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160. Tetsuji Kametani and Haruhiko Yagi*1 : Magnolamine and Related Compounds. Ⅳ.*2 An Alternative Synthesis of D(−) and L(+)-N-Methylcoclaurine.*3

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The optical resolution of Ⅳ was carried out by means of (+)- and (−)-di-*p*-toluoyltartaric acid to give the compounds, Ⅳa and Ⅳb. These compounds were converted into our objective antipodes, Ⅱa and Ⅱb, by hydrolysis. Absolute configuration of the above compounds was confirmed by conversion of Ⅱa and Ⅱb into D(−)- and L(+)-N-methylcoclaurine, respectively.

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The total synthesis of stereoisomeric mixture of magnolamine (Ⅰ) which formed by Ullmann reaction between compound (Ⅱ) and (Ⅲ) has already been described.*2,1,2)

The purpose of the present investigation was to study the resolution of 1-(4-acetoxybenzyl)-7-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (Ⅳ) which seems to be very important as a key compound for the total syntheses of optically active magnolamine, magnoline, and berbamunine. Hydrolysis of the above compound (Ⅳ), followed by debenzylation, was studied, leading eventually to a synthesis of (−)-N-methylcoclaurine (Ⅵa).[3,4]

Attempted optical resolution under various conditions of (±)-7-benzyloxy-1-(4-ethoxycarbonyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (Ⅴ) and its hydrolyzed product (Ⅱ), which was synthesized according to our procedure,*2 with optically active tartaric acid, di-*p*-toluoyltartaric acid, and 10-camphorsulfonic acid resulted in failure.

Accordingly, the resolution of the compound (Ⅳ) with (+)− and (−)-di-*p*-toluoyltartaric acid obtained by the usual method[4,7,8] was examined, giving our expected active compounds Ⅳa and Ⅳb. Namely, the optical resolution of (±)-Ⅳ was successfully effected with an equivalent amount of (+)-di-*p*-toluoyltartaric acid in methanol, affording (−)-O-acetyl-O-benzyl-N-methylcoclaurine (Ⅳa) (+)-di-*p*-toluoyltartrate which was converted into (−)-Ⅳ (Ⅳa) by treatment with sodium carbonate solution. On the other hand, the above filtrate, from which the above di-*p*-toluoyltartrate of Ⅳa was filtered off, was basified with sodium carbonate solution to give the antipode of Ⅳa, that is, Ⅳb, fortunately. Furthermore, the same treatment of (±)-Ⅳ with an equivalent amount of (−)-di-*p*-toluoyltartaric acid gave (−)-di-*p*-toluoyltartrate of (+)-Ⅳ (Ⅳb), which was also converted into (+)-O-acetyl-O-benzyl-N-methylcoclaurine (Ⅳb). Moreover, the antipode of Ⅳb, namely, Ⅳa was obtained by the same treatment of the above filtrate with sodium carbonate solution.

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*2 Part Ⅲ. T. Kametani, H. Yagi, S. Kaneda : This Bulletin, **14**, 974 (1966).

*3 This forms Part CXCⅡ of "Studies on the Syntheses of Heterocyclic Compounds" by T. Kametani.

