stand over night at room temperature, diluted with water, and a small amount of NH_4OH was added. The crude product was taken up in $CHCl_3$ and after evaporation of the solvent the residue was purified by alumina chromatography to give an amorphous product. Yield, 50 mg.

Fifty mg. of the above compound was hydrolyzed with MeOH-KOH solution (50 mg. of KOH in 10 cc. of MeOH) heating on a steam bath for about 30 min. The reaction solution was diluted with water and passed through Amberlite IR-120 column. After extraction of the resulting BzOH with ether the aqueous solution was evaporated to dryness *in vacuo* and 12 mg. of amorphous neutral compound was obtained.

This neutral compound (XIX)(12 mg.) was dissolved in pyridine-water mixture (1 cc. of pyridine and 3 cc. of water) and 13 mg. of $KMnO_4$ was added during 2 hr. at 0° to 5°. After standing at room temperature for further 30 min., the color of MnO_4^- was still observed. After filtration of MnO_2, the reaction solution was evaporated to dryness *in vacuo* at below 50°. The residue was dissolved in water, passed through Amberlite IR-120 column, and the aqueous solution was evaporated to leave an amorphous dicarboxylic acid (XX). Yield, 9 mg. This acid was titrated with 0.02*N* NaOH (F=1.00) and 2.35 cc. of alkali was consumed. Calcd. for 2-COOH : 2.22 cc. IR λ_{max}^{KBr} cm^{-1} : 1708(COOH), 1637 (>N-CO-).

Pyrolysis of the Dicarboxylic Acid (XX)—7 mg. of the acid (XX) was heated in a stream of N_2 and eliminated gas was bubbled through $Ba(OH)_2$ solution. From about 140° precipitation of $BaCO_3$ was observed. After heating up to 170° for about 1 hr., the residue (5.2 mg.) was dissolved in 20% MeOH, and titrated with 0.02*N* NaOH solution (F=1.00). 0.65 cc. of NaOH solution was consumed. Calcd. for 1-COOH : 0.72 cc. IR λ_{max}^{KBr} cm^{-1} : 1712 (COOH), 1620 (>N-CO-).

Summary

The presence of α-methylenecyclohexanol grouping in ignavine or des-N-methylanhydroignavinol was proved by rearrangement reaction to ketone. Oxidative cleavage of the cyclohexanol ring in des-N-methylanhydroignavinol gave a dicarboxylic and one of the carboxyl groups in this acid was confirmed as tertiary. α-Glycol group which is another functional group in des-N-methylanhydroignavinol was also cleaved by oxidation to give a dicarboxylic acid and the glycol was proved to exist at carbons γ ond δ to the nitrogen.

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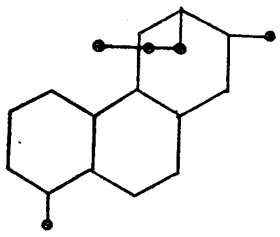
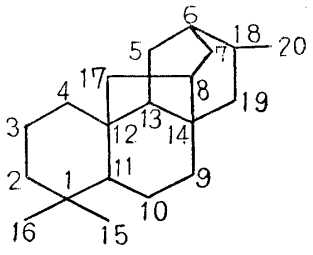
101. Eiji Ochiai and Toshihiko Okamoto : Aconite Alkaloids. XXIV.[1] The Structure of Ignavine. (4).

(*Faculty of Pharmaceutical Sciences, University of Tokyo*[*1])

Previously, the authors reported the isolation of an alkylphenanthrene of m.p. 89~90°, $C_{19}H_{20}$, as a dehydrogenation product of anhydroignavinol,[2] $C_{20}H_{25}O_4N$. Recently, this alkylphenanthrene was identified by syhthesis as 1,7-dimethyl-6-propylphenanthrene.[3]



(I)



(II)

*1 Hongo, Bunkyo-ku, Tokyo (落合英二, 岡本敏彦).

