[Chem. Pharm. Bull. 15(11)1785~1790(1967)]

UDC 547.597.07 : 547.94.07

229. Akira Tahara, Ken-ichi Hirao, and Yasuhiko Hamazaki*1 : Diterpenoids. Ⅷ.*2 Synthesis of Skeleton of Diterpene Alkaloid.*3

(*Rikagagu Kenkyusho, The Institute of Physical and Chemical Research*)

From *l*-abietic acid, a basic skeleton compound (XX) having same absolute configuration and characterized nitrogen bridge of diterpene alkaloid, was accomplished to synthesize.

(Received March 14, 1967)

The study on *Aconitum*, *Garrya* and *Delphinium* alkaloids attacked attention of many chemists for their interesiting toxic character, however, satisfactory solution on their structure had not yet been brought until the physical methods for structural elucidation were widely used in this latter half-century. Now, it is ascertained that the structures of these alkaloids are characterized by a nitrogen bridge in the tricyclic skeleton.

The synthesis of the characterized nitrogen bridge was recently completed by a few groups on the way of their total syntheses[1] of diterpene alkaloids, such as *dl*-atisine (Ⅰ), *dl*-veatchine (Ⅱ) and *dl*-garryine (Ⅲ). While, in the synthesis of the nitrogen bridge using natural product, ApSimon and Edward[2] firstly succeeded to make a compound (Ⅴ) by an application of the photochemical reaction[3] to *d*-podocarpic acid (Ⅳ). Also Ishikawa, *et al.*[4] recently accomplished to synthesize a nitrogen bridge compound (Ⅶ) from sciadin (Ⅵ), diterpene component of Kōya-maki (*Sciadopitys verticillata Sieb. et Zucc.*), whose structure had uncommon oxydated 12-methyl group. In the both cases, the compounds having antipodal skeleton of natural diterpene alkaloid were introduced.

During a recent few years, synthetic utilization of resin acids has been developed in our laboratory. Among the resin acids, *l*-abietic acid (Ⅷ) is most available from Japanese pine trees and also it not only has a secure structure including absolute configuration, but is accomplished its total synthesis. Thus, it is an interesting problem that *l*-abietic acid (Ⅷ) is chosen as expedient starting material and a synthesis of the nitrogen bridge was attempted.

In order to perform a chemical conversion of *l*-abietic acid (Ⅷ) to the basic skeleton (same absolute structure) (XX) of diterpene alkaloid, the following two synthetic points should be subjugated : 1) *Trans* A/B-ring fusion (11α-H, 12β-Me) and axial 1-methyl group (eq. 1-COOH) of *l*-abietic acid should be converted to an antipodal *trans* fusion (11β-H,

---

*1 Yamato-machi, Kita-adachi-gun, Saitama-ken (田原 昭, 平尾健一, 浜崎泰彦).

*2 Previous communication : Chem. Ind., **1965**, 850; Part Ⅶ : This Bulletin, **12**, 1458 (1964). This work was presented at the Local Meeting of the Pharmaceutical Society of Japan, Tokyo, July 24, 1965 and also at 9th Symposium of Natural Organic Compounds, Osaka, October 14, 1965. cf. Symposium Abstract (in Japanese), p. 120~126.

*3 All m.p.s (except mixed m.p.) were measured on the Koflar block and were uncorrected. Gas-liquid chromatograms were measured under guidance of Dr. N. Ikekawa, this Institute, whom authors thank for his advice (abbreviation GCmin. is used as retention time of the glc.).

1) *a*) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, Y. Hayase : J. Am. Chem. Soc., **85**, 2342 (1963); W. Nagata, M. Narisada, T. Wakabayashi, T. Sugasawa : *Ibid.*, **86**, 929 (1964). *b*) S. Masamune : *Ibid.*, **86**, 288, 289, 290, 291 (1964). *c*) Z. Valenta, K. Wiesner, C.M. Wong : Tetrahedron Letters, **1964**, 2437; R.W. Guthrie, A. Philipp, Z. Valenta, K. Weisner : *Ibid.*, **1965**, 2945; R.W. Guthrie, W.A. Henry, H. Immer, C.M. Wong, Z. Valenta, K. Wiesner : Coll. Czech., **31**, 602 (1966); R.W. Guthrie, Z. Valenta, K. Wiesner : Tetrahedron Letters, **1966**, 4645. cf. I. Iwai, A. Ogiso, B. Shimizu: Chem. Ind., **1962**, 1288; I. Iwai, A. Ogiso : *Ibid.*, **1963**, 1084.