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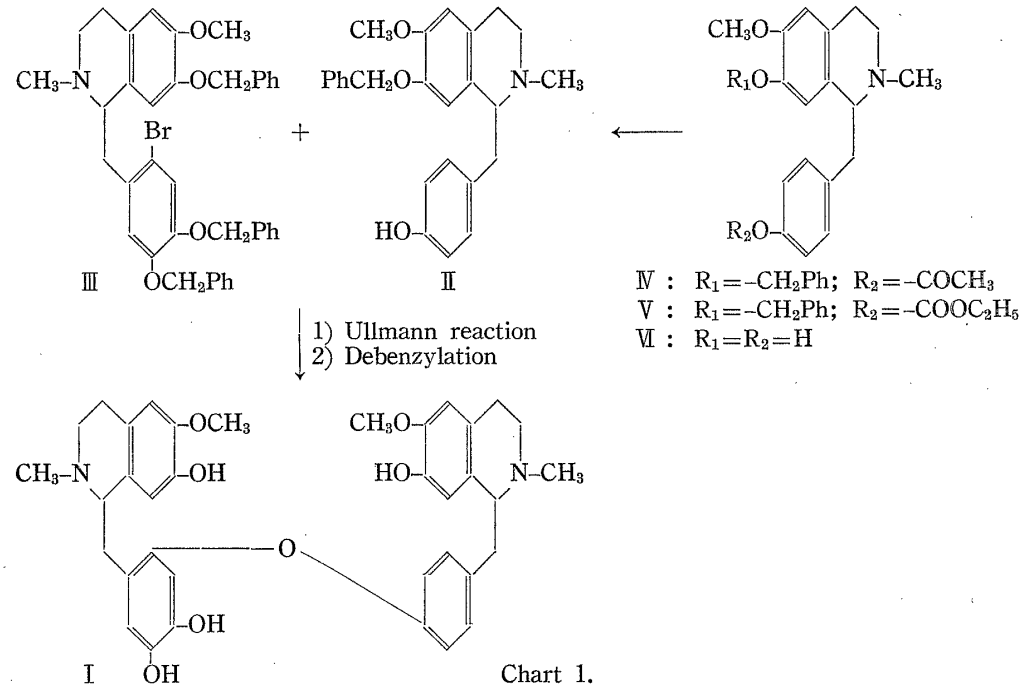
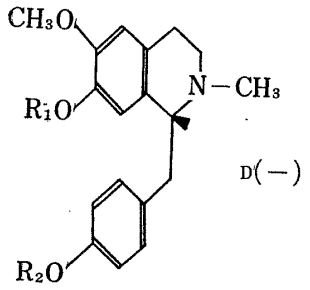
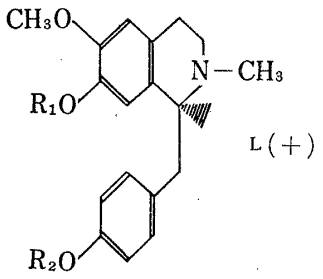


Chart 1.

Hydrolysis of both compounds, (IVa) and (IVb), with 5% aqueous methanolic sodium hydroxide solution gave the corresponding optically active compounds, IIa and IIb, whose debenzylation with concentrated hydrochloric acid afforded (−)- and (+)-N-methylcoclaurine, (VIa) and (VIb), respectively.



IIa : R_1=-$CH_2C_6H_5$; R_2=H
IVa : R_1=-$CH_2C_6H_5$; R_2=-$COCH_3$
VIa : R_1=R_2=H



IIb : R_1=-$CH_2C_6H_5$; R_2=H
IVb : R_1=-$CH_2C_6H_5$; R_2=-$COCH_3$
VIb : R_1=R_2=H

Chart 2.

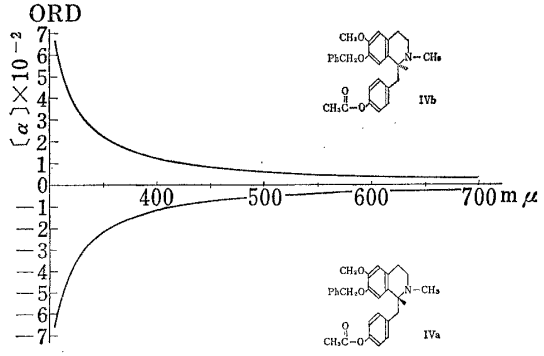


Fig. 1. The ORD Curve of Compounds (IVa) and (IVb) in $CHCl_3$

Optical rotations of these antipodes according to polarimeter were completely symmetrical, and physical characters are shown in Table I. The melting points and optical rotations of VIa and VIb agreed with those of authentic samples.[3,4] Furthermore, optical rotatory dispersion (ORD) curves of IVa and IVb are symmetrical as is shown in Fig. 1.

On the other hand, absolute configuration of VIa and VIb has already been confirmed as D(−)- and L(+)-N-methylcoclaurine by

Table I.

