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# Studies on the Alkaloids of Papaveraceous Plants. XXVI.[1] Stereostructure of Tetrahydroprotoberberine-type Alkaloids[2]

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In the chloroform solution of tetrahydroprotoberberine-type alkaloids, the position of the equilibrium should be shifted to the B/C-*trans* side overwhelmingly in the alkaloids of group I (*e.g.*, tetrahydropalmatine), considerably to the B/C-*cis* side in the group III (*e.g.*, mesocorydaline), and to the B/C-*cis* side compared to that of group I and to the B/C-*trans* side compared to that of group III in the alkaloids of group II (*e. g.*, capaurine), in which the amount of the B/C-*cis* form increases according to the bulkiness of substituent at C-1.

In the crystal state, both the racemates and optically active compounds of groups I and III can adopt the preferred conformation present in the solution, while in the group II, the crystal contains one of the conformations and in certain cases, it adopts a different conformation between optically active compound and racemate.

While a number of tetrahydroprotoberberine-type alkaloids possessing a B/C-*trans* form are known, there has been reported[4] a few examples of a B/C-*cis* form, *e.g.*, *meso*-13-methyltetrahydroprotoberberines. Kametani, *et al.*[5] concluded in their reports that capaurine (**11**) and capaurimine (**15**) may be considered to take a B/C-*cis* form in the crystalline state, and even in solution, from the results of X-ray analyses of hydrobromide of **11** and capaurimine mono-*p*-bromobenzoate (**16**). However, prior to these reports they had suggested[6] that these alkaloids exist in a B/C-*trans* form on the basis of the presence of the so-called Bohlmann bands. The confusion arises from the different interpretation of infrared (IR) absorptions in the 2600—2830 $cm^{-1}$ region, that is, whether the absorption bands can be assigned to the Bohlmann bands or not. Since Bohlmann's IR criterion[7] has been applied[8] successfully to the conformational assignment of the heterocyclic compounds with bridge-head nitrogen atom, detailed examination of the absorption bands in this region is valuable for determination of the configuration of these alkaloids. In this paper, conformation of capaurine, capaurimine, and their derivatives together with related tetrahydroprotoberberines (Table I) both in chloroform solution and in crystalline state will be discussed with reference to IR absorption bands in the 2600—2830 $cm^{-1}$ region.

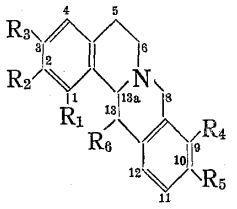
The IR spectra of tetrahydroprotoberberines show two bands at *ca.* 2750 and *ca.* 2800 $cm^{-1}$ (these bands will be termed X and Y bands respectively). The apparent molecular

1) Part XXV: N. Takao, K. Iwasa, M. Kamigauchi, and M. Sugiura, *Chem. Pharm. Bull.* (Tokyo), **24**, 2859 (1976).
2) A part of this work was presented at the 94th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, April 1974.
3) Location: *Motoyama-Kitamachi, Higashinada-ku, Kobe, 658, Japan.*
4) *a*) C.K. Yu, D.B. MacLean, R.G.A. Rodrigo, and R.H.F. Manske, *Can. J. Chem.*, **48**, 3678 (1970); *b*) T.R. Govindachari, K. Nagarajan, R. Charabala, B.R. Pai, and P.S. Subramanian, *Indian J. Chem.*, **8**, 769 (1970).
5) *a*) H. Shimanouchi, H. Sasada, M. Ihara, and T. Kametani, *Acta Cryst.*, **B25**, 1310 (1969); *b*) T. Kametani, M. Ihara, T. Honda, H. Shimanouchi, and Y. Sasada, *J. Chem. Soc.* (*C*), **1971**, 2541; *c*) T. Kametani, M. Ihara, and T. Honda, *J. Chem. Soc.* (*C*), **1970**, 2342.
6) T. Kametani, K. Fukumoto, H. Yagi, K. Ohkubo, H. Iida, and T. Kikuchi, *J. Chem. Soc.* (*C*), **1968**, 1178.
7) *a*) F. Bohlmann, *Angew. Chem.*, **69**, 641 (1957); *b*) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).
8) *a*) J. Skolik, P.J. Krueger, and M. Wiewirowski, *Tetrahedron*, **24**, 5439 (1968); *b*) For a review see T.A. Grabb, R.F. Newton, and D. Jackson, *Chem. Rev.*, **71**, 109 (1971).

