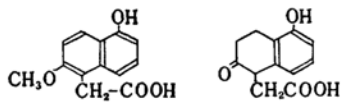
# *Abnormal Reduction of 2-Methoxy-5-hydroxy-1-naphthylacetic Acid**

By Takeshi MATSUMOTO and Akira SUZUKI

(Received February 20, 1959)

In the previous paper[1] the synthesis of 2-methoxy-5-hydroxy-1-naphthylacetic acid (I) was described. The present work was undertaken in an attempt to prepare 1,2,-3,4-tetrahydro-2-oxo-5-hydroxy-1-naphthylacetic acid (II), a potential intermediate for building up the diterpenoid alkaloid framework, by reduction I.




(I) (II)

It is well known that the reduction of a variety of 2-methoxynaphthalene derivatives by alkali metal in alcohol[2] or in alcohol-liquid ammonia[3] yields the corresponding 2-oxotetralins. At first sight, therefore, it seemed easy to prepare tetrahydro-2-oxo-5-hydroxy-1-naphthylacetic acid (II). However, attempted reduction along this line led to unusual results. Depending upon the procedure employed, tetrahydro-5-hydroxy-1-naphthylacetic acid (III) or a mixture of compound III and tetrahydro-2-oxo-4,5-dihydroxy-1-naphthylacetic acid (IV) has been obtained.

At first, the reduction was effected by employing a large excess of sodium (ca. 0.03 mol. per 0.001 mol. of I) in butanol. Product A, which was obtained in good yield, unexpectedly did not react with dinitrophenylhydrazine. The elemental composition corresponded to $C_{12}H_{14}O_3$ rather than to that of the expected product II, $C_{12}H_{12}O_4$. The tests for a methoxyl group (Zeisel) and for a secondary alcohol group (Nessler) were both negative. The infrared spectrum in nujol mull possessed a single sharp band at 1700 $cm^{-1}$ (carboxyl group) and a broad absorption band at 3200~3400 $cm^{-1}$. Of three oxygen atoms, two have thus been shown to be present in a carboxyl group, and one probably as a hydroxyl group. The presence of a hydroxyl group was confirmed by the formation of monoacetate, $C_{14}H_{16}O_4$. The ultraviolet spectrum (Fig 2. curve b) of product A could be superimposed upon that of 1,2,3,4-tetrahydro-5-naphthol (curve c). These results clearly indicate that product A should be expressed by formula III. So far as the authors are aware, the ready conversion of methoxynaphthalenes to desoxygenated tetralins has not hitherto been reported[4]. The formation of the abnormal reduction product must be attributed, at least in part, to the presence

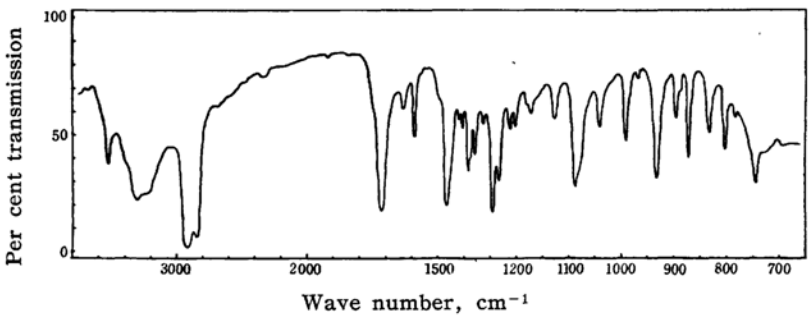



Fig. 1. Infrared spectrum of 1,2,3,4-tetrahydro-2-oxo-4,5-dihydroxy-1-naphthylacetic acid (IV).

* Approaches to the Synthesis of Diterpenoid Alkaloid Models. II.

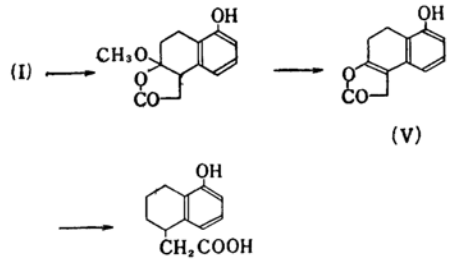
1) T. Matsumoto and A. Suzuki, This Bulletin, in preparation.

2) For example, U. W. Cornforth and R. Robinson, *J. Chem. Soc.*, **1949**, 1861.

