Notes

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Optical Resolution of *dl*-N-Norromneine and Absolute Configuration of Romneine

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A series of studies concerning chemical correlation of absolute configuration of benzylisoquinoline and bisbenzylisoquinoline alkaloids was presented by Tomita and one of the present authors, Kunitomo,[2] and the absolute configuration of these alkaloid families occurring in nature was almost entirely elucidated by chemical correlation with laudanosine (I), which also was perviously correlated with amino acid by Corrodi and Hardegger.[3]

This paper complements the above series of studies, dealing with the chemical determination of absolute configuration of romneine (II), which was recently isolated from the root of a Papaveraceous plant, *Romneya coulteri* var. *trichocalyx* (Eastw.) Jepson, and was shown to have a benzylisoquinoline structure (II) by Stermitz, *et al.*,[4] though the absolute configuration was left undetermined.

Stermitz, *et al.* gave the structure (II) for romneine on the basis of IR, UV, NMR, and mass measurements and from the synthesis of *dl*-romneine through the standard Bischler-Napieralski method. However, the reported $[\alpha]_D$ value for the base hydrobromide, $-275°$ ($CHCl_3$)[5] appeared extraordinarily large for the bases of this type, and led us to synthesize *d*- and *l*-romneine[6] and re-examine the optical rotatory power of the hydrobromides.

1-(3,4-Dimethoxybenzyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (III) was prepared by a method similar to that previously described,[4,7] and was reduced to the corresponding tetrahydro-base with sodium borohydride in methanol, and the resulted *dl*-N-norromneine (IV) was isolated as a crystalline oxalate. Optical resolution of IV was carried out by a combination of N-acetyl-L-leucinate and di-*p*-toluoyl-*d*-tartrate methods. Laevorotatory N-norromneine (IVa) was obtained from its N-acetyl-L-leucinate, and was N-methylated with formalin-sodium borohydride, and the N-methylated base (IIa) hydrobromide was obtained as colorless needles, mp 225—226°, $[\alpha]_D$ +43° (EtOH). This dextrorotatory hydrobromide was found to be identical with natural romneine hydrobromide upon comparison with the authentic specimen[4] (Table I). The NMR spectrum of the free base was completely in accordance with the reported data.[4]

On the one hand, romneine antipode (IIb) was synthesized by the same manner from *d*-N-norromneine (IVb), which was obtained as its di-*p*-toluoyl-*d*-tartrate. Romneine

1) Location: *a*) *Edagawa-cho, Nishinomiya, Hyogo-ken.* *b*) *Yoshida-Shimoadachi-cho, Sakyo-ku, Kyoto.*
2) M. Tomita and J. Kunitomo, *Yakugaku Zasshi*, **82**, 734 (1962); J. Kunitomo, *ibid.*, **82**, 981, 1152, 1577 (1962).
3) H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, **39**, 889 (1956).
4) F.R. Stermitz, L. Chen, and J.I. White, *Tetrahedron*, **22**, 1095 (1966).
5) Professor F.R. Stermitz kindly informed us that the $[\alpha]_D$ value reported was found to be errorneous, and should be corrected as $[\alpha]_D$ +40° (EtOH) (Private communication, dated Aug. 2, 1966).
6) *d*- and *l*-prefixes for bases represent the sings of rotation in EtOH throughout this paper.
7) A. Pictet and A. Gams, *Ber.*, **44**, 2480 (1911).

antipode (IIb) thus obtained as crystalline hydrobromide, mp 224—226°, showed $[\alpha]_D$ −43° (EtOH). IR (KBr) spectrum was completely identical with that of romneine hydrobromide (Table I).

Table I

	Natural romneine HBr salt	Synth. romneine (IIa) HBr salt	Synth. romneine antipode (IIb) HBr salt
mp	224—225°	225—226°	224—226°
crystal form	colorless microneedles	colorless microneedles	colorless microneedles
$[\alpha]_D$ (EtOH)	+40°[5]	+43°	−43°
IR (KBr)	identical		

Thus, synthesis of romneine (IIa) and its enantiomer (IIb) was completed through the optical resolution of *dl*-N-norromneine (IV).