Table I. Tetrahydroprotoberberine-type Alkaloids

| | Sample | (No.) | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ |
|---|---|---|---|---|---|---|---|---|
| I | Tetrahydrojatrorrhzine | (**1**) | H | OMe | OH | OMe | OMe | H |
| | Tetrahydropalmatine | (**2**) | H | OMe | OMe | OMe | OMe | H |
| | Tetrahydroberberine | (**3**) | H | $OCH_2O$ | | OMe | OMe | H |
| | Tetrahydrocoptisine | (**4**) | H | $OCH_2O$ | | $OCH_2O$ | | H |
| | Tetrahydroprotoberberine | (**5**) | H | H | H | H | H | H |
| | Tetrahydrocorybulbine | (**6**) | H | OMe | OH | OMe | OMe | Me |
| | Tetrahydrocorydaline | (**7**) | H | OMe | OMe | OMe | OMe | Me |
| | Thalictricavine | (**8**) | H | $OCH_2O$ | | OMe | OMe | Me |
| | Tetrahydrocorysamine | (**9**) | H | $OCH_2O$ | | $OCH_2O$ | | Me |
| | 13-Methyltetrahydroprotoberberine | (**10**) | H | H | H | H | H | Me |
| II | Capaurine | (**11**) | OH | OMe | OMe | OMe | OMe | H |
| | O-Methylcapaurine | (**12**) | OMe | OMe | OMe | OMe | OMe | H |
| | O-Acetylcapaurine | (**13**) | OAc | OMe | OMe | OMe | OMe | H |
| | Capaurine-*p*-bromobenzoate | (**14**) | OBz | OMe | OMe | OMe | OMe | H |
| | Capaurimine | (**15**) | OH | OMe | OMe | OMe | OH | H |
| | Capaurimine-mono-*p*-bromobenzoate | (**16**) | OH | OMe | OMe | OMe | OBz | H |
| | O,O-Diacetylcapaurimine | (**17**) | OAc | OMe | OMe | OMe | OAc | H |
| | Capaurimine-di-*p*-bromobenzoate | (**18**) | OBz | OMe | OMe | OMe | OBz | H |
| III | Mesocorydaline | (**19**) | H | OMe | OMe | OMe | OMe | Me |
| | Mesothalictricavine | (**20**) | H | $OCH_2O$ | | OMe | OMe | Me |
| | Mesotetrahydrocorysamine | (**21**) | H | $OCH_2O$ | | $OCH_2O$ | | Me |
| | *meso*-13-Methyltetrahydroprotoberberine | (**22**) | H | H | H | H | H | Me |

Compounds 6—10: *cis*-configuration at C-13 and C-13a
Compounds 19—22: *trans*-configuration at C-13 and C-13a
Bz=$COC_6H_4Br(p)$



absorptivity ($\varepsilon$) and apparent integrated intensity[9] (B) of these bands were measured (Table II). The compounds under consideration were conveniently classified into three groups according to the magnitude of these values and the substitution pattern of the A and D rings (Table I and II).