2) J.W. ApSimon, O.E. Edward : Proc. Chem. Soc., **1961**, 461; Canad. J. Chem., **40**, 896 (1962). cf. W.L. Meyer, A.S. Levinson : Proc. Chem. Soc., **1963**, 15; J. Org. Chem., **28**, 2859 (1963).

3) D.H.R. Barton, L.R. Morgan, Jr. : J. Chem. Soc., **1962**, 622.

4) C. Kaneko, T. Tsuchiya, M. Ishikawa : This Bullentin, **11**, 1346 (1963).

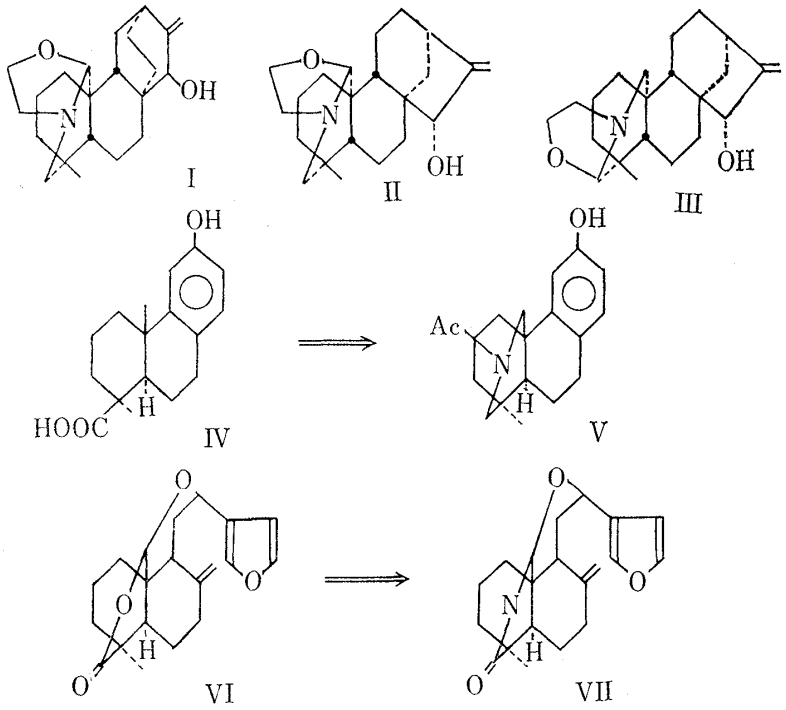

Fig. 1.

12α-Me) and equatorial 1-methyl group (ax. 1-COOH) as shown in the absolute structure of diterpene alkaloid. 2) Subsequently, the chemically inert 12-methyl group observed widely in resin acids as abietic acid (Ⅷ), should be changed to a more active substituent. In order to have satisfactory compound to the above mentioned condition, abietic acid (Ⅷ) was previovsly converted to 10α,17-epoxy compound (X),[5] which have same absolute structure of diterpene alkaloid skeleton and also oxidated 12-methyl group.

Thereupon, in this report, a synthesis of a compound (XX) having the nitrogen bridge from the 10α,17-epoxy compound (X) will be described. Chromium trioxide oxidation (95~100°, 2 hr.) of the potential intermediate (X)[5] prepared from abietic acid (Ⅷ) through the acetate (Ⅸ), gave only monoketone (Ⅺ), m.p. 202~203°, whereas under more drastic condition with chromium trioxide (reflux, 4 hr.), ketolactone (Ⅻ), m.p. 194~195°,*4 was afforded. For reductive cleavage of δ-lactone bridge in (Ⅻ), (Ⅻ) was catalytically reduced in acetic acid (H_2SO_4) with 10% palladium-charcoal at room temperature to give acidic compound (XIII), m.p. 172~173°(12.4%) and neutral part, which was chromatographed to separate acetoxy-lactone (XIV), m.p. 184~186°(44.0%) and the corresponding hydroxy-lactone (XV). m.p. 162~163°*4(26.0%). Acetylation of the hydroxy-lactone (XV) is correlated to the acetoxy-lactone (XIV). In order to increase the yield of the aimed acid (XIII), keto-lactone (Ⅻ) was more drastically reduced in acetic acid (H_2SO_4) at 35~40° with 30% palladium-charcoal to obtain (XIII) in satisfactory yield (84%) in company with small amount of mixed neutral product. When the solvent was changed to ethyl acetate, the reduction product was only the hydroxy-lactone (XV) in 83% yield.

