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New Inter-relationship of Abietic Acid and Agathic Acid*1,*2

A new inter-relationship of abietic acid (I) and agathic acid (IV) by the direct comparisons of monoenones (II), (III) with the corresponding antipodes (VI), (VII) obtained from the respective acids (I) and (IV), is now completed. On the same subject Ruzicka's school had also investigated for the determination of the configuration at C_1, C_{11}, and C_{12} of agathic acid by the indirect methods.[1]

Furthermore, the syntheses of the compounds such as VII,[2] VIII,[3] and IX[4] (*d* or *dl*) attracted attentions of many chemists as the potential intermediates for the syntheses and the structural determinations of some diterpenoids. For the same reason the newly synthesized compounds (II) and (III) are also considered to be important starting materials for the syntheses of the compounds, which are recently found to have an antipodal *trans* A/B ring (C_{12}-Me : α) skeleton, like as (iso)-steviol,[5] daniellic acid,[6] polyalthic acid,[7] oliveric acid,[8] (—) kaurene,[5,9] copalic acid,[10] eperuie acid,[11] some *aconitum* and *garrya* alkaloids,[5,12] and other diterpenoids.[13]

Catalytic hydrogenation[14] (Pd-C, H_2SO_4, AcOH) of 7-nitro α,β-keto-enol ester (XII)*3 and its acetate (XIII),[15] which were obtained from abietic acid (I) *via* 7-nitro diketo ester (XI),[15] directly afforded 7-amino ester (XVII) (A/B ring : *trans*, C_{12}-Me : α), colorless plates, m.p. 146~150° (from MeOH-H_2O); IR ν_{max}^{KBr} cm^{-1} : 3550, 3440, 1720, 1624 (*Anal.* Calcd. for $C_{18}H_{25}O_2N$: C, 75.22; H, 8.77; N, 4.87. Found : C, 75.40; H, 8.90; N, 4.89).

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*1 The communication will be published in detail as Diterpenoids (IV). Part III : Sci. Papers Inst. Phys. Chem. Res., **57**, 19 (1963).

*2 This work was presented at the 16th Annual Meeting of the Pharmaceutical Society of Japan held at Shizuoka on Nov. 3, 1962.

*3 It was reported as a minor product in the nitration of X in our preceding papers.[15] However it was yielded quantitatively by conc. sulfuric acid treatment of XI.

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In the hydrogenation of XII a compound, $C_{18}H_{23}O_3N$, yellow prisms, m.p. 158~161° (from MeOH); IR ν_{max}^{KBr} cm^{-1} : 3480, 3420, 1727, 1700, 1629 (*Anal.* Calcd : C, 71.73; H, 7.69; N, 4.65. Found : C, 71.66; H, 7.36; N, 4.57) was isolated in company with XVII.

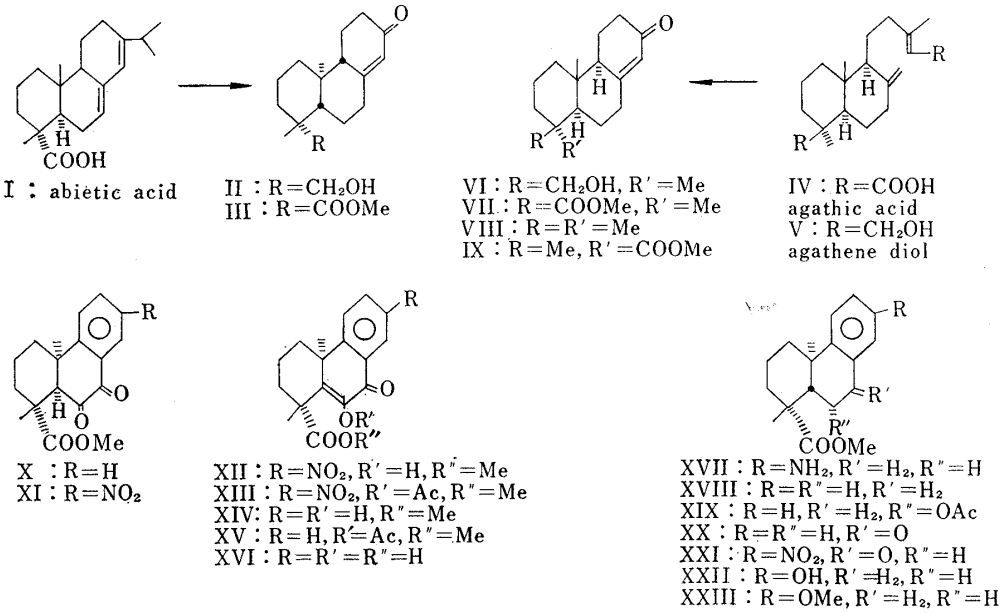

Chart 1.