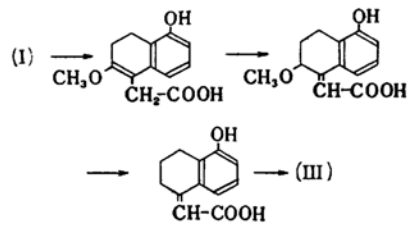
3) A. J. Birch and H. Smith, *Quart. Revs.*, **12**, 17 (1958).

4) A. L. Wilds et al., *J. Am. Chem. Soc.*, **95**, 5360 (1953), have obtained $\Delta^{9-10}$-octahydronaphthalene as a by-product (10~16%) from 5,6,7,8-tetrahydro-1-methoxynaphthalene by reduction with lithium in alcohol-liquid ammonia.

of a carboxyl group, since 1-methyl-2-methoxy-5-hydroxynaphthalene is reported to give smoothly tetrahydro-1-methyl-2-oxo-5-hydroxynaphthalene[5]. On the other hand, Jacobs and Scott[6] have observed that $\beta\gamma$-unsaturated-$\gamma$-lactones are susceptible to catalytic hydrogenolysis to form saturated acids, whereas $\alpha\beta$-isomers give saturated lactones on catalytic hydrogenation. The authors are not aware of any example of reductive cleavage of $\beta\gamma$-unsaturated-$\gamma$-lactone by means of sodium and alcohol. Nevertheless, it seemed likely at that time that the abnormal reduction proceeds under the participation of the carboxyl group through a $\beta\gamma$-unsaturated-$\gamma$-lactone such as V as shown below:




According to this assumption, treatment of methyl ester of I, rather than I itself, under the same conditions was expected to afford methyl ester of the desired tetralone (II). However, reduction of the methyl ester of I with subsequent hydrolysis gave again the tetralin derivative III as a main product. The above assumption therefore became improbable; the tetralin derivative III might be formed through a process which involves reductive elimination of the allylic methoxyl group as outlined below, but further evidence is required to elucidate the pathway.




The authors next examined the reduction employing sodium and boiling ethanol as well as sodium and ethanol-liquid ammonia (Birch's conditions). In both

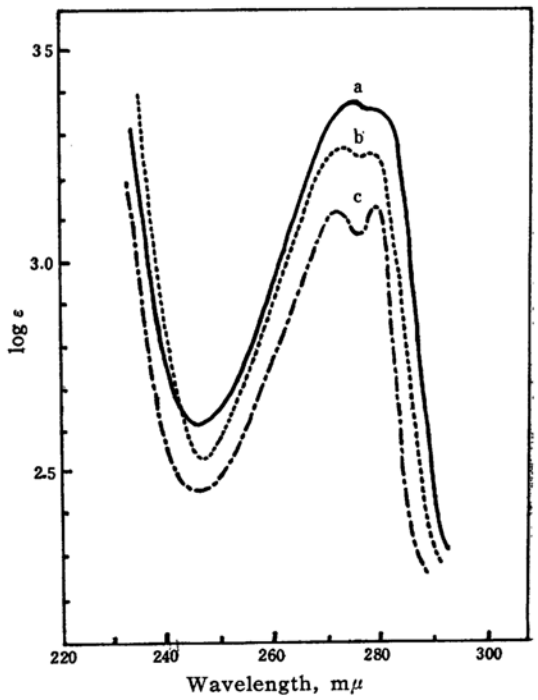



Fig. 2. Ultraviolet spectra.
a (——): 1,2,3,4-Tetrahydro-2-oxo-4,5-dihydroxy-1-naphthylacetic acid (IV) in methanol.
b (------): 1,2,3,4-Tetrahydro-5-hydroxy-1-naphthylacetic acid (III) in methanol.
c (-----): 1,2,3,4-Tetrahydro-5-naphthol in cyclohexane.

cases most of the starting material was recovered, in the former case, probably because of the low reaction temperature and in the latter case, probably owing to the extreme low solubility[7] of the naphthylacetic acid in liquid ammonia. Attempts to reduce I by means of lithium in ethanol-liquid ammonia-dimethoxyethane (Wild's procedure) led to the formation of tetrahydro-5-hydroxy-1-naphthylacetic acid (III) in good yield, even when only 4.7 g. atoms per mol. of lithium was used[8].