In order to determine the absolute configuration of romneine (IIa), the methylenedioxy group of romneine (IIa) was cleaved with phloroglucinol-sulfuric acid to afford the vicinal dihydroxy compound, which in turn was methylated without purification, and a crystalline non-phenolic tetramethoxy base was obtained. This base (mp 89°, $[\alpha]_D$ +106° (EtOH)) was compared with L-laudanosine (I),[3] and was found to be identical in every respect.

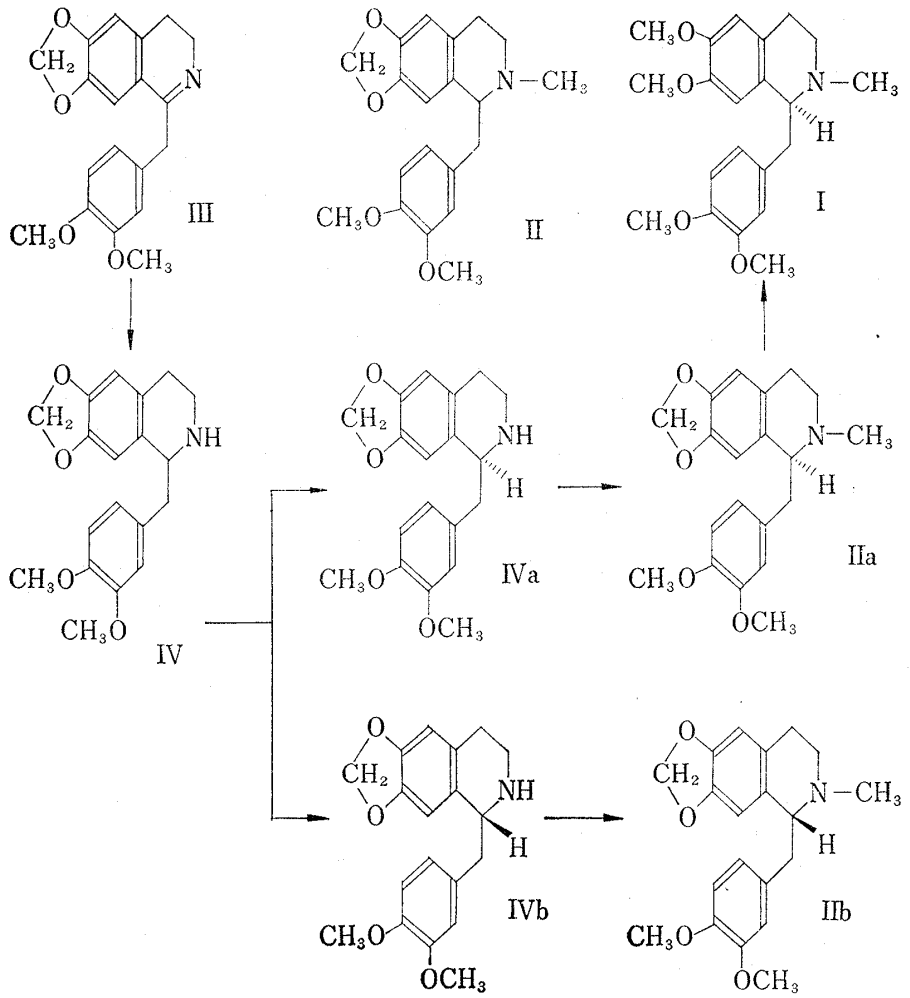

Chart 1

On the basis of the chemical correlation stated above, it was proved that the absolute configuration of romneine is L (S) and represented by the formula (IIa), and consequently, N–norromneine (IVa) has L(S)–configuration and enantiomeric compounds (IVb, IIb) have D(R)–configuration as drawn in Chart 1.

Experimental[8]

1-(3,4-Dimethoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (*dl*-N-Norromneine) (IV)——To a solution of 1–(3,4–dimethoxybenzyl)–6,7–methylenedioxy–3,4–dihydroisoquinoline[9,10] (15 g in 150 ml of MeOH), 10 g of $NaBH_4$ was added in portions with stirring, and the reaction mixture was left standing overnight. Excess reagent was destroyed by adding 10% AcOH, and the solvent was evaporated off *in vacuo*. Residue was made alkaline with 10% and NaOH, extracted with $CHCl_3$. The extract was washed with water, dried over anhyd. $MgSO_4$, and the solvent was evaporated. Residual crude base was treated with oxalic acid–EtOH, and the crystalline (IV) oxalate was recrystallized from EtOH to give 14.8 g of colorless microneedles mp 212—213°. *Anal.* Calcd. for $C_{19}H_{21}O_4N \cdot C_2H_2O_4$: C, 60.42; H, 5.55. Found: C, 60.37; H, 5.16. NMR τ: 3.20—3.43 (5H, arom. H), 4.10 (s. 2H, methylenedioxy), 6.13, 6.15 (s. 2×3H, methoxyls).