Compound	m.p. (°C)	Absolute configuration and $[\alpha]_D$ (solvent)	
		D(−)-Series (°C)	L(+)-Series (°C)
(±)-Ⅱ*2	139～141		
Ⅱa	137.5～138.5	−135.5 (MeOH) − 87.2 ($CHCl_3$)	
Ⅱb	137.5～138.5		+135.1 (MeOH) + 87.6 ($CHCl_3$)
Ⅳa-(+)-D.P.T.a)	158.5 (decomp.)	− 86.0 ($CHCl_3$)	
Ⅳb-(−)-D.P.T.	158.5 (decomp.)		+ 85.8 ($CHCl_3$)
(±)-Ⅳ	89～90		
Ⅳa	110～111	− 50.0 ($CHCl_3$)	
Ⅳb	110～111		+ 51.7 ($CHCl_3$)
(±)-Ⅵ*2,3)	161～163		
Ⅵa4～6)	177～178	−121.1 (MeOH)	
Ⅵb4～6)	177～178		+123.1 (MeOH)

a) D.P.T. means di-*p*-toluoyltartaric acid

Tomita, *et al.*[5,6] These facts reveal that complete optical resolution of our sample (Ⅳ) was carried out and therefore absolute configuration of compounds, $Ⅱ_{a\sim b}$, $Ⅳ_{a\sim b}$, and $Ⅵ_{a\sim b}$ has been determined.

Recently, Arndt[9] reported that (−)-N-methylcoclaurine had been isolated from *Phylica rogrsii* Pillans (Rhamnaceae) in two isomorphic forms, m. p. 154～155° and 184～185°, but our sample agreed with an authentic sample[3,4,6] from the point of melting point and optical rotation. Therefore, our synthetic sample would be one of several isomorphic forms.

Experimental*4

(±)-1-(4-Acetoxybenzyl)-7-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (Ⅳ)——A solution of 10 ml. of Ac_2O and 12 g. of Na_2CO_3 was added to a solution of 4 g. of 7-benzyloxy-1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-6-methoxy-2-methylisoquinoline (Ⅱ)*2 in 40 ml. of $CHCl_3$ and the mixture was violently stirred for 0.5 hr. The reaction mixture was decomposed with water and extracted with $CHCl_3$. The $CHCl_3$ layer separated was washed with water, dried on Na_2SO_4, and distilled to give 4.5 g. of a yellow viscous syrup, which was converted into crystals on being triturated with *n*-hexane. Filtration gave 4.2 g. (95.5%) of Ⅳ as colorless crystals, m.p. 86～88°. Recrystallization from *n*-hexane or MeOH afforded compound (Ⅳ) as colorless feathers, m.p. 89～90°. *Anal.* Calcd. for $C_{27}H_{29}O_4N$: C, 75.15; H, 6.77; N, 3.25. Found: C, 74.99; H, 6.66; N, 3.23. IR cm^{-1} ($CHCl_3$): $\nu_{C=O}$ 1761.

D(−)-1-(4-Acetoxybenzyl)-7-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (+)-di-*p*-toluoyltartrate——(+)-Di-*p*-toluoyltartaric acid (2.690 g.) was added to a solution of 2.917 g. of (±)-Ⅳ in 90 ml. of MeOH, and the mixture was mildly warmed, which became clear. After 20 hr. at 0～7° the crude di-*p*-toluoyltartrate was precipitated and collected by filtration to afford 2.5 g. of colorless needles, m.p. 157.5°(decomp.). Recrystallization from MeOH gave 2.35 g. (84.8%) of colorless scales, m.p. 158.5°(decomp.). *Anal.* Calcd. for $C_{27}H_{29}O_4N \cdot C_{20}H_{18}O_8$: C, 69.01; H, 5.79; N, 1.71. Found: C, 69.07; H, 5.71; N, 1.61. $[\alpha]_D^{12}$ −86.0°(c=1.72 in $CHCl_3$, l=0.25 dm.).