Since all efforts to prepare III were thus unsuccessful, attention was turned again to the first method. The reduction was carried out at this time employing a smaller amount than before (8 atoms per mol.) of sodium. From the resulting reaction mixture, an appreciable amount of a carbonyl compound B, m. p. 121.5~123°C was isolated through its triethylamine salt, together with tetrahydro-5-hydroxy-1-naphthylacetic acid (III) and the

5) Ref. 2.
6) W. A. Jacobs and A. B. Scott, *J. Biol. Chem.*, 87, 601 (1930).
7) For similar examples, see Ref. 3.
8) In this case a portion of the starting material was recovered; see *Experimental Section* below.

unchanged starting material I. Elemental analysis of the carbonyl compound B indicated the formula $C_{12}H_{14}O_6$. The infrared spectrum (Fig. 1) of this compound exhibited absorption bands at 3550 and 1635 $cm^{-1}$ (solvated water), which disappear in a sample dried at 80°C in high vacuum, a broad band extending from 3400 to 3200 $cm^{-1}$ (associated OH) and a single broad band at the carbonyl region (probably superimposed carboxyl and carbonyl bands). The ultraviolet spectrum (Fig. 2, curve a) of the hydrated substance showed almost the same shape as those of 1, 2, 3, 4-tetrahydro-5-naphthol (curve c) and 1, 2, 3, 4-tetrahydro-5-hydroxy-1-naphthylacetic acid (III) (curve b).

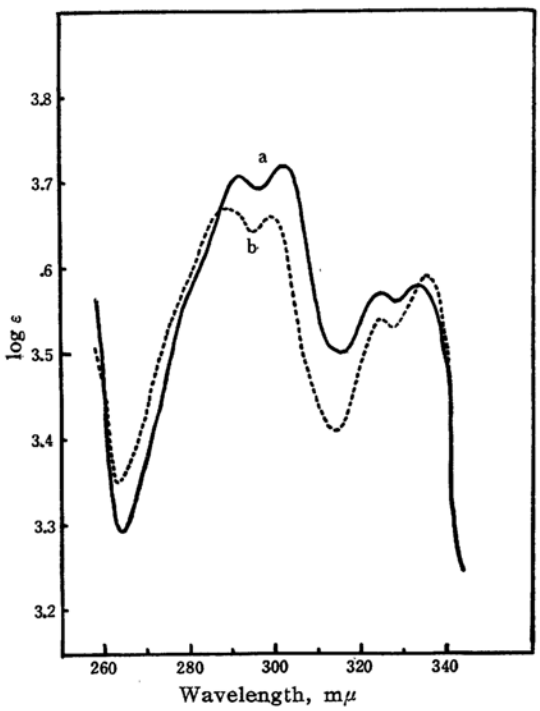



Fig. 3. Ultraviolet spectra in methanol.
a (——): 2-Methoxy-5-hydroxyl-1-naphthylacetic acid (I).
b (------): Methyl 2,5-dihydroxy-1-naphthylacetate (VI).

At this stage the authors supposed that they had the desired product II ($C_{12}H_{12}O_4$) with two moles of water of crystallization at hand, although analytical values for carbon and hydrogen agreed better with $C_{12}H_{14}O_6$. Drying at 80°C in high vacuum was accompanied by decomposition of product B and an analytically pure anhydrous sample could not be obtained. To confirm the above hypothesis, preparation of the methyl ester was then attempted. Contrary to the expectation, treatment with methanolic hydrogen chloride led to two naphthalene derivatives. Presence of the 1-naphthol chromophore in both the products was clearly demonstrated by their ultraviolet spectra. One of the products, $C_{14}H_{14}O_4$, m. p. 155.5~156.5°C, $\nu_{max}^{nujol}$ 3420(OH) and 1735 $cm^{-1}$ (ester) exhibited positive Zeisel test and was readily identified with methyl 2-methoxy-5-hydroxy-1-naphthylacetate (VII)[1], which was obtained separately by esterification of I. The other product, $C_{13}H_{12}O_4$, m. p. 183~184°C, $\nu_{max}^{nujol}$ 3480 (OH) and 1740 $cm^{-1}$ (ester) was formulated as methyl 2,5-dihydroxy-1-naphthylacetate (VI) on the basis of analytical and spectral data (ultraviolet spectrum; Fig. 3, curve b). Formation of these naphthalene derivatives suggests strongly that product B, $C_{12}H_{14}O_6$, is actually a monohydrate of tetrahydro-2-oxo-5-hydroxy-1-naphthylacetic acid with an additional hydroxyl group on the aliphatic portion. Presence of two hydroxyl groups was proved by the formation of a diacetate, $C_{16}H_{14}O_6$. The infrared spectrum (Fig. 4) of the diacetate showed complete absence of a hydroxyl function and presence of the following groups: $\beta\gamma$-unsaturated-$\gamma$-lactone (1795 $cm^{-1}$), phenyl acetate (1765 $cm^{-1}$) and saturated ester (1745 $cm^{-1}$). Therefore, a structural formula like VIII is concluded for this