Alkaline hydrolysis of diacid half ester (XIII) readily afforded diacid (XVI), m.p. 202~204°. Since the diacid (XVI) have two carboxylic acid groups situated closely in 1,3-diaxial stereorelation, a formation of an acid anhydride bridge from (XVI) was performed without difficulty by reflux in acetic anhydride.

5) A. Tahara, K. Hirao: This Bulletin, **12**, 984 (1964); A. Tahara, K. Hirao, Y. Hamazaki: Tetrahedron **21**, 2133 (1965).

*4 M.p. and b.p. reported in the previous communication was revised as follows: (Ⅻ), m.p. 192~193° to 194~195°; (XV), m.p. 159~161° to 162~163° and (XX) b.p. 130~135° (bath temp.)/1 mm. to m.p. 120~122°.

The anhydride (XVII), m.p. 202~204° or diacid (XVI) was converted to imide, m.p. 205~207°, by melting with urea in oil bath (bath temp. 170~180°). Infrared spectrum (KBr) of the anhydride (XVII); 1785, 1755 cm^{-1} and the imide (XVIII); 1715, 1695 cm^{-1}, clearly shows an existence of six-membered anhydride and imide bridge between C_1 and C_{12} respectively.

After the usual reduction of imide (XVIII) with $LiAlH_4$, the resulted secondary amine (XIX), without purifiation, was acetylated to give an oil, which was purified by chromatography and by distillation, b.p. 130~135°(bath temp.)/1 mm. The obtained crystals (XX), m.p. 120~122°,*4 have optical active, $[\alpha]_D^{23.0} = -127.3$ (EtOH, c=0.33) and its infrared spectrum (CCl_4); 1645 cm^{-1}, shows N-acetyl group. The purity was examined by gas-liquid chromatography.

