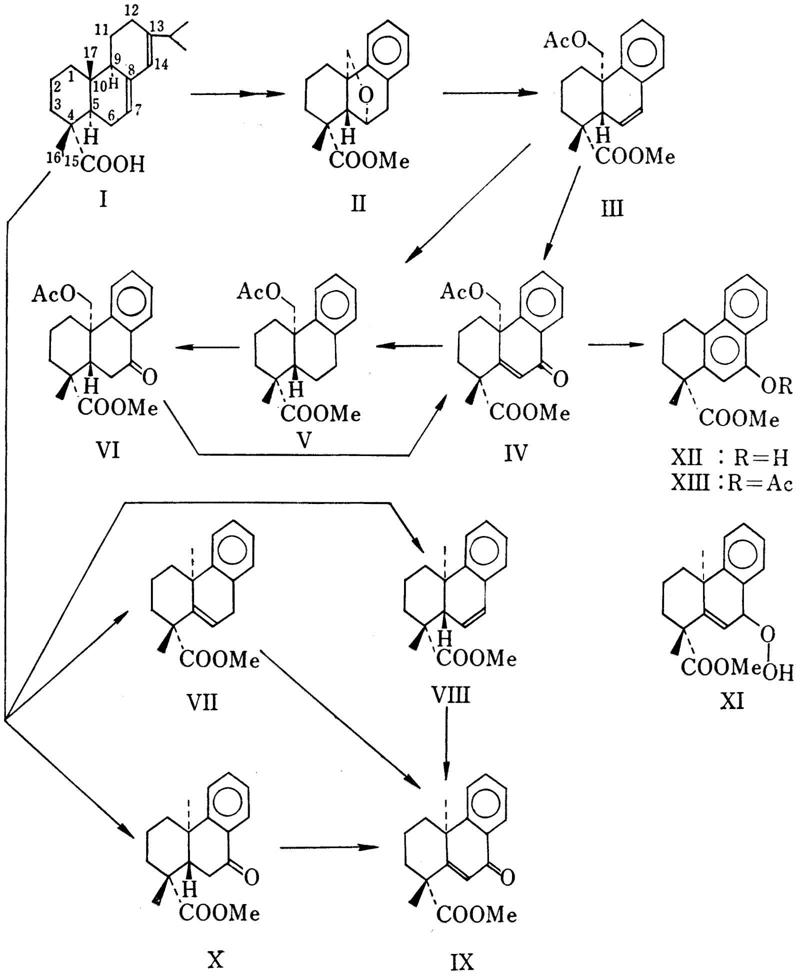

Chart 1

rum of the reaction mixture in the earlier stage did not show any maximum absorption which could be ascribed to an intermediate, such as hydroperoxide (XI). The pure benzonilidene derivative (IX), mp 144—146°, (yield: 82% from VIII and 77% from VII) was identified with the authentic sample[5] synthesized *via* the other route.

The benzonilidene (IX) was also directly obtained from X by dehydrogenation with selenium dioxide.

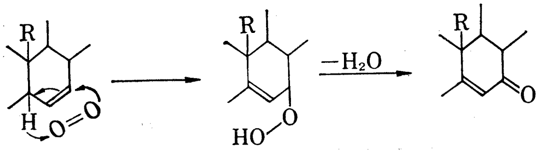

Chart 2

The mechanism of the autoxidation of the stylene type compound (III) and (VIII) can be regarded as one of the "ene" reaction in autoxidation followed by dehydration as shown in Chart 2.[6]

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[5] M. Ohta and L. Ohmori, *Pharm. Bull.* (Tokyo), **5**, 96 (1957). *cf.* E. Wenkert, R. W. T. Carney, and C. Kaneko, *J. Am. Chem. Soc.*, **83**, 4440 (1961).

[6] J. Hamer, "1,4-Cycloaddition Reactions," Academic Press, New York and London, 1967, p. 255.

Generally, hydroperoxide (as in XI) can be isolated as an intermediate and a dehydrating reagent is needed to get carbonyl compound. In the present case, C_7-hydrogen is thought to be easily eliminated due to the activation of adjacent phenyl group.