In the alkaloids of group I, X and Y bands have been regarded as Bohlmann bands, though its proof has not been provided. In order to confirm this point, IR spectra of 13-methyl-tetrahydroprotoberberine (**10**) and its selectively deuterated derivatives (**10a**, **10d**, and **10e**) (Chart 1) were examined. The spectrum of **10** shows X and Y bands at 2755 and 2805 $cm^{-1}$, respectively (Fig. 1). Substitution of the hydrogens at C-8, C-13, and C-13a by deuterium, as 8,8,13,13a-$D_4$ derivative (**10a**) results in the disappearance of X band (Table III, Fig. 1) and, therefore, this band can be assigned to the stretching vibrations of Cα–H[10] ($\nu_{C\alpha-H}$) at C-8 and C-13a. The value of $\varepsilon_Y$ in **10a** is approximately equal to one-third of the sum of $\varepsilon_X$ and $\varepsilon_Y$ in **10** (Table III, Fig. 1). Similar relations are observed in the values of B. In the spectra of 13,13a-$D_2$ and 8,8-$D_2$ derivatives (**10d** and **10e**), the value of $\varepsilon_X$ is reduced to about one-half of that in **10** (Table III, Fig. 1) and, therefore, each $\nu_{C\alpha-H}$ at C-8 and C-13a may contribute to the X band in nearly equally degree. From these observations, the Y band in **10a** may be assigned to $\nu_{C\alpha-H}$ at C-6. Analogous studies on the deuterated derivatives of other alkaloids (**2**, **3**, **4**, **8**, and **9**) of group I supported these considerations (Table III). From

9) D.A. Ramsay, *J. Am. Chem. Soc.*, **74**, 72 (1952).
10) $C_\alpha$-H bond is the axial C-H bond α to the nitrogen atom and *trans* to the nitrogen lone pair of electrons.

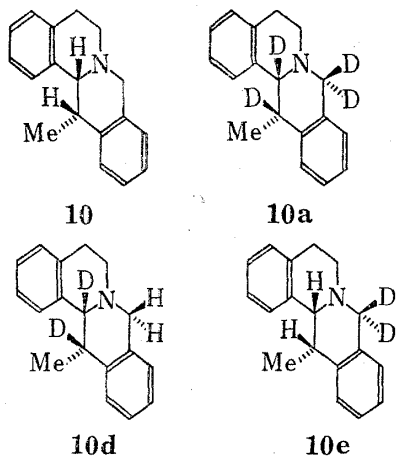
the results discussed above, it can be concluded that X and Y bands of the alkaloids in group I should be the Bohlmann bands.

As shown in Table II, the alkaloids of group III show small values of $\varepsilon_X$ and $\varepsilon_Y$. This may be the reason why they have been thought to exhibit no Bohlmann bands. The IR spectra of *meso*-13-methyltetrahydroprotoberberine (**22**) and its selectively deuterated deriva-

Table II. Apparent Molecular Absorptivity ($\varepsilon$) and Apparent Integrated Intensity (B) of Bohlmann Bands in Tetrahydroprobertoberine-type Alkaloids (in $CHCl_3$)

| | No. | $\varepsilon$ ($mol^{-1}\cdot liter\cdot cm^{-1}$) | | B ($mol^{-1}\cdot liter\cdot cm^{-2}$) | |
|---|---|---|---|---|---|
| | | $\varepsilon_X$[a] | $\varepsilon_Y$[a] | 1[b] | 2[b] |
| I | **1** | 79.0 | 74.7 | 5560 | 6540 |
| | **2** | 79.5 | 76.4 | 5630 | 6570 |
| | **3** | 81.1 | 75.3 | 6370[c] | 7310[c] |
| | **4** | 74.2 | 74.5 | 6610[c] | 7530[c] |
| | **5** | 95.4 | 72.5 | 5520 | 6490 |
| | **6** | 92.6 | 78.0 | 6060[d] | 6950[d] |
| | **7** | 91.4 | 66.3 | 6110[d] | 6960[d] |
| | **8** | 94.3 | 78.0 | 6810[c,d] | 7710[c,d] |
| | **9** | 91.9 | 78.5 | 7280[c,d] | 8100[c,d] |
| | **10** | 91.3 | 69.8 | 6010[d] | 6770[d] |
| II | **11** | 59.4 | 74.4 | 4750 | 5640 |
| | (1-OD)-**11** (**11'**) | 58.5 | 75.7 | 4680 | 5560 |
| | **12** | 44.7 | 58.2 | 4080 | 5040 |
| | **13** | 44.0 | 54.1 | 3740 | 4700 |
| | **14** | 35.8 | 45.3 | 3290 | 4120 |
| | **15** | 52.3 | 65.0 | 4520 | 5420 |
| | **16** | 53.2 | 68.0 | 4490 | 5450 |
| | **17** | 42.2 | 54.0 | 3680 | 4710 |
| | **18** | 37.7 | 49.0 | 3290 | 4230 |
| III | **19** | 15.1 | — | 1790 | — |
| | **20** | 26.6 | — | 2610 | 3910 |
| | **21** | 21.8 | — | 2590 | 3510 |
| | **22** | 27.3 | 20.2 | 1950 | 2580 |