Optical Resolution of *dl*-N-Norromneine (IV) into L-N-Norromneine (IVa) and D-N-Norromneine (IVb)——N–Acetyl–L–leucine (0.7 g) and *dl*–N–norromneine (1.4 g) were dissolved in 10 ml of MeOH, and 10 ml of ether was added to the methanolic solution, and the mixture was kept in a refrigerator overnight. Crystalline N–acetylleucinate was collected and recrystallized from ether–MeOH, to give 0.7 g of colorless microneedles, mp 148.5—150.5°. *Anal.* Calcd. for $C_{19}H_{21}O_4N \cdot C_8H_{15}O_3N$: C, 64.78; H, 7.25. Found: C, 64.95; H, 7.03. $[\alpha]_D$ −54° (c=0.055, l=1, EtOH). Free base: amorphous oil. $[\alpha]_D$ −17° (c=0.154, l=1, EtOH) (*l*–L–N–norromneine (IVa)).

Mother liquor of the N–acetylleucinate was treated in usual manner to give an amorphous free base, and 0.52 g of the liberated base was dissolved in 12 ml of acetone and equimolar amount of di–*p*–toluoyl–*d*–tartaric acid was added to this solution. The mixture was warmed until a homogeneous solution resulted, and left standing overnight. Crystalline di–*p*–toluoyl–*d*–tartrate was obtained by trituration, and recrystallized from MeOH–ethyrate. Colorless needles, mp 165—168°. Yield: 0.5 g. *Anal.* Calcd. for $C_{19}H_{21}O_4N \cdot C_{20}H_{18}O_8$: C, 65.62; H, 5.51. Found: C, 65.78; H, 5.87. $[\alpha]_D$ −28.8° (c=0.011, l=1, EtOH). Free base: amorphous, $[\alpha]_D$ +16° (c=0.052, l=1, EtOH) (*d*–D–N–norromneine (IVb)).

Romneine (IIa)——*l*–L–N–Norromneine (IVa) (0.3 g) was dissolved in a small volume of MeOH, and a solution of HCHO (1 ml of 30% formalin in 10 ml of MeOH) was added. To the methanolic solution, 0.3 g of $NaBH_4$ was added and stirred for 30 min at room temperature. Solvent was removed by evaporation, and excess reagent was decomposed by adding dil. AcOH, then made alkaline with 10% NaOH and extracted repeatedly with ether. Ethereal solution was washed with water and dried over anhyd. $MgSO_4$, and the solvent was removed. Residual oil was crystallized as hydrobromide and recrystallized from EtOH. Colorless microneedles (Yield: 300 mg), mp 225—226°. $[\alpha]_D$ +43° (c=0.064, l=1, EtOH) (lit.[4] mp 224—225°, $[\alpha]_D$ +40°[5](EtOH)). *Anal.* Calcd. for $C_{20}H_{23}O_4N \cdot HBr$: C, 56.88; H, 5.72. Found: C, 57.13; H, 5.91. IR (KBr) was superimposable with that of the authentic specimen of natural romneine hydrobromide. NMR data agreed with the reported spectrum.[4]

Romneine Antipode (IIb)——IIb was prepared by the same procedure described above for IIa, and the IIb hydrobromide was obtained as colorless microneedles, mp 224—226°, $[\alpha]_D$ −43° (c=0.0678, l=1, EtOH). *Anal.* Calcd. for $C_{20}H_{23}O_4N \cdot HBr$: C, 56.88; H, 5.72. Found: C, 56.87; H, 5.81. IR (KBr) was superimposable with that of authentic specimen of natural romneine hydrobromide.

