ammonia to evaporate. The residue is then treated as usual, and separated into a non-phenolic and a phenolic base. By recrystallization of the non-phenolic base from acetone, colorless long plates, m.p. 271°, are obtained, but this is the original cycleanine. Thus about 0.5 g. of cycleanine is recovered.

Treatment of the phenolic base, *l*-1-(4'-hydroxybenzyl)-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (*l*-armepavine) (II)—The yield of the crude bisected phenolic base obtained by this reaction is about 0.75 g. This substance is easily obtained as colorless prismatic crystals, m.p. 139–140°, from a mixed solvent of acetone and ether. By further purification through the oxalate, the pure free base is obtained as colorless prismatic crystals, m.p. 145–146°. This substance often contains 1 mol. of crystal-water according to the condition of recrystallization and in such a case, it melts once at about 100°. $[\alpha]_D^{25} = -109.1^\circ$ (subst. 0.1020 g. in 7 cc. CHCl_3 , $l=1\text{ dm.}$). *Anal.* Calcd. for $\text{C}_{19}\text{H}_{25}\text{O}_3\text{N}$: C, 72.84; H, 7.31; OCH_3 , 19.84. Found: C, 73.11; H, 7.12; OCH_3 , 20.10.

The oxalate is obtained as crystalline deposits comparatively difficult to dissolve in alcohol by the addition of an alcoholic solution of oxalic acid to an alcoholic solution of the free base. By recrystallization from alcohol, it is obtained as colorless needle crystals, m.p. 211–212°. The hydrochloride is gained as colorless needle crystals, m.p. 150–151°, from a mixture of alcohol and ether.

By methylation of this phenolic base with diazomethane in ethereal solution, a non-phenolic base is obtained as colorless prismatic crystals, m.p. 58°, and this substance has the identical properties with *l*-1-(4'-methoxybenzyl)-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (III) (m.p. 62°). We have certified that these are identical by the mixed melting point determination.

Summary

When cycleanine (I) is reacted with metallic sodium in liquid ammonia, it is bisected into *l*-1-(4'-hydroxybenzyl)-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (*l*-armepavine) (II). Therefore, it has been confirmed that the structure of cycleanine and the steric configuration of the two asymmetric centers in the molecule must be represented by (I).

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312. Masao Tomita, Kohei Nakaguchi and Shuzo Takagi: Studies on the Alkaloids of Menispermaceous Plants. LXXXV.* Studies on the Syntheses of Coclaurine and Analogous Compounds. (2). Synthesis of *dl*-Coclaurine.

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Coclaurine¹⁾ is an alkaloid contained in *Cocculus laurifolius*, D.C., that was discovered for the first time by H. Kondo and T. Kondo, and its chemical constitution was settled as (I) as a consequence of several decompositions and synthetic reactions. This alkaloid is regarded with great importance as the original substance of biscoclaurine alkaloids. Several years ago, we began the study on the syntheses of coclaurine and analogous compounds, and, first of all, we synthesized *dl*-4'-methyl-coclaurine (II), which we

* Part LXXXIV: H. Kondo, M. Satomi and T. Odera: The Annual Report of Itsuu Laboratory, **2**, 35 (1951).

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1) H. Kondo and T. Kondo: This Journal, **45**, 876 (1925); *ibid.*, **46**, 1029 (1926); *ibid.*, **48**, 324, 1156 (1928); *ibid.*, **50**, 427 (1930); J. prakt. Chem., **126**, 24 (1930).

reported²⁾ already. We have lately succeeded in the synthesis of *dl*-coclaurine. Meanwhile, on a quite different standpoint from our study, Finkelstein³⁾ has recently synthesized the same substance and reported his result.

When the synthetic procedures of his and ours are compared, the courses are almost identical, the difference being as follows. While the raw materials Finkelstein used were β -(3-methoxy-4-benzyloxy)-phenylethylamine (III) and 4-carbethoxyhydroxyphenylacetyl chloride (IV, $R = -COOC_2H_5$), we used (III) and 4-benzyloxyphenylacetyl chloride (IV, $R = -CH_2C_6H_5$). In other words, the keypoint of this synthesis consisted in the problem of how to protect the phenolic hydroxyl group in the *p*-position of a benzyl radical in the benzylisoquinoline ring during the synthetic processes.

In the present paper, we describe the synthesis of *dl*-coclaurine by our own method, which is as follows:

By the saponification of 4-benzyloxybenzyl cyanide, m.p. 68.5–69°, by alkali, 4-benzyloxyphenylacetic acid is obtained. This substance crystallizes, melts at 121°, and the analytical data are quite identical with the calculated formula. Weiss⁴⁾ prepared this substance via *p*-hydroxyacetophenone $\rightarrow$ *p*-benzyloxy-acetophenone $\rightarrow$ *p*-benzyloxy-phenylthiomorpholide, describing m.p. as 114°; and Corse, et al.,⁵⁾ prepared this substance from ethyl *p*-hydroxyphenyl acetate, showing the m.p. as 120–121°. The substance we obtained indicates the m.p. identical with those of the report made by Corse, et al.