*a*) $\varepsilon_X$: $\varepsilon$ of the band at *ca.* 2750 $cm^{-1}$, $\varepsilon_Y$: $\varepsilon$ of the band at *ca.* 2800 $cm^{-1}$
*b*) 1: 2600—2810 $cm^{-1}$ region, 2: 2600—2830 $cm^{-1}$ region
*c*) The larger values are due to the overlapping of the $\nu_{C-H}$ methylenedioxy group.
*d*) The larger values are due to the increase of B/C-*trans* form.




**10** **10a** **10d** **10e**

Chart 1. This indication expresses the relative configuration at C-13 and C-13a

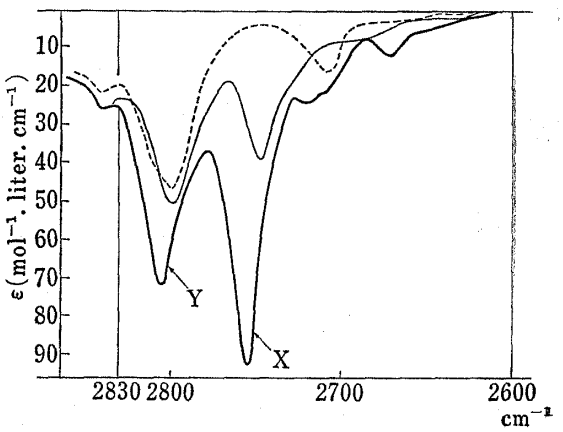



Fig. 1. Bohlmann Bands of 13-Methyl-tetrahydroprotoberberine (**10**) and the Deuterated Derivatives (**10a, 10d**) (in $CHCl_3$)

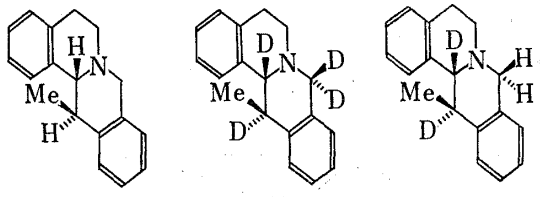
——: **10** ·····: **10a** – – –: **10d**

tives (**22a** and **22d**) (Chart 2) were examined for assignment of X and Y bands. The spectrum of **22** (Fig. 2) shows X and Y bands at 2760 and 2810 $cm^{-1}$ respectively. In 8,8,13,13a-$D_4$ derivatives (**22a**), the X band is absent (Table III, Fig. 2) and, therefore, it may be assigned to $\nu_{C_\alpha-H}$ at C-8 and/or C-13a. There are two $\nu_{C_\alpha-H}$ bonds at C-8 and C-13a in conformation

Table III. Apparent Molecular Absorptivity ($\varepsilon$) and Apparent Integrated Intensity (B) of Bohlmann Bands of Deuterated Tetrahydroprotoberberine-type Alkaloids (in $CHCl_3$)