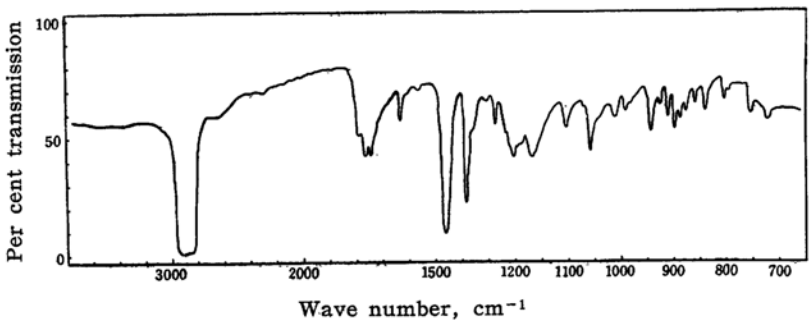
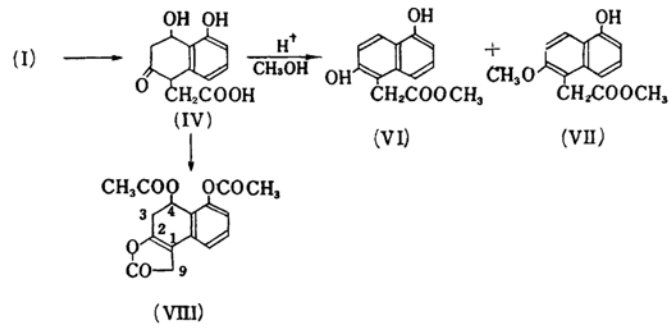



Fig. 4. Infrared spectrum of VIII.



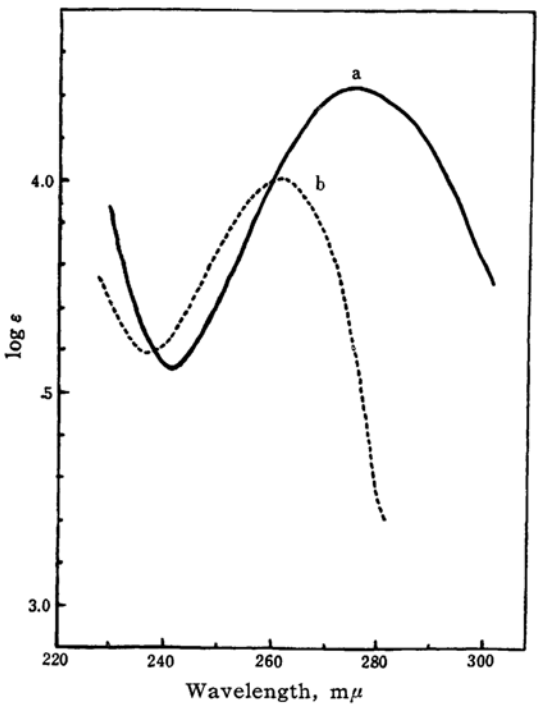
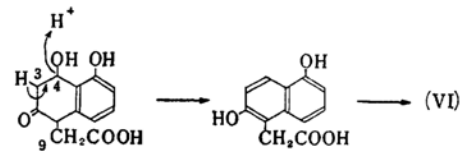




Fig. 5. Ultraviolet spectra.
a (——): VIII in methanol.
b (------): 1,2-Dihydronaphthalene in *n*-hexane.

compound*. The ultraviolet spectrum[9] (Fig. 5, curve a) seems also to agree with this formula. There is a bathochromic shift and an increase in absorption intensity as compared with the spectrum (curve b) of the parent hydrocarbon, 1,2-dihydronaphthalene; these changes can be reasonably ascribed to the presence of an enolic and of a phenolic acyloxy group on the conjugated system.

