was continued at a higher temperature for 3 hrs. The mixture was cooled to about 100° and poured into 50 cc. of water. To this was added with stirring dil. HCl. The thick, gelatinous, colorless solid that separated was digested for 1 hr., collected by filtration, washed with water, and dried. A crude yield of 93% was obtained. m.p. 84~85°. Mixed with the keto-acid (26), m.p. 84~85°, the depression was only 2°.

Summary

ω-Phenyl-fatty acids, ω-phenyl-caproic, -enanthic, -caprylic, -pelargonic, -capric, -undecanoic, -lauric, -tridecanoic, -myristic, -palmitic, -stearic, -arachidic, and -behenic acids, were prepared.

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84. Masao Tomita, Yasuo Inubushi, and Kazuo Ito: Studies on the Alkaloids of Menispermaceous Plants. CXIX.[1] A Bisected Phenolic Product from the Cleavage of Tetrandrine and Isotetrandrine with Metallic Sodium in Liquid Ammonia.

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Several years ago, Tomita, Fujita, and Murai reported that on the fission of isotetrandrine (I(−, +))[2] and tetrandrine (I(+, +))[3] with sodium in liquid ammonia, the former yielded as the bisected bases *l*-O,O,N-trimethylcoclaurine (II) and *d*-N-methylcoclaurine (III), and the latter, *d*-O, O, N-trimethylcoclaurine (II) and *d*-N-methylcoclaurine (III), respectively; and that *d*-N-methylcoclaurine (III) thus obtained formed from methanol colorless prisms, m.p. 139~139.5°, $[\alpha]_D^{16}$: +88.51° ($CHCl_3$), which by analyses, were found to be a hemihydrate with an empirical formula $C_{18}H_{21}O_3N \cdot \frac{1}{2}H_2O$.

Very recently, however, Kidd and Walker[4] applied the same mode of fission process to phaeanthine (I(−, −)), an antipode of tetrandrine (I(+, +)), and O,O-dimethylcurine (IV), and reported that of the two bases (II) and (III) obtained, *l*-N-methylcoclaurine (III), a phenolic base, gave colorless prisms (from benzene or toluene), m.p. 176~177°, $[\alpha]_D^{23}$: -69.6° ($CHCl_3$), corresponding to a composition of $C_{18}H_{21}O_3N$.

It is well established that *dl*-N-methylcoclaurine, when derived from the naturally occurring coclaurine by Tomita and Kusuda,[5] as well as when synthesized by Kidd and Walker,[4] has a definite m.p. of 161~162°. However, a doubt has arisen from the fact that of its optically active substances, the *d*-form shows m.p. 139~139.5°, whereas the *l*-form, m.p. 176~177°, and hence it has become necessary to reinvestigate the *d*-form (III).

On the other hand, just prior to the above British investigators, Bick and Clezy[6] also carried out similar cleavage reactions of O,O-dimethylcurine, O,O-dimethylchondrocurine, phaeanthine, and isotetrandrine, but they characterized the bisected bases as the methiodides or O-methyl ether methiodides without isolating them *per se*. As a result, no further records with reference to the m.p. of N-methylcoclaurine (III) of the bisected bases are available.

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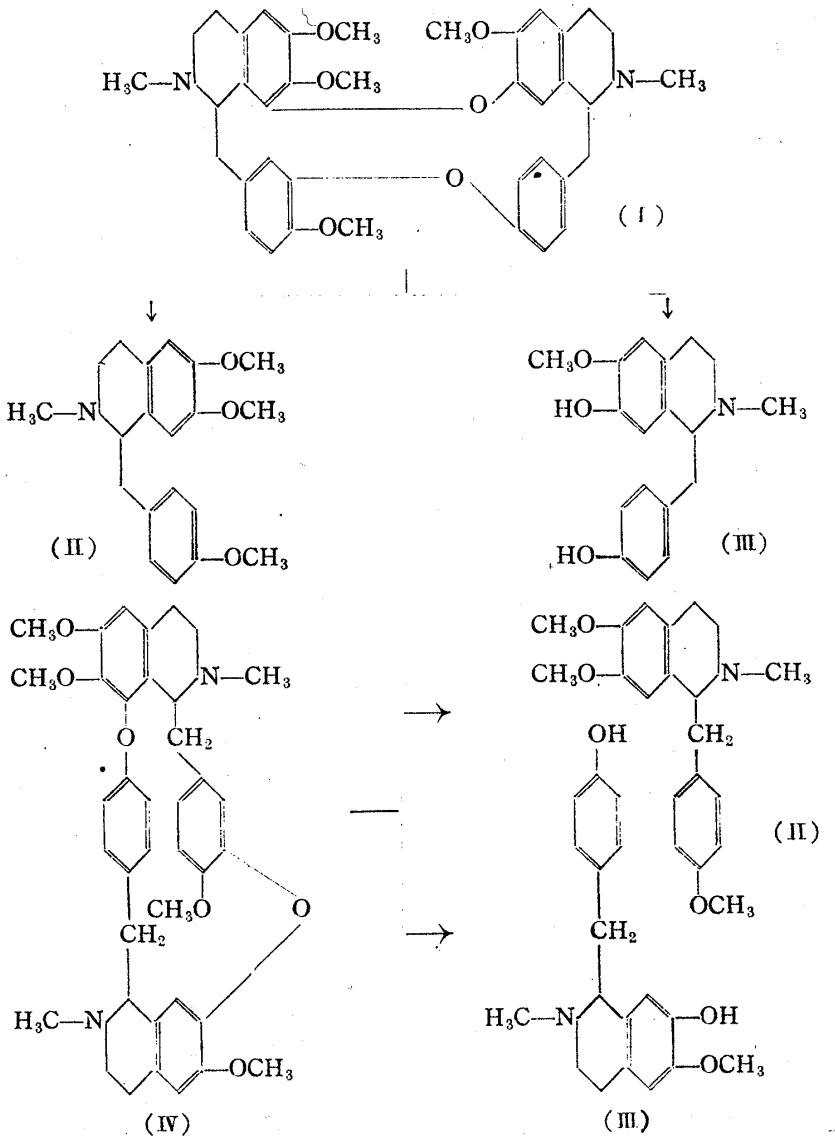