| | Sample | No. | Deuterium[a] content (%) | | $\varepsilon$ ($mol^{-1}$. liter. $cm^{-1}$) | | B ($mol^{-1}$. liter. $cm^{-2}$) | |
|---|---|---|---|---|---|---|---|---|
| | | | C-8 | C-13a | $\varepsilon_X$[b] | $\varepsilon_Y$[b] | 1[c] | 2[c] |
| I | (8,13a-$D_2$)-2 | **2c** | 40 | 75 | 21.7 | 71.4 | 3600 | 4570 |
| | (8,13,13a-$D_3$)-3 | **3b** | 50 | 90 | 17.0 | 69.3 | 3430 | 4420 |
| | (8,13a-$D_2$)-3 | **3c** | 50 | 70 | 22.5 | 72.8 | 3770 | 4800 |
| | (13,13a-$D_2$)-3 | **3d** | | 90 | 40.2 | 72.5 | 4610 | 5580 |
| | (8,8-$D_2$)-3 | **3e** | 80 | | 55.7 | 68.9 | 4740 | 5690 |
| | (13a-D)-3 | **3f** | | 90 | 45.8 | 74.3 | 4730 | 5680 |
| | (8,13a-$D_2$)-4 | **4c** | 40 | 80 | 23.7 | 66.8 | 3920 | 4890 |
| | (8,13,13a-$D_3$)-**8** | **8b** | 40 | 90 | 25.7 | 67.4 | 4160 | 5030 |
| | (13,13a-$D_2$)-8 | **8d** | | 100 | 39.7 | 66.3 | 5050 | 6050 |
| | (8,13,13a-$D_3$)-**9** | **9b** | 20 | 100 | 50.7 | 70.3 | 5110 | 5820 |
| | (8,8,13,13a-$D_4$)-**10** | **10a** | 100 | 100 | 5.1 | 54.9 | 2340 | 2880 |
| | (13,13a-$D_2$)-**10** | **10d** | | 85 | 42.9 | 54.6 | 3670 | 4220 |
| | (8,8-$D_2$)-**10** | **10e** | 80 | | 42.8 | 62.6 | 4340 | 4940 |
| II | (8,13a-$D_2$)-**11** | **11c** | 30 | 80 | 18.3 | 64.1 | 3400 | 4350 |
| III | (8,13,13a-$D_3$)-**20** | **20b** | 40 | 90 | 8.2 | — | 1490 | — |
| | (13,13a-$D_2$)-**20** | **20d** | | 100 | 11.8 | — | 1840 | — |
| | (8,13,13a-$D_3$)-**21** | **21b** | 20 | 100 | 7.0 | — | 1730 | — |
| | (8,8,13,13a-$D_4$)-**22** | **22a** | 100 | 100 | 2.7 | 11.5 | 780 | — |
| | (13,13a-$D_2$)-**22** | **22d** | | 85 | 12.2 | 16.4 | 1440 | — |

a) These values were obtained by PMR and mass spectra methods.
b) $\varepsilon_X$: $\varepsilon$ of the band at *ca.* 2750 $cm^{-1}$, $\varepsilon_Y$: $\varepsilon$ of the band at *ca.* 2800 $cm^{-1}$
c) 1: 2600—2810 $cm^{-1}$ region, 2: 2600—2830 $cm^{-1}$ region




**22** **22a** **22d**

Chart 2. This indication expresses the relative configuration at C-13 and C-13a

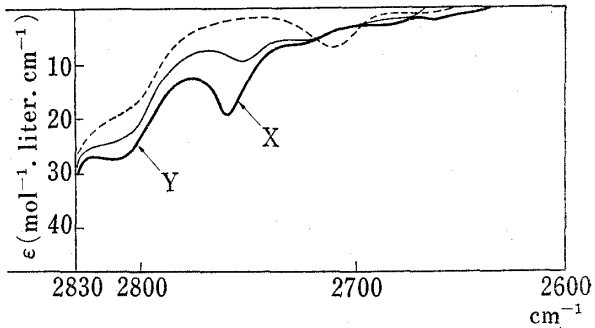
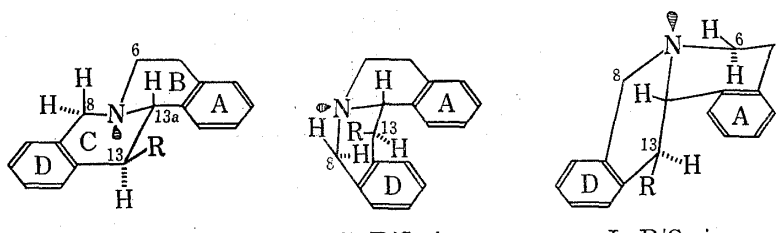