On the other hand, the homostyrene compound (VII) should be oxidized in the other mechanism. The isomerisation of $\Delta^{5,6}$-bond to $\Delta^{6,7}$-bond did not occur under this condition, so this system should be attacked at C_7-position (benzilic and allylic position) by oxygen as in the case of other C-ring aromatic resin acids, such as dehydroabietic acid.[7]

The benzonilidene system is a kind of a dienone system and so, a dienone-like reaction may be expected to occur in IV and IX. One of the representative feature of dienone is its easy aromatization with rearrangement or elimination of the attached group. The rearrangement of C_{10}-acetoxymethyl or methyl group are prevented, but the elimination of the acetoxy methyl group with concomitant aromatization took place. Treatment of acetoxy benzonilidene compound (IV) under alkaline condition (reflux, KOH–MeOH–H_2O) gave a oily phenolic compound (XII) (its acetate, mp 63—65.5°), which is positive to the ferric chloride color test. Its IR spectrum (CCl_4) showed an absorption band at 3680 (sharp, free OH), 3550 (broad, intermolecular hydrogenbonded OH, dilution method), 1740(free COOMe) and 1720 (broad, hydrogenbonded COOMe, dilution method). The structure is also supported by NMR spectrum: 8.42 τ (3H, s; C_4-Me), 6.37 τ (3H, s; COOMe), 3.44 τ (1H s; C_6-H. High field shift by hydroxyl group at *ortho*-position), 1.75—3.05 τ (complex, aromatic H).

The possible mechanism (The retro-aldol type elimination) of XII from VI shows that the generation of formaldehyde should be observed. In fact, the eliminated formaldehyde can be trapped as dimedone complex. It was also shown that the reaction was completed even at room temperature within five minutes.

The above reaction constitutes a good route for the elimination of the angular methyl group in resin acid.

Further work on the characteristic benzonilidene compounds is in progress.

Experimental

Autoxidation of Methyl 17-Acetoxy-5β,10α-podocarpa-6,8,11,13-tetraen-15-oate (III). Methyl 7-Oxo-17-acetoxy-10α-podocarpa-5,8,11,13-tetraen-15-oate (IV)——i) Ether solution of acetoxy styrene compound (III)[2] (10 mg) was evaporated off and (III) was spread over the bottom of a 20 ml Erlenmeyer flask. The flask was left in air at room temperature under the ordinary room light and the rate of the reaction was measured by the area of III and the product (IV) on gas chromatogram. After 7 days, the area of IV increased to 82% of the total area of peaks; 16 days, 91%; 23 days, 92%; 37 days, 100%. ii) For the isolation, acetoxy stylene compound (III) (1.22 g) left in air at room temperature during one year was submitted to the column chromatography on neutral alumina (140 g). From the eluates (petr. ether: ether= 1: 1—1: 2) pure crystals (253 mg) were obtained as colorless needles, mp 148.5—150.5°. *Anal.* Calcd. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.13; H, 6.42. Mass Spectrum *m/e*: Calcd. for $C_{20}H_{22}O_5$ (M^+), 342.14673. Found: 342.14566. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1745 (COOMe, OAc), 1665 (unsatd. C=O). NMR τ: 8.48 (3H, singlet; C_4-Me), 8.30 (3H, singlet; OAc), 6.40 (3H, singlet; COOMe), 5.94 (2H, singlet; C_{17}-H), 3.40 (1H, singlet; C_6-H), 2.4—2.8 (3H; C_{11}, C_{12}, C_{13}-H), 1.8—2.1 (1H; C_{14}-H). UV λ_{max}^{EtOH} mμ: 252.

Catalytic Reduction of Methyl 17-Acetoxy-5β,10α-podocarpa-6,8,11,13-tetraen-15-oate (III). Methyl 17-Acetoxy-5β,10α-podocarpa-8,11,13-trien-15-oate (V)——Acetoxy styrene compound (III) (79 mg) was shaken with EtOH (12 ml) and 10% Pd-C (400 mg) in hydrogen atmosphere at room temperature during 2 hr. Work-up in the usual way yielded crystals (52 mg), mp 74—84°. t_R min (column temp., 200°) 9.8 (single). Recrystallization from aq. MeOH gave saturated ester (V), mp 81—86°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1745, 1740 (COOMe, OAc). NMR τ: 8.73 (3H, singlet; C_4-Me), 8.14 (3H, singlet; OAc), 6.30 (3H, singlet; COOMe), 5.99 (2H, singlet; C_{17}-H), 2.7—3.2 (4H; C_{11},C_{12}, C_{13}, C_{14}-H), no olefinic proton. Mass spectrum gave very weak parent peak (*m/e*: 330) and the heaviest of the eminent peaks was *m/e*: 270 (M^+-60 (AcOH)).