In view of the fact that the *l*-form (m.p. 176~177°), which crystallized from benzene or toluene, has a molecular formula $C_{18}H_{21}O_2N$, whereas the *d*-form (m.p. 139~139.5°) which crystallized from methanol, the molecular formula $C_{18}H_{21}O_3N \cdot \frac{1}{2}H_2O$, the first assumption was that the *d*-form having the m.p. of 139~139.5° may hold a solvent of crystallization.

When the m.p. of a specimen[7] of the *d*-form (III) obtained by the sodium-liquid ammonia fission of isotetrandrine was again measured, it began to sinter at 140° and finally melted at 176~177°. Further recrystallization of this specimen from benzene gave floral aggregates of colorless needles melting at 176~177°. Contrary to this, the m.p. of a specimen[8] of the *d*-form (III) obtained by the same mode of cleavage of tetrandrine was again determined and showed m.p. 176~177°. This phenomenon may be accounted for by the assumption that the substance forming a hemihydrate, m.p. 139~139.5°, just after preparation, forms an anhydrate with elimination of water of crystallization after preservation for a long period of time. Measurement of the m.p. of specimen[9] of the crude substance preserved show about 140°, which after recrystallization from toluene,

7) This specimen had been preserved in this Laboratory since 1951 and recorded as m.p. 139~139.5°.
8) This specimen also had been preseved since 1951 and recorded as m.p. 138~139.5°.
9) Recorded m.p. 136~137°.

rose to 176~177°

In order to clarify these situations, we have again taken up an investigation of isotetrandrine by the sodium-liquid ammonia process in the same way as in the previous paper[2]. When the crude phenolic base hereby obtained was recrystallized from benzene or toluene, it formed colorless prisms melting at 176~177°. On the other hand, however, when it was recrystallized from methanol, in one case, crystals, m.p. 176~177°, were directly obtained, instead of crystals of m.p. 139°, and in another case, prisms of m.p. 138~140° were obtained. These facts may be due to the conditions of recrystallization, depending upon the amount of water or moisture contained in the slovent methanol.

The crystals having m.p. 138~140° melted at 138~140° with some effervescence and on cooling solidified, after which on subsequent heating, they melted at 176~177°, without sintering at 140° any longer. When the crystals, m.p. 138~140°, were further recrystallized from anhydrous ethanol or benzene, they crystallized in colorless prisms melting at 176~177°. Recrystallization of the crystals, m.p. 176~177°, thus obtained, from methanol or hydrous methanol did not furnish a hemihydrate, m.p. 139°, but a product sintering at 140° and finally melting at 176~177°. As a result of the mixed melting point determinations, these crystals showing m.p. 176~177° were found to be identical, and to possess analytical values corresponding to a composition $C_{18}H_{21}O_3N$, having no water of crystallization, $[\alpha]_D^{30}$: +62.8°. Furthermore, the paper chromatography of the *d*-form, m.p. 176~177°, and *dl*-form,[5] m.p. 161~162°, revealed that the two substances have the same Rf value of 0.73.[10]

The foregoing results are thus summarized as follows: *d*-N-Methylcoclaurine, when recrystallized from methanol, is obtained as a hemihydrate, m.p. 139~140°, in some cases, which, after preservation for a long period of time, becomes an anhydrate with elimination of the water of crystallization. On the other hand, however, when it is recrystallized from toluene or benzene instead, it is obtained as m.p. 176~177°, quite identical with that recorded by Kidd and Walker for *l*-N-methylcoclaurine, m.p. 176~177°.