2) M. Tomita, K. Nakaguchi and S. Takagi: This Journal, **70**, 44 (1950); C.A. **44**, 5887 (1950).

3) J. Finkelstein: J. Am. Chem. Soc., **73**, 550 (1951).

4) P. Weiss: J. Am. Chem. Soc., **70**, 4263 (1948).

5) J. W. Corse, R. G. Jones, Q. F. Soper, C. W. Whitehead and O. K. Behrens: J. Am. Chem. Soc., **70**, 2837 (1948).

By the chlorination of 4-benzyloxyphenylacetic acid with phosphorus pentachloride, the acid chloride is obtained as colorless scaly crystals, m.p. 72–74°. Then, by employing the Schotten-Baumann method with 3-methoxy-4-benzyloxyphenylethylamine (III) and the above acid chloride (IV, $R = -CH_2C_6H_5$), an acid amide (V), m.p. 115–117°, is formed. The isoquinoline cyclization of this substance by phosphorus oxychloride in chloroform solution yields a dihydroisoquinoline derivative (VI) (hydrochloride, m.p. 197°). By its reduction with powdered zinc in acetic acid, a tetrahydroisoquinoline derivative (VII) (hydrochloride, m.p. 192°) is gained. Finally, as a result of its debenzilation by boiling it with a mixture of hydrochloric acid and acetic acid, we obtained *dl*-coclaurine, i.e. 1-(4'-hydroxybenzyl)-6-methoxy-7-hydroxy-1, 2, 3, 4-tetrahydroisoquinoline (I). The hydrochloride of this substance is obtained as colorless needle crystals, m.p. 258–259°, and this substance, dried at 100° over phosphorus pentoxide under reduced pressure, corresponds to $C_{17}H_{19}O_3N \cdot HCl \cdot \frac{1}{2} H_2O$ according to its analysis. Comparison of the data of the substance we obtained with the *dl*-coclaurine hydrochloride Finkelstein has prepared show both to be quite identical. He, too, indicates that *dl*-coclaurine hydrochloride forms a hydrate; and, even by hot drying under reduced pressure, it forms a hemi-hydrate without the complete removal of crystal water.

The tribenzoate of *dl*-coclaurine is derived as colorless needle crystals, m.p. 210°.

Of this study, the latter half of the researches were carried out by K. Nakaguchi, one of the authors, in the Research Laboratory of The Nissin Chem. Ind. Co., Ltd., at Niihama, and we wish to express hereby our profound gratitude to its Research Director, Dr. T. Fujimura, who allowed the use of laboratory facilities.

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Experimental

4-Benzyloxybenzyl Cyanide—11.5 g. of potassium hydroxide is dissolved in 115 cc. of alcohol and, to this solution, 23 g. of 4-hydroxybenzyl cyanide, and then, 25 g. of benzyl chloride, are added, and the mixture is boiled with reflux. About 2 hrs. later, this is cooled and the deposited crystals are filtered, the alcohol of the filtrate evaporated, and again the deposited crystals are collected. The crystals thus obtained are recrystallized from methanol containing water. Yield, 28.5 g. Once more the crystals are dissolved in ether, shaken with dil. solution of sodium hydroxide and, after washing with water, the ether is distilled off. By recrystallization from methanol, colorless scaly crystals, m.p. 68.5–69°, are obtained.

4-Benzyloxyphenylacetic Acid—2.2 g. of potassium hydroxide is dissolved in 4.3 cc. of water, 13 cc. of alcohol added, and then, 6.35 g. of 4-benzyloxybenzyl cyanide is added, and the mixture is boiled with reflux. About 0.5 hr. later, crystals of the amide deposits but, by further continuation of the reaction, the crystals again dissolve in the reaction mixture. A solution of 2.2 g. of potassium hydroxide in 4.3 cc. of water is added 5 hrs. later, and this is heated for 1 hr. When a drop of the reaction-liquor dissolves transparently in water, the reaction is stopped. After its cooling, water is added, the mixture acidified by hydrochloric acid, and the precipitate is filtered. This precipitate is extracted with methanol, the insoluble materials are removed and the crystals deposit by the addition of water. Yield, 6.17 g. By further recrystallization from methanol, scaly crystals m.p. 121°, are obtained. *Anal.* Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.62; H, 5.97.

4-Benzyloxyphenylacetyl Chloride (IV, $R = -CH_2C_6H_5$)—To 1.68 g. of 4-benzyloxyphenylacetic acid, 1.44 g. of phosphorus pentachloride is added and, by warming in a water bath at 65–70°, the mixture fuses, evolving HCl gas. Twenty minutes later, when the mixture becomes a uniform solution, the heating is stopped, and crystals deposit by cooling. These crystals are collected and recrystallized from ligroin (b.p. 60–120°), to colorless scaly crystals, m.p. 72–74°.