Conversion of Romneine into L-Laudanosine——One hundred and fifty milligrams of IIa, liberated from the hydrobromide, was refluxed with 300 mg of phloroglucinol and 30 ml of 40% H_2SO_4 over free flame for 30 min. After cooling, the reaction mixture was poured into 100 ml of ice water, and the aqueous solution was washed with ether, then made alkaline with 10% NaOH, and again washed with ether. Alkaline layer was made ammoniacal alkaline with the addition of crystalline NH_4Cl, then extracted with $CHCl_3$. Organic layer was washed with water, and concentrated to give yellow brown-colored oily substance. This oil was dissolved in a small volume of MeOH, and excess CH_2N_2–ethylate was then added. After 2 days, the excess reagent and the solvent was revomed by distillation, and the residual base was taken into 5% HCl, and washed with ether. Acidic layer was made alkaline with NH_4OH and extracted with ether. Ethereal solution was washed with water, dired over anhyd. $MgSO_4$, and the solvent was evaporated off. Residue was purified by column chromatography on Al_2O_3 (from $CHCl_3$ and eluted by the same solvent).

8) Melting points were not corrected. NMR spectra were taken on a Varian A–60 spectromter at 60 Mc in $CDCl_3$ with TMS as an internal standard.
9) F.R. Stermitz, L. Chen, and J.I. White, *Tetrahedron*, **22**, 1095 (1966).
10) A. Pictet and A. Gams, *Ber.*, **44**, 2480 (1911).

Recrystallization from EtOH gave 30 mg of colorless needles, mp 89°, $[\alpha]_D$ +106° (c=0.0214, l=1, EtOH) (lit.[3] mp 89°, $[\alpha]_D$ +104° (EtOH)). Mixed melting point with a sample of L-laudanosine did not depress. IR ($CHCl_3$) spectra were also identical.

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Chichibabin Reaction. III.[1] Chichibabin Reaction of 7-Methylquinoline and Migration of the Methyl Group in Friedel-Crafts Reaction of N-(*m*-Tolyl)- and N-(*p*-Tolyl)-β-chloropropionamide (Studies on the Syntheses of Heterocyclic Compounds. CCXV[2])

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In the previous paper,[1] it has been reported that the Chichibabin reaction of 8-methylquinoline (I) in dimethylaniline with sodium amide afforded our expected abnormal product, namely, 2-amino-3,4-dihydro-8-methylquinoline (II) as in case of the Chichibabin reaction of quinoline.[4] Furthermore, the formation of 3,4-dihydro-5-methylcarbostyril (III) besides the normal product, 3,4-dihydro-8-methylcarbostyril was observed by the migration of methyl group in case of Friedel-Crafts reaction of N-(*o*-tolyl)-β-chloropropionamide with aluminum chloride, whose reaction was found to be different from the results reported by Mayer, *et al.*[5]

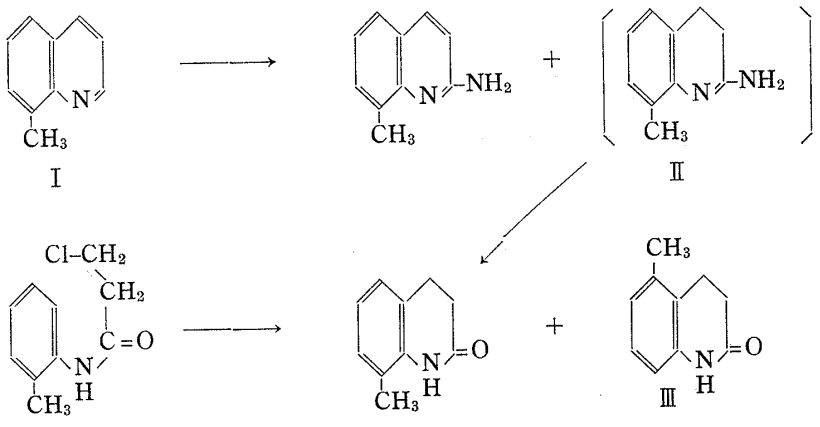

Chart 1

1) Part II: T. Kametani and H. Nemoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 1910 (1967).
2) Part CCXIV: *Chem. Pharm. Bull.* (Tokyo), **16**, 296 (1968).
3) Location: *Kita-4-bancho, Sendai.*
4) T. Kametani, K. Kigasawa, Y. Iwabuchi, and T. Hayasaka, *J. Heterocyclic Chem.*, **2**, 330 (1965).
5) F. Mayer, L. von Zuetphen, and H. Phillips, *Ber.*, **60**, 858 (1927).