In an attempt to obtain the rigid evidences for the absolute configuration of the amine shown as XVII and the further supply of XVII by the more available method, it could be prepared through the following steps. α,β keto-enol ester (XIV), colorless prisms, m.p. 97.5~98.5° (from MeOH-H_2O); IR ν_{max}^{KBr} cm^{-1} : 3400, 1726, 1624, 1601 (*Anal.* Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found : C, 71.73; H, 6.70), yielded by the treatment of diketo ester (X)[15] with conc. sulfuric acid and also of α,β keto-enol acid (XVI)[15] with diazomethane, was catalytically hydrogenated (Pd-C, H_2SO_4, AcOH) to methyl deoxypodocarpate enantiomer (XVIII) (A/B ring : *trans*, C_{12}-Me : α) as a sole product, colorless prisms, m.p. 140~141° (from MeOH-H_2O); IR : ν_{max}^{KBr} 1727 cm^{-1} (*Anal.* Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found : C, 79.19; H, 8.67), whose physical constants were identical with those of the authentic one.[16] However the same treatment (Pd-C, H_2SO_4, EtOAc) of the corresponding acetate (XV),[14] colorless prisms, m.p. 115~117° (from MeOH-H_2O); IR ν_{max}^{KBr} cm^{-1} : 1759, 1718, 1665, 1594 (*Anal.* Calcd. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48 Found : C, 70.06; H, 6.42) afforded a separatable mixture (chromatography on neut. alumina) consisting of the above mentioned ester (XVIII) and its 10-acetoxy ester (XIX), colorless prisms, m.p. 143.5~144.5° (from MeOH-H_2O); IR ν_{max}^{KBr} cm^{-1} : 1724, 1267 (*Anal.* Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found : C, 72.69; H, 7.79) in 1:1.9 ratio.

The desired 7-amino ester (XVII) could be produced from the definite ester (XVIII) by the usual method[15,17]; chromic acid oxidation to mono-9-keto ester (XX), colorless prisms, m.p. 145~147° (from MeOH), IR ν_{max}^{KBr} cm^{-1} : 1721, 1692, 1595 (*Anal.* Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found : C, 75.65; H, 7.85), nitration to 7-nitro-9-keto ester (XXI), colorless needles, m.p. 229~230° (from MeOH); IR ν_{max}^{KBr} cm^{-1} : 1722, 1688, 1603, 1512, 1354

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(*Anal.* Calcd. for $C_{18}H_{21}O_5N$: C, 65.24; H, 6.39; N, 4.23. Found : C, 65.25; H, 6.41; N, 4.24) and catalytic hydrogenation (Pd-C, H_2SO_4, AcOH).

The 7-amino ester (XVII) was converted to 7-methoxy ester (XXIII), colorless prisms, m.p. 91~93° (from MeOH); IR : ν_{max}^{KBr} 1720 cm^{-1} (*Anal.* Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found : C, 75.17; H, 8.56) through 7-hydroxy ester (XXII), colorless prisms, m.p. 144~145° (from ether-petr. ether); IR ν_{max}^{KBr} cm^{-1} : 3440, 1704, 1610 (*Anal.* Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found : C, 74.52; H, 7.94).

Using the lithium-liq. ammonia (ethanol) reduction and the successive acid treatment[2b,3c] of XXIII, the intended compounds (II) and (III) were obtained in the following two ways : 1) the reaction product was chromatographically separated (alumina) into an oily fraction, whose infrared spectrum showed it mainly consisted of III and into a crystallized fraction (II), colorless prisms, m.p. 152~154° (from MeOH-H_2O), IR ν_{max}^{KBr} cm^{-1} : 3465, 1648, 1606 (*Anal.* Calcd. for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found : C, 77.56; H, 9.71), 2) By the oxidation and the methylation of the reduced mixture without purification, monoenone ester (III), colorless prisms, m.p. 114~116° (from petr. benzin); IR ν_{max}^{KBr} cm^{-1}: 1718, 1680, 1618; $[\alpha]_D^{28.5}$ −48.9° *4 (c=0.40, EtOH) (*Anal.* Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found : C, 74.93; H, 8.78) was chromatographically isolated (alumina).

On the other hand, *d*-monoenone ester (VII),[2a] m.p. 114~116°; $[\alpha]_D^{28.5}$ +47.1°*4 and *d*-monoenon-ol (VI), colorless prisms, m.p. 153~155° (*Anal.* Calcd. for $C_{17}H_{26}O_2$: C,77.82; H, 9.99. Found : C, 77.86; H, 9.91) were led from agathic acid (IV)*5 and agathene diol (V) respectively.

Proof on the antipodal relationships between *l*- (III) and *d*-monoenone ester (VII) and also between *l*- (II) and *d*-monoenon-ol (VI) were afforded by the facts that the physical properties (m.p., infrared, $[\alpha]_D$ value and retention time of gaschromatography*6) of the pairs of the compounds were identical except opposite sign of $[\alpha]_D$ value, the optical rotatory dispersion curves*6,18) of the esters (III and VII) were mirror image (Fig. 1) and the synthetic 1:1 mixture of the aforementioned *l*- (III) and *d*-ester (VII) yielded a racemic compound, m.p. 96~98°, synthesized by Barltrop, *et al.*[2b]