Fig. 2. Bohlmann Bands of *meso*-13-Methyl-tetrahydroprotoberberine (**22**) and the Deuterated Derivatives (**22a**, **22d**) (in $CHCl_3$)

——: **22** ·····: **22a** ——: **22d**




Ia B/C-*trans* Ib B/C-*cis* Ic B/C-*cis*

Fig. 3. Conformation of Tetrahydroprotoberberine-type Alkaloid

of Ia, at C-8 in Ib, and at C-6 in Ic (Fig. 3). These facts indicate that **22** should contain Ia and/or Ib besides Ic. In the spectrum of 13,13a-$D_2$ derivative (**22d**) (Fig. 2), the value of $\varepsilon_X$ is reduced to about one-half of that of **22** (Table III). From these observations, the conformational contribution of Ia cannot be excluded. As the presence of the conformationally mobile nitrogen atom at the bridge-head permits ready interconversion between the B/C-*trans* and -*cis* forms, the B/C-*trans* form in this case is expected to be minor, but a component of the equilibrium mixture. These conclusions are also substantiated by analogous studies on the deuterated derivatives of other alkaloids (**20**, **21**) of group III (Table III).

The results of studies on the alkaloids in group II may be summarized as follows: Kametani, *et al.*[5c] attributed X and Y bands of capaurine (**11**) to the hydroxyl group at C-1. The X and Y bands do not change on deuteration of the hydroxyl proton (Table II). These evidences indicate that the hydroxyl group of **11** is not responsible for X and Y bands.

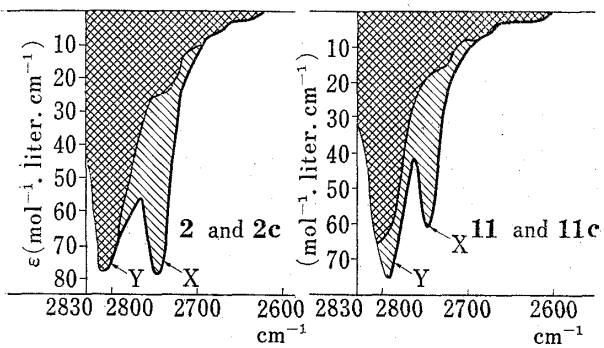



Fig. 4. Bohlmann Bands of Tetrahydropalmatine (**2**), 8,13a-$D_2$-Tetrahydropalmatine (**2c**), Capaurine (**11**), and 8,13a-$D_2$-Capaurine (**11c**) (in $CHCl_3$)

▩+▨: nondeuterated alkaloids
▩ : 8,13a-$D_2$ derivatives

TABLE IV. C-D Stretching Vibration ($\nu_{C-D}$) of Deuterated Tetrahydroprotoberberine-type Alkaloids (in $CHCl_3$)

| | No. | $\nu_{C-D}$ ($cm^{-1}$) | | |
|---|---|---|---|---|
| I | **2b** | 2030 | 2150[a] | 2200[a] |
| | **3b** | 2030 | 2155[a] | 2200[a] |
| | **8b** | 2025 | 2145[a] | |
| | **9b** | 2020 | 2140[a] | |
| | **2c** | 2040 | | |
| | **3c** | 2040 | | |
| | **4c** | 2040 | | |
| | **3d** | 2025 | 2135[a] | 2200[a] |
| | **8d** | 2025 | 2140[a] | |
| | **3e** | 2035 | 2150[a] | 2190[a] |
| | **3f** | 2030 | | |
| II | **11c** | 2045 | | |
| III | **19b** | | 2140 | |
| | **20b** | | 2140 | |
| | **21b** | | 2140 | |

a) C-D stretching vibration ($\nu_{C-D}$) of axial and equatorial deuterium on C-13 and equatorial deuterium on C-8 and C-13a