1) Part XXIII : This Bulletin, **7**, 550(1959).

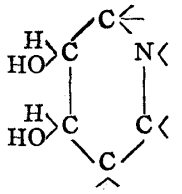
2) E. Ochiai, *et al.* : *Ibid.*, **2**, 388(1954).

3) E. Ochiai, *et al.* : *Ibid.*, **6**, 327(1958).

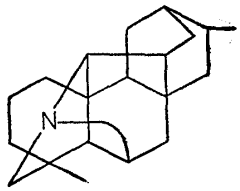
Therefore, 19 carbon atoms in anhydroignavinol would be formulated as (I), which has a perhydro structure of the alkylphenanthrene.

Considering the diterpenoid structure of aconite alkaloids and also the fact that the oxidative cleavage of the α-methylenecyclohexanol part of des-N-methyl-oxo-anhydroignavinol formed a dicarboxylic acid which has a tertiary carboxyl group,[1] structure (II) should be given for the carbon skeleton of anhydroignavinol. C-20 is considered to exist as a terminal methylene group and consequently the hydroxyl group of the allyl alcohol should be attached to C-19. Further, from the fact that anhydroignavinol has one C-methyl group, C-15 or -16 should be present as a methyl group in the alkaloid.

Additional nitrogen is needed in the structure (II) to complete the skeleton of anhydroignavinol. This nitrogen should be placed between C-15 or -16 and -17, considering the partial structure (III), which was given in the preceding paper,[1] and also considering the structure of other aconite alkaloids. This position satisfies the six-membered character of the nitrogen-containing ring. The third bond of the nitrogen should be linked to 10-position which is in the nearest position. Thus, structure (IV) is considered to show the skeleton of ignavine and anhydroignavinol.



(III)



(IV)

Ignavine has one benzoyloxyl group which is an acylated form of one hydroxyl group of a glycol.[4] To clarify this point, oxidation of ignavine was examined. Ignavine was oxidized with chromium trioxide in pyridine and a small amount of a diketone of m.p. 294~296° was obtained besides an amorphous monoketone. In the infrared spectrum this diketone showed bands assignable to α,β-unsaturated ketone at 1708 and 1630 cm^{-1}, and also the bands assignable to a ketol benzoate at 1740 and 1722 cm^{-1}. This diketone was positive to Zimmermann's test at room temperature and therefore, a methylene group adjacent to the ketone of the ketol benzoate is considered. When heated with sodium hydroxide solution the diketone gave a positive result to Tollens' reagent and was also positive to triphenyltetrazolium chloride which is a characteristic reagent to ketol. From this experiment the benzoyloxy group should be in 2-position.

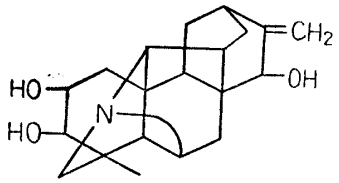
From these experiments, the nature of four oxygens in ignavine and three oxygens in anhydroignavinol was clarified, but ignavine has two more oxygens while anhydroignavinol has one more. Ignavine loses one mole of water on hydrolysis, acylation, formation of the methiodide, and also on rearrangement reaction to the ketone. This easy dehydration suggests the possibility of the presence of water of crystallization in ignavine, but even by the Karl-Fisher method,*2 water of crystallization was not detected. On hydrogenation over platinum catalyst in acetic acid, only one double bond was shown in anhydroignavinol and two double bonds were determined in des-N-methylanhydroignavinol. Further, no hydroxyl band was observed in the infrared spectra of tribenzoylanhydroignavinol, tribenzoyl-des-N-methylanhydroignavinol, and tribenzoyl-des-N-methyl-oxo-anhydroignavinol in chloroform solution. Therefore, formation of an ether group by dehydration from two hydroxyl groups is considered rather than formation

*2 The authors thank Dr. Z. Tamura of this Faculty for the determination of water of crystallization by this method.

