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A TOTAL SYNTHESIS OF DITERPENE ALKALOIDS*

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Recent achievements on the total syntheses of diterpene alkaloids, such as dl-atisine, dl-garryine and dl-veatchine, independently submitted from three laboratories (1) have drawn much interest. However, many chemists are still making the attempt to synthesize the diterpene alkaloids by chemical conversion from other natural diterpenoids, but their efforts have not yet been rewarded with success up to the present.

Since a few years ago, our attentions have been focussed on the preparation of physiologically active compounds, such as gibberelline group and diterpene alkaloids, from

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* This communication will be published in detail as Diterpenoids (X). A part of this work was presented at the Local Meeting of the Pharmaceutical Society of Japan, Tokyo, July 24, 1965, and also at the 9th Symposium of Natural Organic Compounds, Osaka, October 14, 1965. cf. Symposium Abstracts (in Japanese) pp. 120-126.
New compounds indicated by m.p. gave satisfactory analytical values and had gas-liquid or thin-layer chromatographic purity.

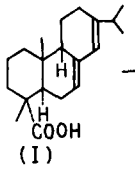
l-abietic acid, which is readily available from oleoresin of many kinds of common Japanese pine trees. l-Abietic acid (I) has an undisputed structure with absolute configuration and its total synthesis has been accomplished (2). Therefore, the chemical correlation of the above-mentioned natural products from l-abietic acid can be regarded as formal total synthesis of the optically active compounds.

According to our intention as stated above, the syntheses were carried out for the compounds (XI) and (XII), having common skeleton with the same absolute configuration as aconitum and garrya alkaloids, from l-abietic acid (I) through the keto-lactone (V)(3).

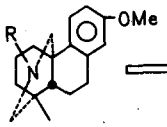
In extention of the above chemical process, a total synthesis of diterpene alkaloids by chemical conversion from l-abietic acid (I) is herein described.

As a follow-up of our previous chemical studies in this field, the keto-lactone (V), m.p. 194-195°,** as potential intermediate for the diterpene synthesis, was converted from l-abietic acid (I) via several steps (4). First, our efforts were directed towards a preparation of the compound, having a nitrogen bridge being characteristic of the diterpene alkaloid and still leaving the oxygen function at C-9 from the keto-lactone (V). As the direct starting material for this purpose, the hydroxy-lactone (VII), m.p.

** M.p. and b.p. reported in the reference (3) was revised as follows: (V), m.p. 192-193° to 194-195°, (VII), m.p. 159-161° to 162-163°, and (XII), b.p. 130-135°(bath temp.)/1 mm to m.p. 120-122°.

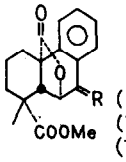


(I)

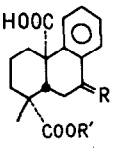


(II, R=Ac(l))
(III, R=Ac(dl))
(IV, R=H)

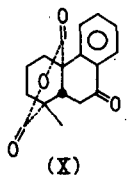
Atisine
Veatchine
Garryine



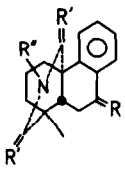
(V, R=O)
(VI, R=<H, OAc)
(VII, R=<H, OH)



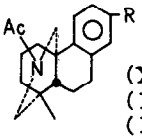
(VIII, R=H₂, R'=Me)
(IX, R=O, R'=H)



(X)



(XI, R=H₂, R'=H₂, R"=H)
(XII, R=H₂, R'=H₂, R"=Ac)
(XIII, R=O, R'=O, R"=H)
(XIV, R=<H, OH, R'=H₂, R"=H)
(XV, R=<H, OAc, R'=H₂, R"=Ac)
(XVI, R=<H, OH, R'=H₂, R"=Ac)
(XVII, R=O, R'=H₂, R"=Ac)



(XVIII, R=NO₂)
(XIX, R=NH₂)
(XX, R=OH)

162-163°,** quantitatively obtained by $NaBH_4$ reduction of (V), was chosen. It is noted, as previously reported, that the keto-lactone (V) is hydrogenolysed to give a mixture consisting of the following three compounds : the acetoxy-lactone (VI), the hydroxy-lactone (VII) and the monoacid (VIII), and the synthesis of the compounds (XI) and (XII), m.p. 120-122°,** were completed using the monoacid (VIII) as the starting material (3).