From formula VIII thus assigned to the diacetate, it follows that two hydroxyl groups (except one hydroxyl group of water of crystallization) are present in product B, and moreover, the hydroxyl group does not occupy the 1-position.

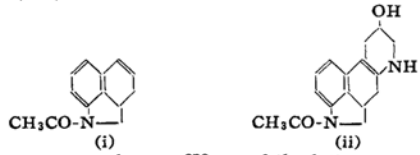
Concerning the position of the aliphatic hydroxyl group in compound B, there remain possibilities of its presence at $C_3$, $C_4$ and $C_9$ positions, of which the $C_4$ position is the most likely one, since the formation of the naphthalene derivatives[10] is readily explained by a $\beta$-elimination reaction:




However, the possibilities of $C_3$ and $C_9$ positions can not be conclusively excluded at this stage, since substituents at these positions, being placed respectively at $\alpha\beta$-position to the phenyl and carbonyl groups, are expected to be also susceptible to undergoing an elimination reaction. In the case of $C_9$ position, subsequent rearrangement of the resultant unsaturated compound would lead to the naphthalene derivatives. The presence of the hydroxyl group at the $C_4$ position, however, has been demonstrated by the following evidence: product B does not reduce triphenyltetrazolium chloride and hence does not contain an $\alpha$-ketol system, and moreover, the fact that p$K$a value (6.20) of the product is very close to that (6.12)

* At this stage the position of the alicyclic acetoxyl group is uncertain.

9) Compound i has been reported to possess bands at 241, ($\varepsilon$ 22500), 254 ($\varepsilon$ 23000), 307 ($\varepsilon$ 1600) and 316 ($\varepsilon$ 1300) m$\mu$; absorption bands at 252 ($\varepsilon$ 2060) and 328 ($\varepsilon$ 1500) m$\mu$ are recorded for compound ii. E. C. Kornfeld, E. J. Kornfeld, G. B. Kline, M. T. Mann, D. E. Morrison, R. G. Jones and R. B. Woodward, *J. Am. Chem. Soc.*, **78**, 3087 (1956).




Low $\varepsilon$ max value at 252 m$\mu$ of the latter compound is quite unusual.

10) 2-Naphthols are readily methylated by methanol in the presence of acidic catalysts; W. A. Davis, *J. Chem. Soc.*, **77**, 33 (1900).

of the tetrahydro-5-hydroxy-1-naphthylacetic acid (III), clearly indicates that the hydroxyl group is not located at the $\alpha$-position ($C_9$) relative to carboxylic function. Although the structure of product B has thus been shown to be IV, the mechanism of conversion I→IV is quite obscure. No example of this kind of reaction seems ever to have been recorded. Although it is out of the scope of the authors' immediate purpose to study in detail the reaction process, it may be noted that the effective reagent which causes the conversion seems not to be sodium butoxide, but to be sodium itself; IV could not be obtained by a mere boiling of I in butanolic sodium butoxide solution.

## Experimental[11]

**Reduction of 2-Methoxy-5-hydroxy-1-naphthylacetic Acid (I) with Sodium and *n*-Butanol.**—A solution of I (230 mg.; 0.001 mol.) in butanol (7 cc.) was boiled under reflux in an oil-bath at 120～130°C with stirring, sodium (730 mg.; 0.032 g. atom) was added in small pieces during 15 min. A further quantity of butanol (3 cc.) was then added to dissolve precipitated sodium butoxide. When the sodium had completely dissolved, the mixture was poured into an equal volume of water. The alkaline aqueous layer was separated, extracted twice with ether, acidified with concentrated hydrochloric acid and allowed to stand overnight. The crude reduction product, which separated out, was collected by filtration. When the filtrate was extracted three times with ether and the ether was evaporated, an additional amount of the above product was obtained. Total yield, 130 mg. (63%). After recrystallization from water, product A (tetrahydro-5-hydroxy-1-naphthylacetic acid) had m. p. 144～145°C and exhibited $\nu_{max}^{nujol}$ 3200～3400 (OH) and 1700 $cm^{-1}$ ($CO_2H$). Ultraviolet absorption bands at 272 (log $\varepsilon$ 3.27) and 278 m$\mu$ (log $\varepsilon$ 3.26).