***N*-(3-Methoxy-4-benzyloxyphenethyl)-4'-benzyloxy-phenacetamide (V)**—3.8 g. of phosphorus pentachloride and 4.4 g. of 4-benzyloxyphenylacetic acid are mixed, 20 cc. of completely anhydrous ligroin (b.p. 60–120°) added, and the mixture is warmed at 65–70°. After completion of the evolution of HCl gas, the mixture is immediately cooled by ice, the crystals of the chloride

separated from ligroin by decantation, and this chloride is well washed twice with ligroin, then dissolved in 20 cc. of chloroform.

Meanwhile, the free amine obtained from 5 g. of 3-methoxy-4-benzyloxy- β -phenylethylamine formate is dissolved in 20 cc. of chloroform. To this solution, 3% aqueous solution of potassium hydroxide and a chloroform solution of the above acid chloride are added alternately with ice-cooling, and the mixture is well shaken. After the reaction, the chloroform layer is washed with dil. hydrochloric acid, then with water and the chloroform is distilled away. The residue is dissolved in acetone and, by the addition of water, crystals, m.p. 114–117°, deposit. By one recrystallization 4.83 g. of colorless, long needle crystals (V), m.p. 115–117°, are obtained. On the other hand, by repeated recrystallization from methanol, the m.p. of this substance is gradually raised, until finally, needle crystals, m.p. 136°, are obtained. These crystals melting at 136°, are identical with its monobenzyl compound as a result of analysis and this is considered to be a substance which has lost the benzyl radical at the 4'-position. *Anal.* Calcd. for $C_{24}H_{25}O_3N$: C, 73.6; H, 6.4. Found: C, 73.6; H, 5.7.

1-(4'-Benzyloxybenzyl)-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline (VI)—4 g. of the acid amide (V), m.p. 115–117°, is dissolved in 10 cc. of chloroform, 9.4 g. of phosphorus oxychloride added, and the mixture is gently boiled with reflux. Petroleum ether is added 2 hrs. later and an oily substance deposits on standing, which later crystallizes. The petroleum ether is separated and, after washing the substance again with petroleum ether, the crystals are dissolved in methanol, from which they deposit again as crystals when ether is added. Thus 3.3 g. of prismatic crystals, m.p. 164° (decomp.), are obtained. After two recrystallizations from absolute alcohol, these crystals are dissolved in absolute alcohol, and are precipitated as crystals by the gradual addition of ether. The crystals are dried over phosphorus pentoxide, and the hydrochloride of our objective compound is obtained as slightly yellow, short prismatic crystals, m.p. 197° (decomp.). The free amine is unstable in the air.

1-(4'-Benzyloxybenzyl)-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline (VII)—1 g. of dihydroisoquinoline hydrochloride (VI) is dissolved in 20 cc. of 50% acetic acid, 2 g. of powdered zinc is added, and the mixture is boiled for 2 hrs. The reaction mixture is alkalinized by ammonia and extracted with a mixture of ether and ethyl acetate. After drying the solution, the solvent is distilled off, the residue is dissolved in absolute alcohol, and slightly yellow crystals (0.7 g.) deposit by the dropwise addition of hydrochloric acid. These are again dissolved in alcohol, and the product deposits with the addition of ether as colorless crystals, m.p. 192° (decomp.). *Anal.* Calcd. for $C_{31}H_{31}O_3N \cdot HCl$: C, 74.16; H, 6.43. Found: C, 73.86; H, 6.06.

dl-Coclaurine Hydrochloride (I)—To 0.6 g. of the hydrochloride of the above dibenzyl compound (VII), 10 cc. of 18% hydrochloric acid and 5 cc. of glacial acetic acid are added, and boiled for about 20 minutes. After the end of the reaction, the solvents are evaporated to dryness under reduced pressure, and the residue is recrystallized from a large quantity of alcohol. Crystals of m.p. 250° (decomp.) are gained, which are dissolved in alcohol, the substance made to deposit by the addition of ether, and this manipulation is repeated. Crystals, m.p. 258–259° (decomp.), are obtained after drying over phosphorus pentoxide, with heating under reduced pressure. *Anal.* Calcd. for $C_{17}H_{19}O_3N \cdot HCl \cdot \frac{1}{2} H_2O$: C, 61.72; H, 6.40. Found: C, 61.5; H, 6.3.

The tribenzoate of *dl*-coclaurine is also obtained as colorless needle crystals, m.p. 210°, from a mixture of isoamyl alcohol and acetone. *Anal.* Calcd. for $C_{38}H_{31}O_6N$: C, 76.38; H, 5.23. Found: C, 75.99; H, 5.22.

Summary

The authors synthesized *dl*-coclaurine hydrochloride from β -(3-methoxy-4-benzyloxy)-phenylethylamine (III) and 4-benzyloxyphenylacetyl chloride (IV, $R = -CH_2C_6H_5$). Comparison of the substance here obtained with the one Finkelstein recently prepared showed that both gave identical data.

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