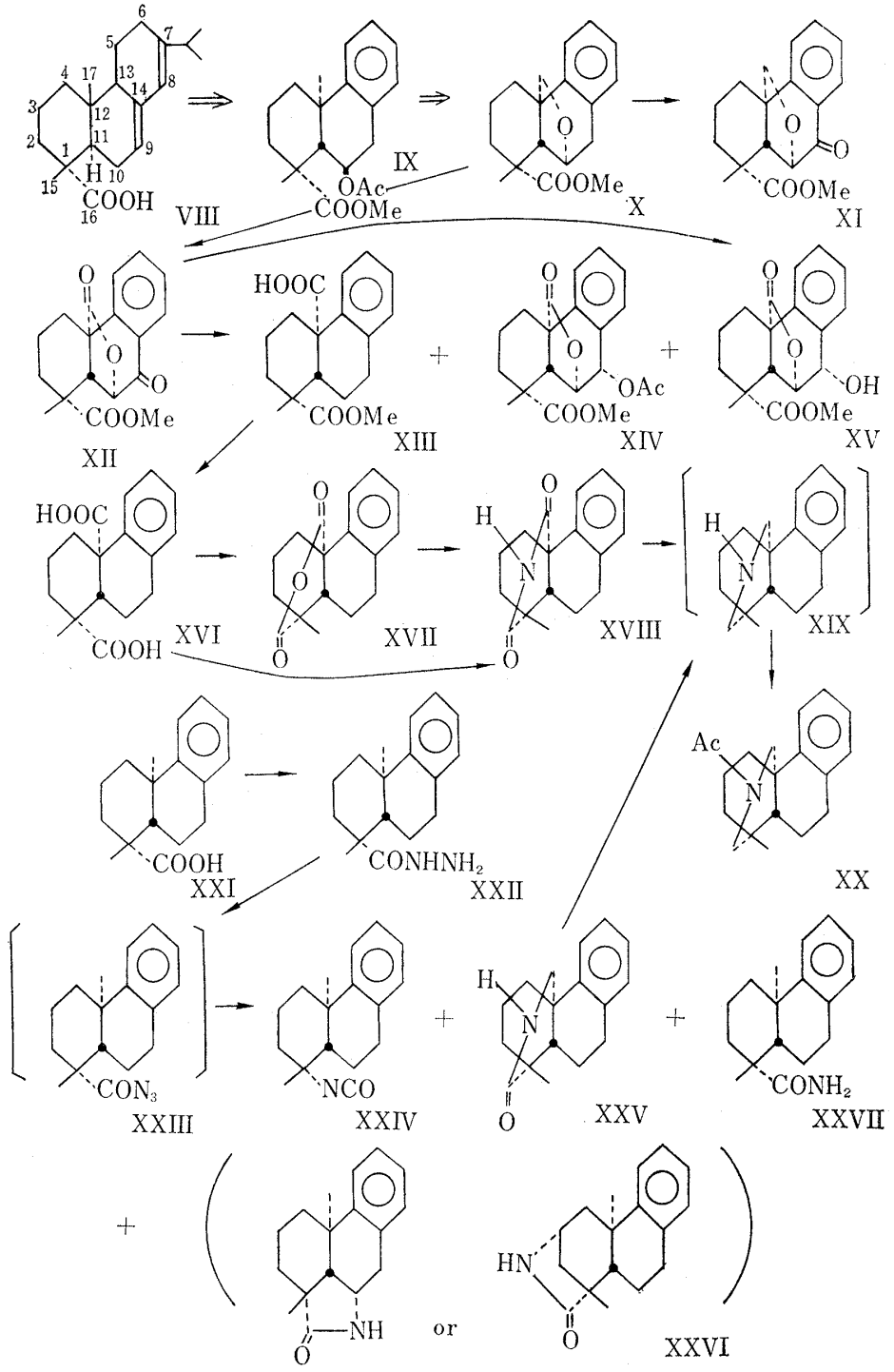

Fig. 2.

The structure of the amino acetate (XX) having atisine-like nitrogen bridge, can be considered to be indubitable by the above synthetic route. However, an additional evidence will be adduced by an application of the known photochemical reaction.[2,3] Since deoxy *enantio*-podocarpic acid (XXI) prepared from abietic acid (Ⅷ), have an antipodal structure of *d*-podocarpic acid, the ApSimon and Edward's photochemical method can be similarly used.

Accordingly, the acid (XXI) was converted to azide (XXⅢ) *via* hydrazide (XXⅡ), m.p. 179~180°, by usual method. A hexane solution of the azide (XXⅢ) was illuminated by ultraviolet lamp (30 W low pressure Hg-lamp) under nitrogen atmosphere. As the reaction time went on, a distinguished infrared absorption of the reaction solution at 2150 cm^{-1} due to azide group was gradually decreased, while an absorption at 2250 cm^{-1} corresponding to isocyanate was newly appeared. Illuminating for 32 hr., the resulted reaction product was chromatographed to separate isocyanat (XXIV),*5 m.p. 93.5~94.5°, aimed δ-lactam (XXV), m.p. 226~228.5° and unsettled crystals, $C_{17}H_{21}ON$, m.p. 208~209,*6 whose infrared absorption (KBr) shows at 3230, 1710 and 1650 cm^{-1}. The photochemical result is very analogous to the observation by Canadian chemists.[2]

Reduction of the δ-lactam (XXV) with $LiAlH_4$ afforded a basic oil (XIX), whose infrared absorption due to δ-lactam was disappeared. Subsequently, the obtained oily amine (XIX), without purification, was acetylated to give amino acetate (XX). Infrared spectrum and retention time of gas-liquid chromatography of the amino acetate (XX) were observed to be completely superimposable with the amino acetate (XX) synthesized otherwise *via* (X).

In conclusion, a total synthesis of the basic skeleton (XX) having same absolute configuration of diterpene alkaloid, was accomplished by use of *l*-abietic acid (Ⅷ) as starting material.