L(+)-1-(4-Acetoxybenzyl)-7-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (−)-di-*p*-toluoyltartrate——(−)-Di-*p*-toluoyltartaric acid (2.763 g.) was added to a solution of 3 g. of (±)-Ⅳ in 60 ml. of MeOH, and the mixture was mildly warmed to give a clear solution. After 24 hr. at 0～7° the crude salt was precipitated and collected by filtration to afford 2.7 g. of colorless needles. Recrystallization from MeOH gave 2.52 g. (88.4%) of the (−)-di-*p*-toluoyltartrate as colorless scales, m.p. 158.5°(docomp.). *Anal.* Calcd. for $C_{27}H_{29}O_4N \cdot C_{20}H_{18}O_8$: C, 69.01; H, 5.79; N, 1.71. Found: C, 69.12; H, 5.95; N, 1.99. $[\alpha]_D^{12}$ +85.8°(c=3.17 in $CHCl_3$, l=0.25 dm.).

*4 All melting points were not corrected.

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D(−)-1-(4-Acetoxybenzyl)-7-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (IVa)——a) To a solution of 2.0 g. of (−)-O-acetyl-O-benzyl-N-methylcoclaurine (+)-di-*p*-toluoyltartrate in 100 ml. of $CHCl_3$ was added a saturated Na_2CO_3 solution and the mixture was shaken for a few minutes. The $CHCl_3$ layer was separated, washed with water, and dried on K_2CO_3. Removal of the solvent gave a colorless syrup which solidified on being triturated with *n*-hexane and was collected by filtration. Recrystallization of the above crystals (1.0 g.) from *n*-hexane afforded colorless feathers, m.p. 110～111°. *Anal.* Calcd. for $C_{27}H_{29}O_4N$: C, 75.15; H, 6.77; N, 3.25. Found: C, 75.28; H, 6.70; N, 3.21. $[\alpha]_D^7$ −50.0°(c=3.2 in $CHCl_3$, l=0.25 dm.).

b) The above filtrate, from which (+)-O-acetyl-O-benzyl-N-methylcoclaurine (−)-di-*p*-toluoyltartrate was filtered off, was concentrated under reduced pressure, and the residue was dissolved in 100 ml. of $CHCl_3$. The solvent layer was basified with a saturated Na_2CO_3 solution. The $CHCl_3$ layer was separated, washed with water, dried on K_2CO_3, and distilled to give 1.30 g. of a yellow viscous syrup. Recrystallization from MeOH gave 0.95 g. of colorless feathers, m.p. 110～111°, which was identical with the above sample (IVa) by mixed melting point test. Furthermore, the infrared (IR) spectrum and ORD curve of both specimens were completely identical.

L(+)-1-(4-Acetoxybenzyl)-7-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (IVb)——a) An excess of a saturated Na_2CO_3 solution was added to a solution of 2.5 g. of (+)-O-acetyl-O-benzyl-N-methylcoclaurine (−)-di-*p*-toluoyltartrate in 100 ml. of $CHCl_3$ and the mixture was shaken for a few minutes. The solvent layer was separated, washed with water, dried on K_2CO_3, and distilled to give a colorless syrup. After being triturated with *n*-hexane 1.3 g. of (+)-IVb was collected by filtration. Recrystallization from *n*-hexane gave colorless feathers, m.p. 110～111°. *Anal.* Calcd. for $C_{27}H_{29}O_4N$: C, 75.15; H, 6.77; N, 3.25. Found: C, 74.91; H, 6.56; N, 3.35. $[\alpha]_D^7$ +51.7°(c=3.4 in $CHCl_3$, l=0.25 dm.).

b) The above filtrate, from which (−)-O-acetyl-O-benzyl-N-methylcoclaurine (+)-di-*p*-toluoyltartrate was filtered off, was concentrated and the residue was dissolved in 100 ml. of $CHCl_3$. The solution was basified with a saturated Na_2CO_3 solution. The solvent layer was separated, washed with water, dried on K_2CO_3, and distilled to give 1.42 g. of a yellow viscous syrup. Recrystallization from MeOH gave 1.01 g. of the compound (IVb) as colorless feathers, m.p. 110～111°, which was identical with the above sample (IVb) by mixed melting point test, IR spectrum, and ORD curve. $[\alpha]_D^{12}$ +51.0°(c=3.3 in $CHCl_3$, l=0.25 dm.).