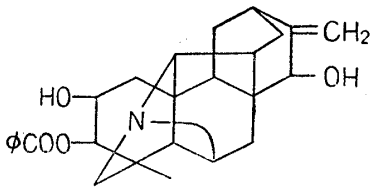
4) Yakugaku Zasshi, 72, 812(1952).

of a double bond by elimination of a hydroxyl group.[5] Ignavine has a normal pK′ value of 7.7 for tertiary amine and rather difficult to consider a carbinolamine type. Consequently, to form an ether group from two hydroxyl groups, a β-glycol type combination of hydroxyl groups are available in the structure (IV). Those are 5–7, 8–9, 9–13, and 11–13 combinations. In order to confirm the positions of the hydroxyl groups, further data are required.

The authors wish to present tentative structures for anhydroignavinol (V) and for ignavine (VI).



(-O-)
(V)



$(-OH)_2$
(VI)

The authors are indebted to Dr. J. Matsumura of Hokuriku Hygienic Chemical Laboratory for his kind help in the collection of the aconite roots. Thanks are due to Mr. Tanikawa of this Faculty for the determination of infrared spectra and to the members of the Central Microanalysis Room in this Faculty for the microanalyses.

Experimental

C-Methyl Determinations of Anhydroignavinol and Des-N-methylanhydroignavinol—The determination was carried out by the Kuhn-Roth method.[6]

Anhydroignavinol,[7] 14.835 mg., *N*/50 NaOH (F=1.225), 0.85 cc. Blank, 0.20 cc. C-methyl, 0.34.

Des-N-methylanhydroignavinol, 15.335 mg., *N*/50 NaOH (F=1.225), 1.11 cc. Blank, 0.20 cc. C-methyl, 0.52.

Determination of Water of Crystallization of Ignavine by the Karl-Fischer Method—Sample, 237.8 mg. (dried over P_2O_5 at 110° for 2 hr.). Water, 0.43 mg., 0.019%.

Determination of Double Bond in Anhydroignavinol and Des-N-methylanhydroignavinol—Determined by the Tsuda-Sakamoto method.[8]

Anhydroignavinol, 19.710 mg., AcOH, 4 cc. at 35°. h=5.23 cm., K=0.249 : F=1.02.

Des-N-methylanhydroignavinol, 20.847 mg., AcOH, 2 cc. at 32°. h=10.50 cm., K=0.255 : F=2.05.

Oxidation of Ignavine with Chromium Trioxide in Pyridine—To the suspension of CrO_3 (220 mg.) in pyridine (3 cc.), 100 mg. of ignavine was added and the mixture was allowed to stand over night. The reaction mixture was diluted with water, extracted with $CHCl_3$-MeOH mixture, and evaporation of the solvent gave a resinous compound (67 mg.). The crude product was separated by alumina chromatography (Al_2O_3 : 10 cc.) using $CHCl_3$ (containing 1~5% of MeOH) as the solvent.

Fract. No.	Solvent	Product (mg.)	m.p. (°C)
1~6	$CHCl_3$-MeOH (1%)	5	265~270
7~9	$CHCl_3$-MeOH (2%)	35	amorphous
10~	$CHCl_3$-MeOH (5%)	ca. 10	amorphous

Fractions 1~7 (5 mg.) were purified again by alumina chromatography and recrystallized from acetone to needles of m.p. 294~296° (3 mg.). Zimmermann's test, positive (at room temperature). When heated with NaOH solution, the substance was positive to the Tollens' reagent and to triphenylterazolium chloride. IR λ_{max}^{KBr} cm^{-1} : 1708, 1603 (C=C-CO), 1740, 1722 (φ-COO-C-CO).