Catalytic Reduction of Methyl 7-Oxo-17-acetoxy-10α-podocarpa-5,8,11,13-tetraen-15-oate (IV). Methyl 17-Acetoxy-5β,10α-podocarpa-8,11,13-trien-15-oate (V)——Acetoxy benzonilidene (IV) was shaken with EtOH (4 ml) and 10% Pd–C (250 mg) in hydrogen atmosphere at room temperature during 2.5 hr. Work-

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[7] A.E. Drake, U.S. Patent, 2434643 (1948).

up in the usual way yielded crystals (37 mg), mp 65—81°. t_R min (column temp., 220°) 7.55 (single). Recrystallization from MeOH gave saturated diester (V), mp 82—85°. This was identified with methyl 17-acetoxy-5β,10α-podocarpa-8,11,13-trien-15-oate (V), previously obtained, by GLC, IR, NMR, and mass spectrum.

Chromic Acid Oxidation of Methyl 17-Acetoxy-5β,10α-podocarpa-8,11,13-trien-15-oate (V). Methyl 7-Oxo-17-acetoxy-5β,10α-podocarpa-8,11,13-trien-15-oate (VI)——To the AcOH (10 ml) solution of saturated diester (V) (250 mg), 90% AcOH aq. solution (10 ml) of CrO_3 (250 mg) was added dropwise during 25 min with stirring at 70°. Stirring was continued at the same temperature still more 160 min. Work-up in the usual way yielded the resinous substance (177 mg). t_R min (column temp., 220°) 14.45, 6.0 (ratio 3: 1). The mixture (152 mg) was chromatographed over neutral alumina (11 g), and elution with petr. ether–ether (10: 1) gave 7-oxo diester (VI) (40 mg) as the main product. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1745 (COOMe), 1690 (unsatd. C=O). This was used without further purification in the next step.

Selenium Dioxide Dehydrogenation of Methyl 7-Oxo-17-acetoxy-5β,10α-podocarpa-8,11,13-trien-15-oate (VI). Methyl 7-Oxo-17-acetoxy-10α-podocarpa-5,8,11,13-tetraen-15-oate (VI)——Selenium dioxide (80 mg) in water (4 drops) was added to 7-oxo diester (VI) (40 mg) in AcOH (4 ml), and it was refluxed at 135° for 45 min. After the precipitates were filtered, solvent was distilled out *in vacuo*. The residue was dissolved in ether and this solution was washed with NaCl aq., $NaHCO_3$ aq., NaCl aq. and water successively. After dried over Na_2SO_4, evaporation of the solvent yielded colorless crystals (35 mg). t_R min (column temp., 220°) 13.7 (singlet). Recrystallization from MeOH gave acetoxy benzonilidene (VI) as colorless needles, which was identified with the autoxidated product (VI) of (III) by mix. melting point, GLC, IR, and NMR spectrum.

Chromic Acid Oxidation of Methyl 17-Acetoxy-5β,10α-podocarpa-6,8,11,13-tetraen-15-oate (III). Methyl 7-Oxo-17-acetoxy-10α-podocarpa-5,8,11,13-tetraen-15-oate (IV)——Chromium trioxide (95 mg) in AcOH (5 ml) was added to acetoxy stylene compound (III) (62 mg) in 90% AcOH aq. (5 ml), and the mixture was heated at 97° for 50 min. After CrO_3 was decomposed with MeOH, the reaction mixture was left overnight at room temperature. Work-up in the usual manner yielded crystals (44 mg). t_R min (column temp., 230°) 6.2 (single). Recrystallization from MeOH gave acetoxy benzonilidene compound (IV) as colorless prisms, mp 148.5—151.5°. This was identified with autoxidated product of III by mix. melting point, GLC and IR spectrum.

Autoxidation of Methyl 5β,10α-Podocarpa-6,8,11,13-tetraen-15-oate (VIII). Methyl 7-Oxo-10α-podocarpa-5,8,11,13-tetraen-15-oate (IX)——Compound (VIII)$^{2)}$ (150 ml) was dissolved in ether and the solvent was evaporated to give a thin film. And it was left at room temperature in air for 40 days. The resulted resinous substance was chromatographed on alumina. Elution with *n*-hexane–ether (30: 1—20: 1) gave crystals (130 mg, 82% yield, GLC: single), which yielded (IX), colorless prisms, mp 145—147°, after twice recrystallization from MeOH. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740 (COOMe), 1665 (conj. C=O), 1605 (C=C). This was identified with an authentic sample$^{4)}$ by mix. melting point, GLC and IR spectrum.