D(−)-7-Benzyloxy-1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-6-methoxy-2-methylisoquinoline (IIa)——A mixture of 2.12 g. of IVa and 20 ml. of 5% NaOH-H_2O-MeOH solution was heated on a water-bath at 60～70° for 0.5 hr. The bulk of MeOH was removed by distillation, and the residual solution was admixed with 30 ml. of water and basified with crystalline NH_4Cl to give a solution showing pH 9～10. The organic material (2.04 g.) separated was collected on a filter as colorless crystals, m.p. 137～138°. Recrystallization from benzene-*n*-hexane gave colorless prisms, m.p. 137.5～138.5°. *Anal.* Calcd. for $C_{25}H_{27}O_3N$: C, 77.09; H, 6.99; N, 3.60. Found: C, 77.45; H, 6.78; N, 3.41. $[\alpha]_D^7$ −135.5°(c=3.1 in MeOH, l=0.25 dm.). $[\alpha]_D^{12}$ −87.2°(c=3.15 in $CHCl_3$, l=0.25 dm.).

L(+)-7-Benzyloxy-1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-6-methoxy-2-methylisoquinoline (IIb)——A solution of 1.3 g. of IVb in 10 ml. of 5% NaOH-H_2O-MeOH was heated on a water-bath at 60～70° for 0.5 hr. and the bulk of MeOH was removed under reduced pressure. To the residual solution was added 30 ml. of water, and the same treatment as usual gave 1.1 g. of IIb as colorless crystals, m.p. 137～138°. Recrystallization from benzene-*n*-hexane afforded colorless prisms, m.p. 137.5～138.5°. *Anal.* Calcd. for $C_{25}H_{27}O_3N$: C, 77.09; H, 6.99; N, 3.60. Found: C, 77.33; H, 6.88; N, 3.52. $[\alpha]_D^7$ +135.1°(c=3.02 in MeOH, l=0.25 dm.), $[\alpha]_D^{12}$ +87.6°(c=3.15 in $CHCl_3$, l=0.25 dm.).

D(−)-1,2,3,4-Tetrahydro-7-hydroxy-1-(4-hydroxybenzyl)-6-methoxy-2-methylisoquinoline [D(−)-N-Methylcoclaurine (VIa)]——A mixture of 100 mg. of IIa and 3 ml. of conc. HCl was heated in the presence of N_2 on a water-bath at 90° for 2 hr. The above reaction mixture was admixed with 50 ml. of water, and extracted with benzene. The resultant acidic aqueous layer was separated and made basic with 10% NH_4OH solution to give a solution showing pH 9～10. The organic material separated was extracted with ether. The solvent layer was washed with water, dried on K_2CO_3, and distilled to give 75 mg. of colorless crystals. Recrystallization from ether-*n*-hexane gave VIa as colorless needles, m.p. 177～178°(lit.,[4] 178°). *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.22; H, 7.12; N, 4.46. $[\alpha]_D^{12}$ −121.1° (c=3.08 in MeOH, l=0.25 dm.), (lit.,[4] $[\alpha]_D^{24}$ −121.8°(c=0.475 in MeOH, l=0.5 dm.)).

L(+)-1,2,3,4-Tetrahydro-7-hydroxy-1-(4-hydroxybenzyl)-6-methoxy-2-methylisoquinoline [L(+)-N-Methylcoclaurine (VIb)]——A mixture of 200 mg. of IIb and 5 ml. of conc. HCl was heated in the presence of N_2 on a water-bath at 90° for 2 hr. and treated as usual, to give 140 mg. of VIb as colorless crystals. Recrystallization from ether-*n*-hexane gave colorless needles, m.p. 177～178°(lit.,[8] 178～179°). *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.25; H, 7.10; N, 4.33. $[\alpha]_D^{12}$ +123.1°(c=3.03 in MeOH, l=0.25 dm.), (lit.,[4] $[\alpha]_D^{22}$ +124.2°(c=0.95 in MeOH, l=2 dm.)).

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