the up-and-down method are approximate but closely similiar to the one by the probit analysis, and the computation in the former is, in fact, far less laborious than the one in the latter.

Therefore, the up-and-down method can be recommended as a pilot test[5], when the ED_{50} of the stimulus in question is entirely unknown, and each test does not need long periods. Thus, after sufficient experimental data are obtained, the way to analyse the results is just up to the experimenter's choice, depending on his practical purpose. Thereafter, he may sequentially perform the up-and-down procedure to the pilot test until he will get the desirable fiducial interval, or on the other hand, he may plan the standard probit method for the estimation, based upon the results obtained by the previous pilot test, or he may take the modified up-and-down method by the simultaneous performance of several short up-and-down series[5], if each test needs considerably long period.

Summary

The original up-and-down method was applied for the mouse method of insulin assay and the results were compared to the one analyzed by the probit analysis. The biological significance of ED_{50} obtained by the up-and-down method was discussed in comparison with the one by the standard probit method.

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53. Tyunosin Ukita and Satoshi Nakazawa : Santonin Analogs. III.* On Monocarboxylic Acid obtained from Dihydroalantolactone.

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An interesting observation during the catalytic hydrogenation of dihydroalantolactone (I) was reported in the 1st paper of this series[1]. Thus, although, dihydroisoalantolactone (III) quantitatively yielded tetrahydroalantolactone (II) after consumption of one mole of hydrogen, smaller yield of (II) was obtained in the case of dihydroalantolactone (I) after an exceeded consumption of hydrogen.

This paper describes the isolation and identification of a monocarboxylic acid from a mixture of catalytic hydrogenation products of (I).

The hydrogenation of (I) with both Adams' platinum oxide in glacial acetic acid and 6% palladium-charcoal in ethanol produced a saturated monocarboxylic acid (IV) in the yields of 65.7% and 16.6%, respectively. (II) was the other component in these reaction mixtures.

(IV) was recrystallized from aqueous methanol to give small cubelets, $C_{15}H_{26}O_2$, m.p. 65~67°, $[\alpha]_D^{17}$: +36.1°, and this saturated acid was converted to an acid amide (V), $C_{15}H_{27}ON$, m.p. 138~140°. Methylation of (IV) with diazomethane gave a methyl ester (VI), $C_{16}H_{28}O_2$, $b.p_{0.05}$ 91°, which was reduced to a carbinol (VII), $C_{15}H_{28}O$, $b.p_{0.1}$ 116°, by lithium aluminum hydride. (IV) was recovered again from (VII) by oxidation with dichromate.

* Part II : J. Pharm. Soc. Japan, **72**, 1327(1952).

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1) T. Ukita, R. Matsuda, S. Nakazawa : J. Pharm. Soc. Japan, **72**, 796 (1952).