Experimental

Chromium Trioxide Oxidation of 10α,17-Epoxy Ester (X) i) 9-Oxo-10α,17-Epoxy Ester (XI)——A reaction mixture of epoxy ester (X)[5] (50 mg.), m.p. 128~129°, and CrO_3 (75 mg.) in AcOH (11 ml.) containing small amount of H_2O, was warmed at 95~100° (bath temp.) for 2 hr. After MeOH was added to decompose excess CrO_3, the solvent was evaporated in reduced pressure (below 35°) and then H_2O was added. Appeared white solid (37 mg.) was collected by filtration and was recrystallized from MeOH-H_2O to m.p. 159~168° (gas-liquid chromatogram shows the solid contains (XI) and keto lactone (XⅡ) in ratio of 1:1), which was chromatographed on alumina (8 g.) to separate fine needles in petr. ether-ether (10:1) elution. The crystals were recrystallized from MeOH-H_2O to fine needles (XI), m.p. 202~203°. *Anal.* Calcd. for $C_{18}H_{20}O_4$: C, 71.79; H, 6.70. Found: C, 71.98; H, 6.71. IRν_{max}^{KBr} cm^{-1}: 1720 (COOMe), 1690 (Ph-CO). GC min.: 5.7 (2.0% XE-60 on Anakrom (80~100 mesh), 1.5 m.×4 mm. 225°).

ii) 9-Oxo Lactone (XII)——A solution of epoxy ester (X)[5] (500 mg.) and CrO_3 (2.0 g.) in AcOH (17 ml.) containing small amount of H_2O, was refluxed for 2 hr. Again an AcOH (5 ml. and small amount of H_2O) solution of CrO_3 (1.2 g.) was added to the reaction mixture, which was continued to reflux for 2 more hr. Same procedure was treated as in the case of i). Appeared white solid was collected by filtration and was recrystallized from MeOH-H_2O to colorless fine plates (234 mg.) (XⅡ), m.p. 194~195°.*4 *Anal.* Calcd. for $C_{18}H_{18}O_5$: C, 68.77; H, 5.77. Found: C, 69.05; H, 5.88. IRν_{max}^{KBr} cm^{-1}: 1785 (γ-lactone), 1730 (COOMe), 1700 (Ph-CO).

Catalytic Hydrogenation of 9-Oxo Lactone (XII). Diacid Half Ester (XIII), 9-Acetoxy Lactone (XIV) and 9-Hydroxy Lactone (XV). i)——A solution of keto lactone (XⅡ) (250 mg.) in AcOH (200 ml.) containing conc. H_2SO_4 (0.5 ml.) was shaken under H_2 atmosphere in presence of 10% Pd-C (300 mg.) at room temperature. After H_2-absorption had almost ceased, the catalyst was filtrated off and, then H_2O (50 ml.) and K_2CO_3 powder (4.5 g.) was added. The solvent was removed in reduced pressure (below 30°), then H_2O was added and the resulted solution was extracted with ether.

*5 Under illumination by 100W high pressure Hg-lamp, amide (XXⅦ)[6] was yielded, instead of the isocyanate (XXⅣ), with the same products (XXV) and (XXⅥ).

*6 The structure is considered to be likely γ-lactam (XXⅥ).

6) A. Tahara, K. Hirao: This Bulletin, **12**, 1121 (1964).

The ether extract was separated to an acidic and a neutral part by usual method.

a) Acidic part : The obtained crystals (31 mg., 12.4% yield) were recrystallized twice from MeOH-H_2O to colorless fine plates (XIII), m.p. 172~173° (crystalline form was changed at about 80°). *Anal.* Calcd. for $C_{18}H_{22}O_4 \cdot {}^1/_2H_2O$: C, 69.42; H, 7.45. Found : C, 69.61; H, 7.47. Calcd. for $C_{18}H_{22}O_4$ (crystals were dried in vacuum) : C, 71.50; H, 7.33. Found : C, 71.23; H, 7.22. IRν_{max}^{KBr} cm^{-1} : 1725 (COOMe), 1700 (COOH).