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Experimental[11]

Cleavage of Isotetrandrine by Metallic Sodium in Liquid Ammonia—(a) A solution of 2 g. of isotetrandrine in a mixture of 15 cc. of benzene and 15 cc. of toluene was added dropwise to about 300 cc. of liquid NH_3 placed in a 1-L. three-necked flask. The temperature was kept at -35°, and 1.5 g. of Na was then added in small portions with vigorous stirring until the blue color of the solution persisted for about half an hour, whereafter the mixture of an orange yellow color was kept overnight to permit evaporation of NH_3. The residue was treated with 100 cc. of water and the resulting solution was extracted with several portions of ether. The ethereal phase was washed with 2% NaOH solution and the alkaline washings were combined with the aqueous layer. The ether-benzene-toluene solution was exhaustively extracted with 5% HCl, and the extract made alkaline with 2% aq. NaOH. The non-phenolic base was re-extracted with ether, and the ethereal solution was dried over anhyd. K_2CO_3 and evaporated, yielding 0.86 g. of an orange red oil.

Meanwhile, the aqueous layer containing the phenolic fraction was neutralized with HCl, made alkaline with K_2CO_3, and extracted with ether. The ethereal phase was washed with 2% NaOH solution, to which the phenolic base was transferred. The resulting alkaline solution was made acid with HCl and, after being alkalized with K_2CO_3, re-extracted with ether. The ethereal solution was dried over anhyd. K_2CO_3 and the ether removed, leaving the crude phenolic base as an orange oil. The oil was dissolved in a small amount of acetone and ether, and the solution allowed to stand,

10) As described in the experimental section, it was carried out according to the method of Kidd and Walker; they also recorded Rf value of 0.73 for the *l*-form and *dl*-form.

11) All melting points are uncorrected. The microanalyses were carried out in the Microanalytical Laboratory of this Institute by Mr. K. Hozumi and his staff.

whereupon 0.57 g. of slightly yellowish crystals of m.p. 168~173° deposited. Further recrystallization from benzene or toluene yielded floral aggregates of colorless needles, m.p. 176~177°; $[\alpha]_D^{30}$: +62.8° (7.966 mg. Subst. in 1 cc. $CHCl_3$, l=0.5 dm.). *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.10. Found: C, 72.26; H, 7.19.

(b) 2 g. of isotetrandrine dissolved in 20 cc. of toluene was cleaved by a procedure similar to that described in the previous paper[2] and the products were separated as above. The yellowish oily phenolic fraction was dissolved in a small portion of MeOH, and by allowing the solution to stand, 0.6 g. of the crude white crystals were obtained. By recrystallization from MeOH they crystallized in colorless prisms. A sample, when heated, melted at 138~140° with frothing, and upon cooling solidified, after which, when again heated, it melted at 176~177° without melting at around 140° any longer. Crystallization from abs. EtOH or benzene, however, did not afford the product of m.p. 138~140°, but of m.p. 176~177°.

Paper Chromatography—The paper chromatography was carried out according to the method of Kidd and Walker.[4] Toyo Roshi No. 50 paper was immersed in 0.2 *M* aq. KH_2PO_4, pressed between filter papers to remove excess of the liquid, dried at 100°, and allowed to equilibrate against atmospheric moisture for several hours before use. Development was effected by the descending method with the upper layer of a mixture of 63 cc. BuOH, 10 cc. AcOH, and 27 cc. of water. The Rf values for *d*-N-methylcoclaurine (m.p. 176~177°) obtained by the above fission, and for *dl*-N-methylcoclaurine[5] (m.p. 161~162°)(ca. 60 γ used in each case) were both 0.73 using the Dragendorff reagent.

Summary

Evidence has been presented that *d*-N-methylcoclaurine (III) forms a hemihydrate having the m.p. of 139~139.5°, and its anhydrate shows the m.p. 176~177°, quite identical with that recorded by Kidd and Walker[4] for *l*-N-methylcoclaurine, m.p. 176~177°.

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85. **Masao Tomita and Yoshio Sasaki**: Studies on the Alkaloids of Menispermaceous Plants. CXX[1]. Cleavage of Cepharanthine by Metallic Sodium in Liquid Ammonia. (3)[2].

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In an earlier paper[2] of this series, it was shown that as a result of the fission of cepharanthine (I) by the sodium-liquid ammonia process, a base possessing two phenolic hydroxyl and no methoxyl groups, corresponding to *d*-1-(4′-hydroxybenzyl)-6-hydroxy-N-methlyl-1,2,3,4-tetraydroisoquinoline (II), was obtained in a crystalline form after chromatography, and on this basis formula (I) was proposed for cepharanthine. At that time, however, attempts to isolate the other phenolic fragment in crystalline form, corresponding to *l*-1-(4′-methoxybenzyl)-6-methoxy-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (III), were unsuccessful. Although the *l*- and *d*-forms of (III) were obtained previously from O-methyloxyacanthine[3] and O-methylrepandine,[4] respectively, by the same mode of cleavage, at that time, they were characterized as the corresponding *l*- and *d*-O,O,N-trimethylcoclaurine (IV), respectively, because of the difficulty of crystallization.

In the present series of experiments, special attention was placed on the base (III) obtainable by the cleavage of cepharanthine, and this paper deals with the isolation of this particular base (III) from the resinous phenolic fraction left after the removal of the base (II). As described in the experimental section, a product forming a crystalline

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