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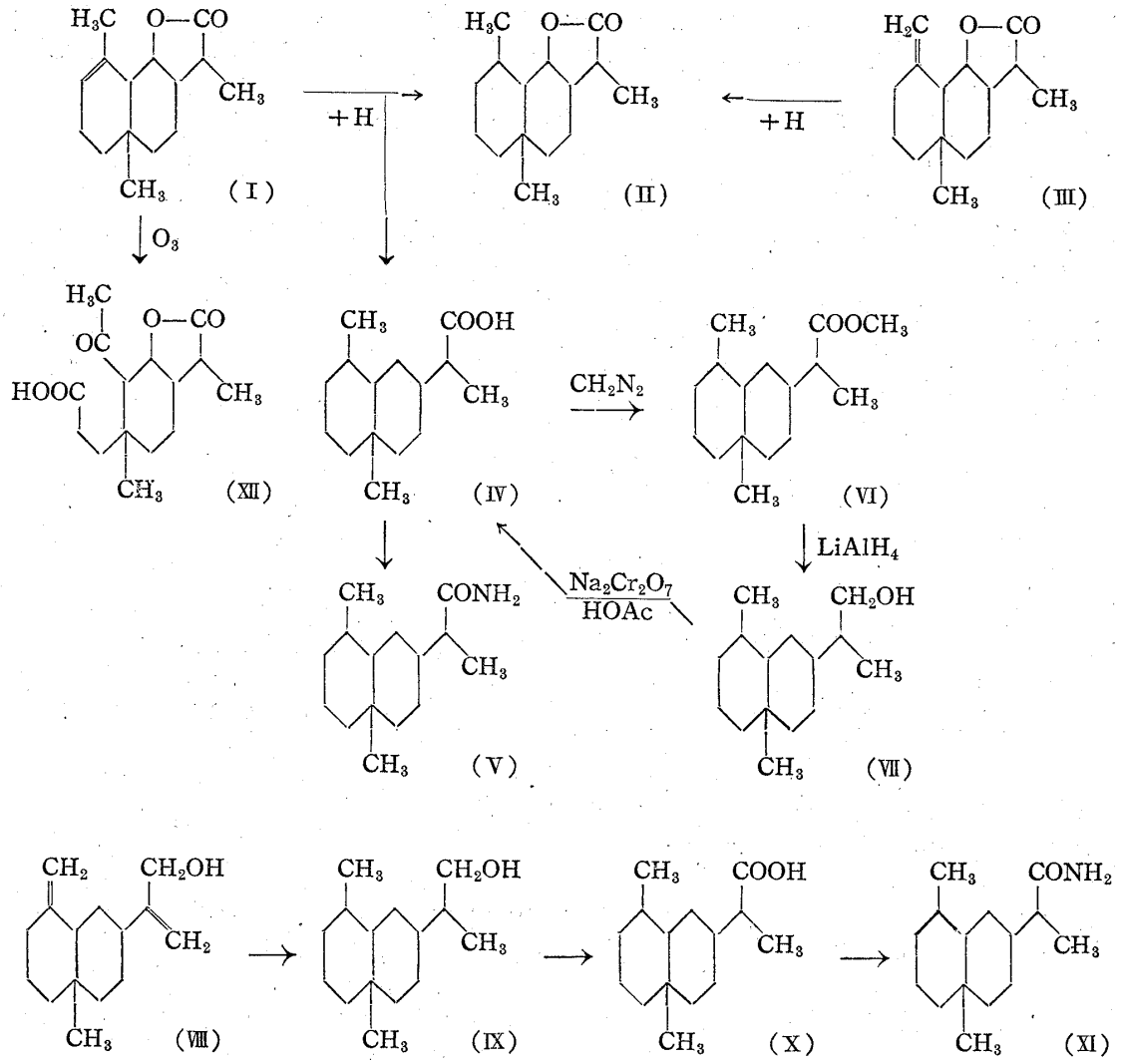

Some time ago, Katsura[2] postulated structure (VIII) for sesquibenihiol, $C_{15}H_{24}O$, b.p$_3$ 137°, $[\alpha]_D^{18}$: +8.84°, an unsaturated alcohol isolated by the author from an oil from the root of *Chamaecyparis formosensis* Matsum.

Catalytic hydrogenation of (VIII) gave a tetrahydro derivative (IX), $C_{15}H_{28}O$, b.p$_3$ 140°, $[\alpha]_D^{18}$: +14.80°, and on further oxidation of the latter, a saturated monocarboxylic acid, $C_{15}H_{26}O_2$, was obtained to which the structure (X) was assigned. The acid amide (XI) of (X) was reported to have a melting point of 137~138°. Comparing the optical rotation of tetrahydro-alcohol (IX) with that of (VII), and further the melting point of the acid amide (XI) with that of (V) (cf. Table I), it seemed very reasonable that (IV), (V), and (VII) may be the same compounds as (X), (XI), and (IX), respectively.

TABLE I.

	Specific Rotation		m.p., °C
Tetrahydrosesquibenihiol (IX)	$[\alpha]_D^{18}$: +14.80°	Amide (XI)	137~138
Saturated alcohol (VII)	$[\alpha]_D^{14}$: +14.6°	Amide (V)	138~140

On admixture of (V) with (XI)[3] no depression of the melting point was observed. Therefore, the structure of the saturated acid obtained by the catalytic hydrogenation of of (I) must be (IV).

The structure of dihydroalantolactone (I) has already been established both by Ruzicka,

2) S. Katsura : J. Chem. Soc. Japan, **63**, 1465(1942).
3) The authors thank Dr. S. Katsura from whom the preparation of this compound was obtained.

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et al.[4] and by Hansen[5], and the position of its double bond was confirmed by them to be $\Delta^{1,2}$ from the results of ozonolysis of (I). Furthermore, the present authors also confirmed the position by the same oxidation procedure yielding a keto-carboxylic acid (XII)[1], $C_{15}H_{22}O_5$, m.p. 193~195°. It is of interest that a saturated monocarboxylic acid is obtained by the catalytic reduction of (I).