b) Neutral part : The resulted oily crystals (206 mg.) (gas-liquid chromatogram shows two peaks) were chromatographed on Al_2O_3 (10 g.) to give colorless needles (XIV) (130 mg., 44.0% yield) in petr. ether-ether (10:1) elution and colorless prisms (XV) (65 mg., 26.0% yield) in petr. ether-ether (1:1) elution successively. The former crystals were recrystallized from ether to needles (XIV), m.p. 184~186°. *Anal.* Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found : C, 67.09; H, 6.32. IRν_{max}^{KBr} cm^{-1} : 1775 (γ-lactone), 1735 (OAc), 1720 (COOMe), 1240 (OAc). GC min.: 12.0 (1.5% SE-30 on Chromosorb G (80~100 mesh), 1.5 m.×4 mm. 207°). On the other hand, the latter fraction was recrystallized from ether to prisms (XV), m.p. 162~163°.[*4] *Anal.* Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found : C, 68.35; H, 6.27. IRν_{max}^{KBr} cm^{-1} : 3460 (OH), 1775 (γ-lactone), 1715 (COOMe). GCmin.: 6.1 (1.5% SE-30 on Chromosorb G (60~80 mesh), 1.5 m.×4 mm., 211°).

ii)——A solution of keto lactone (XII) (150 mg.) in AcOH (60 ml.) containing conc. H_2SO_4 (6 drops) was shaken under H_2 atmosphere in presence of 30% Pd-C (200 mg.) at 35~40° for 1.5 days. The reaction mixture was treated as in the case of i).

a) Acidic part : The resulted crystals (XIII) (125 mg., 84% yield) were recrystallized from MeOH-H_2O to colorless fine plates (XIII), m.p. 170~173°.

b) Neutral part : The gas-liquid chromatogram of the obtained oily solid (27 mg.) shows two peaks due to (XIV) and (XV).

iii)——A solution of keto lactone (XII) (60 mg,) in AcOEt (35 ml.) containing conc. H_2SO_4 (3 drops) was shaken under H_2 atmosphere in presence of 10% Pd-C (60 mg.) at room temperature. After H_2-absorption had ceased, the reaction mixture was treated as in the case of i).

a) Acidic part : Nothing.

b) Neutral part : The obtained crystals (XV) (50 mg., 83.3%) were recrystallized from MeOH-H_2O to colorless prisms (XV), m.p. 159~160°.

Acetylation of 9-Hydroxy Lactone (XV)——The reaction mixture of hydroxy ester (XV) (32 mg.) in acetyl chloride (0.7 ml.) and pyridine (0.4 ml.) was left standing for 6 hr. at room temperature. It was diluted with H_2O and then was extracted with ether. The ether extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The resulted crystals (XIV) (29 mg.) were recrystallized from ether to colorless needles (XIV), m.p. 183~187°, whose m.p. (m.m.p.) and infrared spectrum ($CHCl_3$) was identical with acetoxy lactone (XIV) obtained otherwise by hydrogenolysis of keto lactone (XII).

Diacid (XVI)——A solution of diacid half ester (XIII) (233 mg.) and KOH (1.0 g.) in diethylene glycol (10 ml.) and H_2O (1 ml.) was refluxed in oil bath (bath temp., 195~210°) for 1 hr. The reaction mixture was diluted with H_2O, acidified and was extracted with ether. An acidic fraction was separated from the ether extract by usual method. The resulted gummy acidic residue (207 mg.) was recrystallized from MeOH-H_2O to colorless prisms (XVI), m.p. 202~204° (Crystalline form was changed to needles from prisms at 170~180°. Diacid (XVI) presumably formed anhydride (XVII) at this temperature). *Anal.* Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found : C, 71.18; H, 6.98. IRν_{max}^{KBr} cm^{-1} : 3600~3300 (broad, OH), 1703 (CO).

Anhydride (XVII)——A solution of diacid (XVI) (45 mg.) in acetic acid anhydride (3 ml.) was refluxed for 3 hr. After solvent was evaporated and H_2O was added, it was extracted with 10% KOH aq., with H_2O successively, dried over Na_2SO_4 and evaporated. The obtained needles (XVII) (43 mg.) were sublimated at 150~170°/2 mm.Hg and then were recrystallized from ether to colorless fine needles (XVII), m.p. 202~204°. *Anal.* Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found : C, 75.56; H, 6.66. IRν_{max}^{KBr} cm^{-1} : 1785, 1755, 1025 (six-membered anhydride ring). GCmin.: 6.1 (1.5% SE-30 on Chromosorb G (80~100 mesh), 1.5 m.×4 mm., 207°).