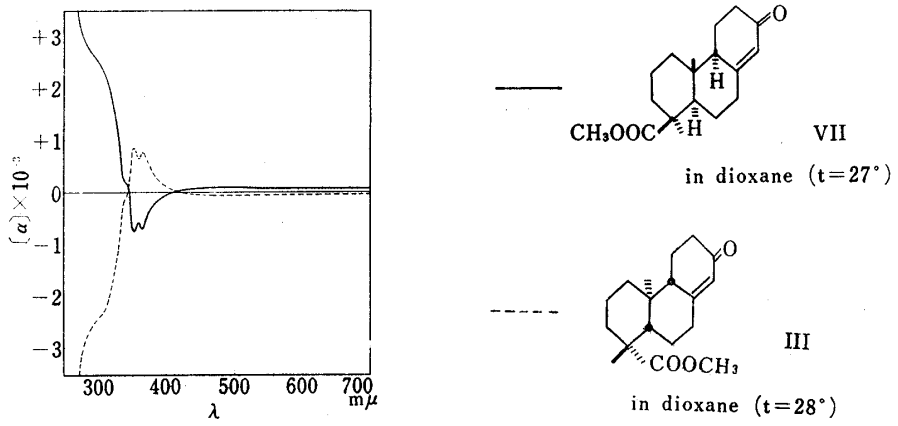

Fig. 1.

The authors are indebted to Prof. Emeritus E. Ochiai, Tokyo Univ., for his valuable advice and encouragement.

*4 This value was measured by authors. cf. m.p. 117~118°, $[\alpha]_D^{15}$ +51.1° ($CHCl_3$).[2a]

*5 Authors thank to Dr. H. Ageta, Showa Pharm. College, for his kind informations of the unpublished data on agathic acid extraction.

*6 Authors thank to Dr. K. Kuriyama, Shionogi & Co., Ltd., for his measurement of ORD curves and also to Dr. N. Ikekawa, this Institute, for his advice on the gaschromatography.

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Reactions of Quinoline 1-Oxide with Enamines of Cyclohexanone

Recent reports[1,2] from this laboratory have shown that quinoline 1-oxide reacts smoothly with compounds containing reactive hydrogens, *e.g.* ethyl cyanoacetate, in the presence of acetic anhydride, producing the corresponding 2-substituted quinolines in good yield, but no reaction occurs with less reactive compounds such as acetone or acetophenone. In an extension of this work we found that cyclohexanone, which was inactive as it was, could readily enter into the reaction under the similar condition when it was modified as an enamine.

When benzoyl chloride (1.2 equiv.) was added to the chloroform solution of quinoline 1-oxide and morpholine enamine of cyclohexanone (2 equiv.) under ice cooling, an exothermic reaction took place and the solution turned to deep red. Treatment of the reaction mixture with 20% hydrochloric acid gave 2-(2-quinolyl)cyclohexanone as a major product (74% yield), which crystallized as orange prisms from methanol, m.p. 121~122°, UV λ_{max}^{EtOH} mμ (log ε) : 216.5 (4.57), 278 (3.95), 440 (3.89). λ_{max}^{NHCl} mμ (log ε): 237 (4.52), 317 (4.06). (*Anal.* Calcd. for $C_{15}H_{15}ON$: C, 79.97; H 6.71; N, 16.22. Found : C, 79.95; H, 6.72; N, 5.75). Oxime, white lieflets, m.p. 190~192° (from EtOH, *Anal.* Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.71; N, 11.66. Found : C, 75.04; H, 7.00; N, 11.21).

Without benzoyl chloride, quinoline 1-oxide could not react with the enamine of cyclohexanone. The reaction should be considered to proceed through the following couse.

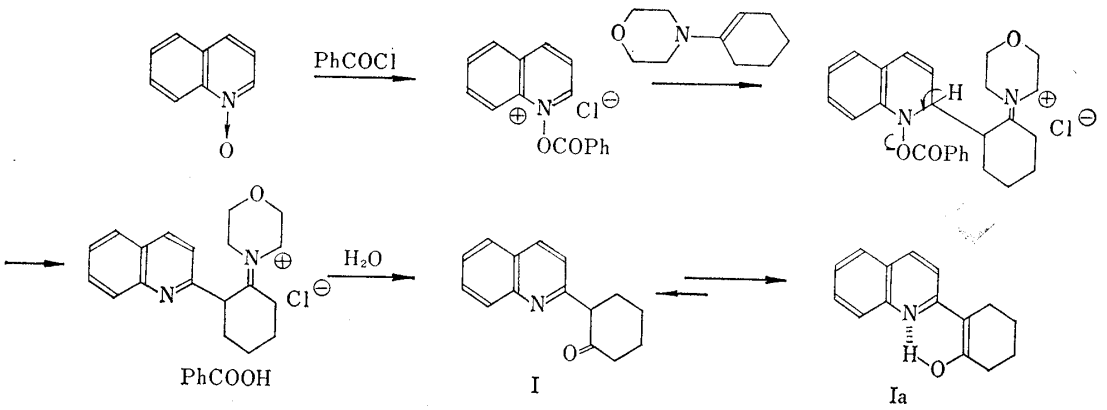

Chart 1.

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2) *Idem* : *Ibid.*, **11**, 415 (1963).