The catalytic hydrogenolysis of the enol-lactones has been observed by Asahina, *et al.*[6] and Jacobs, *et al.*[7], and a similar hydrogenolysis for α,β-unsaturated acetoxyl group was reported recently by Carter, *et al.*[8] It is of interest that hydrogenolysis has been observed for a lactonic hydroxyl group having a double bond in its β,γ-position. Research is being continued on the mechanism of this reaction.

The authors are indebted to Prof. S. Akiya for his encouragement, and wish to thank Misses R. Ohta, E. Kondo, and Mr. B. Kurihara for carrying out the microanalyses.

Experimental

Catalytic Hydrogenation of Dihydroalantolactone—a) Using Adams' Platinum Catalyst: A solution of 0.70 g. of dihydroalantolactone in 50 cc. of glacial AcOH was poured into a suspension of active platinum prepared from 0.35 g. of Adams' platinum oxide in 20 cc. of glacial AcOH. The mixture was shaken in a hydrogen atmosphere, and 126 cc. of hydrogen was consumed during 4 hrs. at 15°, 756.4 mm. Hg (calcd. for one double bond, 72 cc.). After removal of the catalyst by filtration, the solvent was evaporated *in vacuo*. The residue was separated into acidic and neutral parts by shaking with 5% sodium carbonate solution and ether, respectively. On standing, the oily acidic fraction crystallized; yield, 0.46 g. This was recrystallized from aq. MeOH to give colorless cubelets, m.p. 65~67°. *Anal.* Calcd. for $C_{15}H_{23}O_2$: C, 75.63; H, 10.92; COOH, 18.91. Found: C, 75.56; H, 10.59; COOH, 18.60. $[\alpha]_D^{17}$: +36.1° (24.927 mg./cc. in EtOH).

The crystalline neutral fraction was identified as tetrahydroalantolactone; yield, 0.23 g.

b) Using Palladium-charcoal as a Catalyst: A solution of 0.12 g. of dihydroalantolactone was reduced in a similar manner using 0.27 g. of 6% palladium-charcoal in 40 cc. of EtOH. The amount of hydrogen consumed was 17 cc. during 4 hrs. under the condition of 19°, 763 mm. Hg (calcd. for one double bond, 12.5 cc.). The reaction mixture was treated as described above to give 0.02 g. of monocarboxylic acid and 0.10 g. of tetrahydroalantolactone. The monocarboxylic acid was identical with that from (a).

The hydrogenation curves for both (a) and (b) are shown in Fig. 1. The greater yield of the acidic compound obtained from the reaction mixture of (a) is in agreement with the increased hydrogen consumption shown in curve (a). Likewise, a smaller yield of this compound was obtained from the reaction mixture of (b) which is also in agreement with the lower hydrogen consumption shown in curve (b).

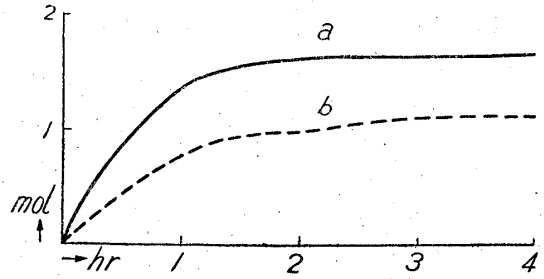

Fig. 1. Hydrogenation Curves of Dihydroalantolactone

a: Platinum oxide in glacial acetic acid.
b: Palladium-charcoal in ethanol.

Methyl Ester (VI) of Monocarboxylic Acid (IV)—1.14 g. of (IV) was dissolved in ether and methylated by the ordinary diazomethane procedure. A colorless oily ester was obtained; yield, 1.14 g. This was purified by distillation, b.$p_{0.05}$ 91°. *Anal.* Calcd. for $C_{16}H_{28}O_2$: C, 76.19; H, 11.11. Found: C, 76.38; H, 10.97. $[\alpha]_D^{17}$: +41.4° (27.776 mg./cc. in EtOH).

Reduction of (VI) with Lithium Aluminum Hydride—To an ethereal solution of 0.50 g. of $LiAlH_4$,

4) L. Ruzicka, P. Pieth: Helv. Chim. Acta, **14**, 1090(1931).
5) Karl Fr. W. Hansen: J. prakt. Chem., (N. F.) **136**, 176(1933).
6) Y. Asahina, A. Fujita: J. Pharm. Soc. Japan, **39**, 471(1919).
7) W. A. Jacobs, A. B. Scott: J. Biol. Chem., **87**, 601(1930).
8) H. E. Carter, F. H. Glick, W. P. Norris, G. E. Phillips: *Ibid.*, **170**, 285(1947); H. E. Carter, C. G. Humiston: *Ibid.*, **191**, 727(1951).