Fractions 7~9, combined with the sample obtained from another experiment (total 50 mg.), was

5) cf. This Bulletin, **1**, 60(1953). Previous conclusion which was discussed in this reference should be corrected.
6) Ber., **66**, 1274(1933).
7) Platinum catalyst was used for the oxidation. cf. P. Karrer, *et al.* : Helv. Chim. Acta, **35**, 862 (1952).
8) Yakugaku Zasshi, **57**, 1037(1937).

hydrogenated over Pd-C (H_2 consumed was not determined). The product was purified by alumina chromatography (Al_2O_3 : 15 cc.) using CH_2Cl_2 (containing 3% of MeOH) as a solvent. Fractions 3~5

Fract. No.	Product (mg.)	m.p. (°C)
1~2	2	amorphous
3~5	24	256~259
6~	9	amorphous

were recrystallized from acetone to needles, m.p. 256~259°. This showed no depression on admixture with anhydrodihydroignavinone.[1]

Summary

The results of dehydrogenation of anhydroignavinol and oxidation of des-N-methyl-anhydroignavinol are discussed and tentative structures for anhydroignavinol and ignavine are presented.

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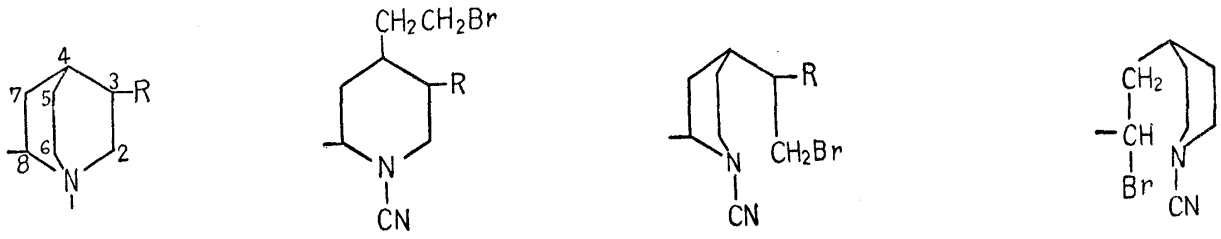
UDC 547.942

102. Eiji Ochiai und Masayuki Ishikawa : Synthese von Derivaten der Cinchona-Alkaloide. XXXI.[1] Ableitung der Alkaloide des Corynanthein-Typus aus Chinin.

(*Pharmazeutische Fakultät, Universität Tokyo*[*1])

Der Erfolg der Überführung von Chinin über 2'-Hydroxydihydronichin in eine Verbindung mit dem Tetrahydro-β-carbolin-Skelett[1] hat unseren Versuch erleichtert, aus Chinin eine Verbindung des Corynanthein-Typus abzuleiten. Zu dieser Synthese muss man vorerst den Chinuclidin-Ring an der Bindung zwischen dem Stickstoff und dem Kohlenstoff-6 aufspalten und in das entsprechende sekundäre Amin überführen. Ein möglicher Weg dazu ist der Bromcyan-Abbau. Hierbei sind jedoch die dreiartigen Spaltungen (a), (b) und (c) denkbar, von denen nur die Spaltung nach (a) wünschenswert ist.



(a) (b) (c)

Ferner ist die direkte Einwirkung von Bromcyan auf Chinin oder Dihydrochinin nicht geeignet, weil der Chinolinkern in ihm der Reaktion eingreift.[2] Es wurde daher zuerst die Reaktion mit 2'-Oxo-9-benzoylhexahydrochinin (I) untersucht, bei welchem keine Gefahr des Eingreifens des Chinolin-Stickstoffes vorhanden ist. Die Reaktion wurde mit 1.1 Mol Bromcyan in einer Chloroform-Lösung durchgeführt und zwei kristallinische

*1 Hongo, Tokyo (落合英二, 石川正幸).
1) XXX. Mitt. Y. Kobayashi : Dieses Bulletin, **7**, 472(1959).
2) T. Shimidzu : Yakugaku Zasshi, **48**, 31(1928) (C. A., **22**, 1780(1928)).