*Anal.* Found: C, 69.79; H, 6.98. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84%.

**1, 2, 3, 4-Tetrahydro-5-acetoxy-1-naphthylacetic Acid.**—The above acid (III) (100 mg.) was dissolved in absolute pyridine (1.5 ml.). Pure acetic anhydride (0.5 ml.) was added with shaking and the reaction mixture was set aside overnight. The most of pyridine and excess of acetic anhydride was then evaporated. To the residue was added 2 N hydrochloric acid and the mixture was extracted three times with ethyl acetate. The extract was washed twice with water, dried and evaporated. The solid residue on being crystallized from ligroin afforded 100 mg. (83.5%) of the acetoxy acid. Recrystallization from ligroin gave an analytical sample as colorless needles, m. p. 125～126.5°C, $\nu_{max}^{nujol}$ 1750 (phenylacetate) and 1700 $cm^{-1}$ ($CO_2H$).

*Anal.* Found: C, 67.74; H, 6.60. Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50%.

**1, 2, 3, 4-Tetrahydro-2-oxo-4, 5-dihydroxy-1-naphthylacetic Acid (IV).**—To a boiling solution of I (1.84 g.; 0.008 mol.) in 40 cc. of butanol, sodium (1.47 g.; 0.064 g. atom) was added rapidly in small pieces during 10 min. with stirring. After the sodium had completely dissolved, the mixture was treated with 40 cc. of water, and the two layers were separated. After the aqueous layer had been washed twice with ether, 8 cc. of concentrated hydrochloric acid was added under ice cooling and the solution was warmed in a water bath at 70～80°C for 30 min. When the mixture had cooled, an oily substance was separated out; the aqueous layer was then extracted three times with ethyl acetate. The oil and the ethyl acetate extract were combined and the whole was washed twice with water, dried with sodium sulfate, and evaporated to dryness. The oily residue (1.82 g.) was then dissolved in 50 cc. of ethyl acetate; to this solution an excess of triethylamine was added in small portions and the solution was allowed to stand for 5 days. At the end of this period, a considerable amount of triethylamine salt and viscous gum precipitated on the bottom of the flask. The solvent was removed by decantation and the viscous gum was removed by washing the residue quickly with a small amount of cold absolute ethanol. The crystalline triethylamine salt thus obtained melted at 152°C with decomposition.

The salt was then dissolved in 5 cc. of water; the solution was acidified with 6 N hydrochloric acid and extracted with ethyl acetate; the extract was washed with water, dried and evaporated. On being triturated with ether, the residue crystallized to furnish crude tetrahydro-2-oxo-4, 5-dihydroxy-1-naphthylacetic acid (IV), which was recrystallized from water as colorless solvated prisms (0.3 g.; 15%), m. p. 121.5～123°C. Ultraviolet absorption band at 274 m$\mu$ (log $\varepsilon$ 3.38).

*Anal.* Found: C, 56.92; H, 5.75. Calcd. for $C_{12}H_{12}O_5 \cdot H_2O$: C, 56.69; H, 5.55%.

The viscous part, which was separated from the triethylamine salt of IV, on being acidified with hydrochloric acid afforded a mixture of the starting material and III, which was separated by virtue of higher solubility of the latter compound in water.

**Reduction of I by Nelson-Wild's Method.**—Sample of compound I (920 mg.; 0.004 mol.) was placed in a three-necked flask equipped with stirrer, dropping funnel and drying tube (soda-lime). To the vessel was added enough anhydrous dimethoxyethane (20 ml.) to dissolve I. The flask was cooled to −40～−50°C. Liquid ammonia (45 ml.) was added to the solution and then lithium (0.5 g.; 0.072 g. atom) in small pieces during 2 min. After stirring for 10 min. absolute

11) All melting points are uncorrected. Infrared spectra were taken on a Koken model DS-301 infrared spectrophotometer with sodium chloride optics. Ultraviolet spectra were measured by means of a Beckman model DK-2 spectrophotometer. The authors are indebted to Mr. O. Yonemitsu of the Pharmaceutical Institute of Hokkaido University for infrared spectra data and to Miss Noriko Fujino for microanalyses.

ethanol was added dropwise for a period of 15 min. When the blue color of the solution had disappeared, ammonia was expelled, the residue was then treated with cold water and acidified with 6 N hydrochloric acid. The acidic aqueous solution was extracted three times with ethyl acetate. After the combined extracts had been washed with saturated sodium chloride solution and dried over sodium sulfate, the solvent was evaporated and the residue was crystallized from water. A yield of 500 mg. (61%) of 1, 2, 3, 4-tetrahydro-5-hydroxy-1-naphthylacetic acid (III) was obtained. Recrystallization from water gave a pure material of m. p. 144~145°C as colorless needles. No depression at the melting point was observed on admixture with the product obtained by the use of sodium and butanol.