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an ethereal solution of 1.53 g. of (VI) was added dropwise with stirring. After additional 2 hours of stirring, the mixture was treated in a usual manner giving 1.40 g. of a crude product. Distillation gave a colorless oil, b.$p_{0.1}$ 116°. *Anal.* Calcd. for $C_{15}H_{23}O$: C, 80.36; H, 12.12. Found: C, 80.37; C, 12.08. $[\alpha]_D^{14}$: +14.6° (26.027 mg./cc. in EtOH).

Oxidation of (VII)—To a solution of 0.19 g. of (VII) in 4 cc. of glacial AcOH was added dropwise a solution of 0.09 g. of sodium dichromate in 2 cc. of the same solvent. The reaction mixture was poured into 30 cc. of water and extracted with ether. The ethereal solution was shaken with 5% Na_2CO_3 solution and the aqueous layer was acidified to give 0.12 g. of an acidic compound. After recrystallization from aq. MeOH the product was found to be identical with the monocarboxylic acid (IV).

Amide of (IV)—0.64 g. of (IV) was warmed with 1.5 cc. of $SOCl_2$ on a steam bath at 40° for an hour. The excess of the reagent was removed by distillation, and the residue was poured into aq. ammonia. The solidified acid amide, 0.60 g., was successively recrystallized from petroleum benzine and aq. MeOH to yield colorless needles, m.p. 138~140°. On admixture of this amide with the preparation[3] obtained from the oxidation of tetrahydrosesquibenihiol no depression of the melting point was observed. *Anal.* Calcd. for $C_{15}H_{27}ON$: C, 75.95; H, 11.39; N, 5.91. Found: C, 76.36; H, 11.41; N, 5.81. $[\alpha]_D^{17}$: +31.7° (23.619 mg./cc. in EtOH).

Summary

A saturated monocarboxylic acid, $C_{15}H_{26}O_2$, was isolated from the reaction mixture of catalytic hydrogenation of dihydroalantolactone, and the structure of this compound was confirmed to be 1,10-dimethyl-7-(2'-carboxyethyl)-decaline by comparison with the oxidation product of tetrahydrosesquibenihiol.

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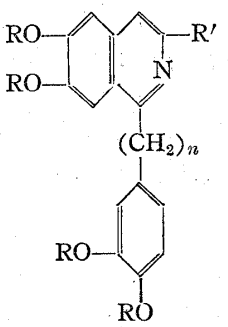
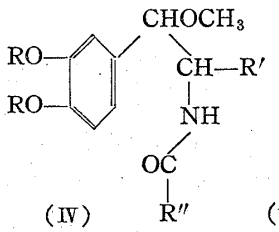
54. Shigehiko Sugasawa and Tohru Hino: Synthesis of 1-(3,4-Methylenedioxyphenyl)-3,5-dimethyl-7,8-methylenedioxyisoquinoline.

(*Pharmaceutical Instituie, Medical Faculty, University of Tokyo**)

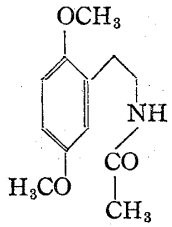
The well-known isoquinoline type of spasmolytics such as papaverine (I), eupaverine (II), and neupaverine (III) bases are all 1-substituted 6,7-dihydroxyisoquinoline derivatives which can be synthesized by cyclizing appropriately substituted β-(3,4-dihydroxyphenethyl)-amides (IV) with phosphoryl chloride. In these cases the cyclization takes place only at 6-position, i.e. *para* to the 3-hydroxyl group. That the isoquinoline ring-closure



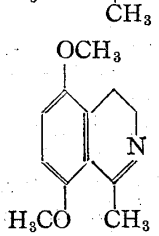
I : R=CH_3, R'=H, n=1
II : R-R=-CH_2-, R'=CH_3, n=1
III : R-R=-CH_2-, R'=CH_3, n=0



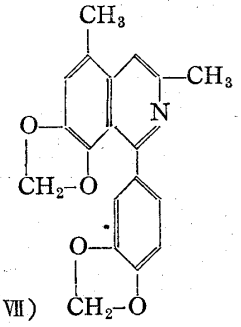
(IV)



(V)



(VI)



(VII)

* Hongo, Tokyo (菅沢重彦, 日野 亨).

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