Imide(XVIII)——i) From anhydride (XVII). A pulverized mixture of anhydride (XVII) (31 mg.) and urea (80 mg.) was melted at 170~185° (bath temp.) for 20 min. After H_2O (10 ml.) was added to the reaction mixture, it was extracted with $CHCl_3$. The extract was washed with H_2O, dried over calcium chloride and evaporated. The resulted prisms (24 mg.) were recrystallized from MeOH-H_2O to colorless prisms (XVIII), m.p. 205~207°. *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11; N, 5.20. Found : C, 75.91; H, 6.79; N, 5.29. IRν_{max}^{KBr} cm^{-1} : 3260 (NH), 1715, 1695 (six-membered imide ring).

ii) From diacid (XVI). A pulverized mixture of diacid (XVI) (145 mg.) and urea (300 mg.) was melted at 180~200° (bath temp.). The reaction mixture was treated as in the case of i). The obtained prisms (XVIII) (138 mg.) were recrystallized from MeOH to colorless prisms (XVIII), m.p. 203~207°.

Amino Acetate (XX)——A solution of imide (XVIII) (77 mg.) in dioxane (20 ml.) was added to $LiAlH_4$ reagent (350 mg.) in absolute ether (5 ml.). The reaction mixture was refluxed for 6 hr. After only ether was evaporated and $LiAlH_4$ (150 mg.) was added again, the mixture was refluxed for 5 more hr. H_2O (5 ml.) was added to the reaction mixture, then the solvent was evaporated, again H_2O (30 ml.) was added and it was extracted with ether. Neutral and basic part was isolated from the ether extract by usual method.

a) Neutral part : The ether layer was washed with H_2O, dried over Na_2SO_4 and evaporated. Infrared spectrum of the resulted needles (12 mg.) showed it was impure imide (XVIII).

b) Basic part : The HCl aq. extract was neutralized with 20% KOH aq. under cooling. Its ether extract was washed with H_2O and dried over Na_2SO_4. Removal of solvent gave colorless fine needles (XIX) (40 mg.), which were used without purification as follows.

A solution of the secondary amine (XIX) (40 mg.) in acetic acid anhydride (3 ml.) and pyridine (2ml.) was refluxed for 1 hr. The reaction mixture was diluted with H_2O and was extracted with ether. The ether extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The obtained oil (38 mg.) was chromatographed on Al_2O_3 (3 g.) to give colorless oil (XX) (31 mg.) in petr. ether–ether (15 : 1) elution. The oil was crystallized as colorless needles (XX), m.p. 120~122°.*4 *Anal.* Calcd. for $C_{19}H_{25}ON$: C, 80.52; H, 8.89; N, 4.94. Found : C, 79.95; H, 8.61; N, 4.75. IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1645 (N-Ac). GC min. : 5.2 (1.5% SE-30 on Anakrom (80~100 mesh), 1.75 m. × 4 mm., 200°). $[\alpha]_D^{23.0} = -127.3$ (EtOH, c=0.33).

Acid Hydrazide (XXII)——To a solution of deoxy-*enantio*-podocarpic acid (XXI) (1 g.) in absolute benzene (45 ml.) and pyridine (5 drops), thionyl chloride (3 ml.) was added. After the solution was refluxed for 2 hr., the solvent was completely evaporated. The obtained oily acid chloride (900 mg.) in absolute ether (80 ml.) was usually treated with hydrazine hydrate (5 ml.) in EtOH (12 ml.) at 0° for 3 min. The reaction mixture was diluted with H_2O and then extracted with ether. The extract was dried over Na_2SO_4 and evaporated to give needles, m.p. 155~167° (950 mg.), which were recrystallized from ether–petr. ether to colorless needles (XXII), m.p. 179~180° (decomp.). *Anal.* Calcd. for $C_{17}H_{24}ON_2$: C, 74.96; H, 8.88; N, 10.39. Found: C, 74.41; H, 8.69; N, 10.29. IR ν_{max}^{KBr} cm^{-1} : 3305 (NH), 1635 (CO).