Alkaline hydrolysis of the hydroxy-lactone (VII) in diethylene glycol-H_2O afforded the keto-diacid (IX), m.p. 257-261°(decomp.), γ_{max}^{KBr} 3100(broad), 1725, 1690, 1650, 1600 cm^{-1}, in company with about an equal amount of uninvestigated oily part. Subsequently, the keto-diacid (IX) was dehydrated by refluxing in acetic anhydride to give the keto-anhydride (X), m.p. 218-220°, γ_{max}^{KBr} 1800, 1760, 1688, 1600 cm^{-1}, which was heated with urea to yield the keto-imide (XIII), m.p. 239-240°, γ_{max}^{KBr} 3330, 1710, 1680, 1603 cm^{-1}. Treatment of the keto-imide (XIII) with $LiAlH_4$ in dioxane-ether solution followed by acetylation with acetic anhydride containing a small amount of pyridine, yielded the acetoxy-acetylamine (XV), m.p. 190-191°, γ_{max}^{KBr} 1730, 1720, 1640, 1620 cm^{-1}, via the hydroxy-amine(XIV).

In order to obtain a reliable evidence for the structure of these compounds, the hydroxy-acetylamine (XVI), m.p. 180-181°, γ_{max}^{KBr} 3320, 1608 cm^{-1}, obtained readily by hydrolysis from the acetoxy-acetylamine (XV), was oxidized with 2,3-dichloro-5,6-dicyanoquinone or chromium trioxide

to the keto-acetylamine (XVII), m.p. 164-166°, γ_{max}^{KBr} 1685, 1644, 1630, 1598 cm^{-1}. The compound (XVII) was identical with the product obtained by the oxidation of authentic acetylamine (XII) having undeniable structure (3).

Finally, for the synthesis of the intended 7-methoxy-acetylamine (II) from the keto-acetylamine (XVII) prepared through the above two routes, the following usual treatments were performed successively without purification at each step. Nitration of (XVII) to 7-nitro-keto-acetylamine (XVIII), $\gamma_{max}^{CHCl_3}$ 1690, 1640, 1550, 1350 cm^{-1}; hydrogenolysis of (XVIII) on palladium-charcoal in acetic acid containing a small amount of sulphuric acid to 7-amino-acetylamine (XIX), $\gamma_{max}^{CCl_4}$ 3550, 3400, 1640 cm^{-1}; and treatment of (XIX) with sodium nitrite, followed by diazomethane after hydrolysis of the diazonium salt to yield (II) through 7-hydroxy-acetylamine (XX). The 7-methoxy-acetylamine (II) is optically active, $[\alpha]_D^{26.5°}$ -131.3 (EtOH, c=0.21), and has the following physical constants; m.p. 146-147°, $\gamma_{max}^{CCl_4}$ 1645, 1050 cm^{-1}, retention time of gas-liquid chromatography (1.5% SE-30 on Anakrom (Mesh 80-100), 4 mm x 1.85 m, 227°), 12.4 min.***

On the other hand, W. Nagata et al. had accomplished the total synthesis of dl-atisine, dl-veatchine and dl-garryine using dl-7-methoxy-amine (IV) as the key inter-

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mediate (1), therefore, their amine (IV)*** was acetylated with acetic anhydride containing pyridine to give the dl 7-methoxy-acetylamine (III), m.p. 167-169°, whose infrared spectrum (CCl_4) and gas-liquid chromatogram were found to be superimposable with those of our corresponding l-7-methoxy-acetylamine (II).

Since the dl-7-methoxy-acetylamine (III) was reverted to the original dl-7-methoxy-amine (IV) by alkaline hydrolysis with potassium hydroxide and hydrazine in diethylene glycol, the present work represents a total synthesis of the diterpene alkaloids. Furthermore, it also constitutes the first example of transformation to the diterpene alkaloids from the other naturally occurring diterpenes.

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