Autoxidation of 10α-Podocarpa-5,8,11,13-tetraen-15-oate (VII). Methyl 7-Oxo-10α-podocarpa-5,8,11,13-tetraen-15-oate (IX)——Methyl homostylene compound (VII)$^{2)}$ (150 mg) was subjected to autoxidation in the same manner as methyl styrene compound (VIII) for 40 days. Purification was done by chromatography on alumina to give IX (122 mg, 77% yield), which yielded colorless prisms, mp 146—147° after twice recrystallization from MeOH. This was identified with an authentic sample$^{4)}$ by mix. melting point, GLC and IR spectrum.

Selenium Dioxide Dehydrogenation of Methyl 7-Oxo-5β,10α-podocarpa-8,11,13-trien-15-oate (X). Methyl 7-Oxo-10α-podocarpa-5,8,11,13-tetraen-15-oate (IX)——Selenium dioxide (1 g) in water (2 ml) was added to A/B *trans*-7-oxo compound (X) (500 mg) in AcOH (30 ml). The mixture was refluxed (bath temp., 133°) for 135 min. After removal of the solvent *in vacuo*, the residue was dissolved in ether followed by filtration and washing with $NaHCO_3$ aq. and water. Work-up in the usual manner yielded colorless crystals. t_R min (column temp., 200°) 10.7 (single). Recrystallization from MeOH gave methyl benzonilidene compound (IX), colorless prisms, mp 144—146°. *Anal.* Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.39; H, 7.07. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740 (COOMe), 1660 (conj. C=O), 1605 (C=C). NMR τ: 8.63 (3H, singlet) and 8.44 (3H, singlet) (C_4- and C_{10}-Me), 6.32 (3H, singlet; COOMe), 3.55 (1H, singlet; C_6-H), 2.4—2.9 (3H; C_{11}-, C_{12}-, C_{13}-H), 1.8—2.1 (1H; C_{14}-H). Mass Spectrum *m/e*: Calcd. for $C_{18}H_{20}O_3$ (M^+), 284.14125. Found, 284.14193.

Alkali Treatment of Methyl 7-Oxo-17-acetoxy-10α-podocarpa-5,8,11,13-tetraen-15-oate (IV). Methyl 7-Hydroxy-17-nor-podocarpa-5(10),6,8,11,13-pentaen-15-oate (XII)——To acetoxy benzonilidene (IV) (130 mg) in MeOH (13 ml), 10% KOH aq. (1.3 ml) was added, and the mixture was refluxed (bath temp., 72°) for 30 min. After removal of the solvent and dilution with water, the usual extraction treatment gave a resinous substance (XII) (103 mg), which is positive (green) to color test of phenolic compound with $FeCl_3$–pyridine–$CHCl_3$ reagent.

Acetate (XIII): Naphthol (XII) (83 mg) was acetylated with acetic anhydride (6 ml)–pyridine (0.6 ml) to give colorless resinous substance (95 mg). t_R min (column temp., 220°) 6.8 (single). Recrystallization from MeOH, *n*-hexane and EtOH aq. successively yielded acetate (XIII), colorless prisms, mp 63—65.5°. *Anal.* Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.85; H, 6.36. UV λ_{max}^{EtOH} mμ (log ε): 231 (5.18), 287 (3.76). IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1780 (aromatic OAc), 1740 (COOMe), 1200 (C–O). NMR τ: 8.45 (3H, singlet; C_4-Me), 7.67 (3H, singlet; OAc), 6.92 (2H, triplet (J=6 Hz); C_1-H), 6.43 (3H, singlet; COOMe), 3.05 (1H, singlet; C_6-H), 2.00—2.85 (4H, multiplet). Mass Spectrum *m/e*: Calcd. for $C_{19}H_{20}O_4$ (M^+), 312.13616. Found: 312.13773.

Trapping of Formaldehyde Generated in the Course of Retro Aldol Elimination Reaction (IV→XII)—— To the compound (IV) (579 mg) in MeOH (50 ml), 10% KOH aq. (5.9 ml) was added and it was refluxed for 15 min. (bath temp., 72°) under N_2 stream. Then generated formaldehyde was steam-distilled into saturated dimedone aq. solution (120 ml). Cooling the mixture yielded crystalline precipitate. After it was filtered, washed with water and dried, needle crystals (57 mg), mp 181—186°, were obtained. Recrystallization from MeOH gave colorless needles, mp 188—189.5° (11.5% yield). Mix. melting point of the above crystals and standard formaldehyde–dimedone complex[8] was not deppressed. On the other hand, the compound (XII) (266 mg) was obtained from the reaction mixture.

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[8] E.C. Horning and M.C. Horning, *J. Org. Chem.*, **11**, 95 (1946).