Photochemical Reaction of Azide (XXIII). Isocyanate (XXIV), δ-lactam (XXV), γ-lactam (XXVI) and Acid Amide (XXVII)——To a solution of hydrazide (XXII) (900 mg.) in AcOH (36 ml.), saturated aqueous solution of $NaNO_2$ (500 mg.) was slowly added under violently shaking below 15°. After the reaction mixture was continued to shake for 3 min., it was diluted with H_2O and extracted with *n*-hexane. The hexane extract was washed with sat. $NaHCO_3$ aq., then sat. NaCl aq. and was dried over Na_2SO_4 (IR of the *n*-hexane solution shows an absorption at 2150 cm^{-1} due to CON_3). Under N_2 gas stream and ice cooling, the dried *n*-hexane solution (about 200 ml.) was illuminated for 32 hr. by mercury-lamp (30 W low pressure). Reaction time was determined by disappearance of infrared absorption corresponding to azide. The solvent was evaporated in vacuum and the resulted oil (700 mg.) was chromatographed on neut. alumina (20 g.) to give the following fractions : a) Crystallized isocyanate (XXIV) (150 mg.) in hexane, hexane–benzene (20:1) and hexane–benzene (10:1) elution. b) γ-Lactam (XXVI) in benzene and the first part of benzene–chloroform (20:1) elution. c) Impure δ-lactam (XXV) (300 mg.) in the last part of benzene–chloroform (20:1) and chloroform elution.

The first fraction (a) was recrystallized from MeOH to isocyanate (XXIV), colorless prisms, m.p. 93.5~94.5°. *Anal.* Calcd. for $C_{17}H_{21}ON$: C, 79.96; H, 8.29; N, 5.49. Found : C, 79.97; H, 8.02; N, 5.49. IR ν_{max}^{KBr} cm^{-1} : 2290 (NCO). The second fraction (b) was recrystallized from acetone to colorless needles, m.p. 208~209°. *Anal.* Calcd. for $C_{17}H_{21}ON$: C, 79.96; H, 8.29; N, 5.49. Found : C, 79.65; H, 8.05; N, 5.52. IR ν_{max}^{KBr} cm^{-1} : 3230 (NH), 1710 (CO), whose structure is within the bound of possibility of (XXVI). The last fraction (c) was rechromatographed on neut. Al_2O_3 (12 g.) to give δ-lactam (XXV) (120 mg.) in benzene–ether (10:1) elution. δ-Lactam was recrystallized from acetone–petr. ether to colorless needles, m.p. 226~228.5°. *Anal.* Calcd. for $C_{17}H_{21}ON$: C, 79.96; H, 8.29; N, 5.49. Found : C, 79.96; H, 8.29; N, 5.49. IR ν_{max}^{KBr} cm^{-1} : 3450, 3170 (NH), 1650 (CO).

When the photochemical reaction was performed for 8 hr. under illumination by 100 W high pressure mercury-lamp, amide (XXVII)[6] was produced in 10~30% yield, instead of the isocyanate (XXIV), in company with the same other product (XXV) and (XXVI).

Amino Acetate (XX) from δ-Lactam (XXV)——A solution of δ-lactam (XXV) (113 mg.) in dioxane (50 ml.) was added to $LiAlH_4$ reagent (300 mg.) in absolute ether (8 ml.). After the reaction mixture was refluxed for 7 hr., H_2O was added to decompose the reagent and the solvent was evaporated. The resulted residue was extracted with ether. The ether layer was extracted again with dil. HCl aq. The acid extract was alkalized with K_2CO_3 aq. and then was extracted with ether. The ether extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The resulted oil (XIX) (77 mg.) was dissolved in acetic anhydride (5 ml.) and pyridine (5 ml.). The solution was refluxed for 40 min. and then the solvent was evaporated in vacuum. Successively, 10% HCl aq. was added and it was extracted with ether. The ether extract was washed with 10% Na_2CO_3 aq., then with H_2O, dried over Na_2SO_4 and was evaporated.

The resulted oil (74 mg.) was chromatographed on neut. Al_2O_3 (5 g.) to give crystals (XX), m.p. 103.5~113.5°, in petr. ether–ether (20:1 and 10:1) fraction. The crystals were recrystallized from ether to colorless needles, m.p. 120~122°, which were completely superimposable (m.m.p., IR and GC min.) with sample synthesized by another route *via* (X).

The authors thank Professor Emeritus E. Ochiai, University of Tokyo, for his valuable advice and encouragement. Financial support from the Ministry of Education (Grant-in-Aid for Scientific Research, No. 750294) and from Hōan-sha, are gratefully acknowledged.