When reduction had been effected employing 0.92 g. (0.004 mol.) of compound I, 20 cc. of dimethoxyethane, 50 cc. of ammonia, 0.13 g. (0.0188 mol.) of lithium and 1.2 cc. of ethanol, there were obtained 310 mg. of III and 560 mg. of I. Presence of a small amount of carbonyl compound in the crude reaction product was indicated by the dinitrophenylhydrazine test, but the compound could not be isolated.

**Aromatization of Product B.**—Sample of product B (210 mg.) was suspended in 5% methanolic hydrogen chloride (10 cc.). The reaction mixture was refluxed on a steam bath for a period of 2 hr. After it had cooled, the solution was evaporated to dryness in vacuo. To the viscous residue were added water and ethyl acetate; the aqueous layer was separated and was re-extracted with ethyl acetate. The combined extracts were washed successively with water, 5% sodium bicarbonate and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. After removal of the solvent, 192 mg. of a solid product was obtained. Crystallization of the product from benzene gave 50 mg. of methyl 2, 5-dihydroxy-1-naphthylacetate (VI) with a melting point 180~183°C, which raised to 183~184°C (decomp.) on recrystallization from benzene. Ultraviolet absorption bands at 288 (log $\varepsilon$ 3.67), 299 (log $\varepsilon$ 3.66), 324 (log $\varepsilon$ 3.54) and 335 m$\mu$ (log $\varepsilon$ 3.59). Infrared spectrum (nujol): 3480 (OH) and 1740 cm$^{-1}$ (ester group).

*Anal.* Found: C, 67.46; H, 5.51. Calcd. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21%.

From the above benzene filtrate, after removal of the solvent and crystallization from aqueous methanol, 100 mg. of methyl 2-methoxy-5-hydroxy-1-naphthyl acetate (VII), m. p. 146~149°C, was obtained. An analytical sample, obtained by recrystallization from a small amount of benzene, had m. p. 155.5~156.5°C.

Infrared spectrum[12]: 3400 (OH) and 1720 cm$^{-1}$ (ester group).

*Anal.* Found: C, 68.15; H, 5.95. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73%.

**Acetylation of the Tetralon Derivative (IV).**—The keto acid (IV) (47 mg.) was added to a solution of acetic anhydride (0.5 cc.) in anhydrous pyridine (1.5 cc.) and the mixture was allowed to stand overnight. After concentration of the reaction mixture to a small volume, water and 2 N hydrochloric acid were added. The mixture was then shaken three times with ethyl acetate. The organic layers were combined, washed twice with water and dried over sodium sulfate. Removal of the solvent in vacuo left 33 mg. of an oily residue from which on trituration with petroleum ether, 24 mg. of crystalline material was obtained. For analysis the product was recrystallized from benzene, m. p. 176~176.5°C.

Ultraviolet absorption band at 276 m$\mu$ (log $\varepsilon$ 4.22).

*Anal.* Found: C, 63.86; H, 4.67. Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67%.

*Dissociation constants* of III and IV were measured at 25°C in 50% ethanol using HRL model M-3 pH meter.

## Summary

1, 2, 3, 4-Tetrahydro-5-hydroxy-1-naphthylacetic acid has been obtained from 2-methoxy-5-hydroxy-1-naphthylacetic acid by reduction either with sodium and *n*-butanol, or with lithium and liquid ammonia-ethanol. In the former case, under moderate conditions, 1, 2, 3, 4-tetrahydro-2-oxo-4, 5-dihydroxy-1-naphthylacetic acid has been isolated as a by-product.

*Department of Chemistry*
*Faculty of Science*
*Hokkaido University*
*Sapporo*

12) In the 1650~1500 cm$^{-1}$ region, the dihydroxynaphthylacetate (VI) absorbs at 1630, 1608, 1590, 1524 cm$^{-1}$. See Ref. 1.