Deuteration of capaurine (**11**) at C-8 and C-13a results in the decrease of $\varepsilon_X$ in proportion to the deuterium content (Table III, Fig. 4). This tendency is also found in the case of **2c** (Table III, Fig. 4). This fact indicates that the $\nu_{C_\alpha-H}$ at C-8 and C-13a in **11** contributes to X and Y band in a similar manner as those in group I alkaloids. In the $\nu_{C_\alpha-D}$ region, the absorption band of 8,13a-$D_2$ capaurine (**11c**) also resembles those of the deuterated alkaloids of group I rather than those of group III (Table IV). From these results, X and Y bands of **11** can be assigned to the Bohlmann bands. The proportion of B/C-*trans* form in the equilibrium mixture is lower than those in group I but higher than those in group III. This conclusion will be supported by the consideration of PMR spectra. It has been shown[4] that in a B/C-*trans* form the two protons on the C-8 methylene adjacent to nitrogen have a much larger difference in chemical shift than the analogous protons in a B/C-*cis* form and that the proton in a lower field in the *trans*-form is the quasi equatorial proton. As shown in Table V, values of the chemical shift of the quasi-axial proton at C-8 and of the difference in chemical shift of the geminal protons at C-8 are intermediate between those observed for the group I and III. It is seen that among the alkaloid of group II, the values of $\varepsilon_X$ and $\varepsilon_Y$ decrease in the order of the bulkiness of the substituent at C-1, *i.e.*, $OH < OCH_3 < OCOCH_3 < OCOC_6H_4Br$ (Table II). Thus, the amount of the B/C-*cis* form in the equilibrium mixture increases in the order of the bulkiness of the substituent.

Table V. Chemical Shifts of C(8)-H and Differences in Chemical Shifts of C(8)-H in PMR Spectra of Tetrahydroprotoberberine-type Alkaloids (ppm, $CDCl_3$)

| | No. | C-8 | | Difference in chemical shifts of C(8)-H |
|---|---|---|---|---|
| | | eq'-H[a] | ax'-H[a] | |
| I | **1** | 4.22 | 3.47 | 0.75 |
| | **2** | 4.23 | 3.48 | 0.75 |
| | **3** | 4.22 | 3.47 | 0.75 |
| | **4** | 4.07 | 3.46 | 0.63 |
| | **6** | 4.18 | 3.44 | 0.74 |
| | **8** | 4.17 | 3.43 | 0.75 |
| | **9** | 4.05 | 3.42 | 0.63 |
| II | **11** | 4.20 | 3.80 | 0.40 |
| III | **19** | 4.07 | 4.04 | 0.03 |
| | **20** | 4.05 | 4.02 | 0.03 |
| | **21** | 3.92 | 3.92 | 0 |

a) ax'=quasi-axial eq'=quasi-equatorial

It may therefore be concluded that in tetrahydroprotoberberines, the B/C-*trans* form should predominate overwhelmingly in the equilibrium mixture of the group I and the B/C-*cis* form in that of group III, while the position of the equilibrium should be shifted to the B/C-*trans* side in the group II compared to that of group III. It is interesting to note that the substitution of the proton at C-1 and/or C-13 increases the proportion of B/C-*cis* form. Since the substituents at C-1 and C-13 are closer to each other in the B/C-*trans* form, substitution at these positions should decrease the stability of the B/C-*trans* form more than that of the B/C-*cis* form.

Table VI. Apparent Molecular Absorptivity ($\varepsilon$) of Bohlmann Bands in 13-Methyltetrahydroprotoberberine (**10**) and Deuterated Derivatives, **10a**, **10b**, and **10e** (in KBr)

| No. | $\varepsilon$ ($mol^{-1}.g.cm^{-1}$) | | Deuterium content (%)[a] | |
|---|---|---|---|---|
| | $\varepsilon_X$ | $\varepsilon_Y$ | C-8 | C-13a |
| **10** | 117.0 | 71.7 | | |
| **10a** | 9.9 | 66.8 | 100 | 100 |
| **10b** | 23.8 | 71.2 | 50 | 100 |
| **10e** | 87.5 | 70.2 | 50 | |

a) These values were determined by PMR spectral method.

An experiment was undertaken to confirm the configuration of the B/C ring in the crystalline state. The IR spectra of the foregoing compounds, **10**, **10a**, and **10d**, were examined for assignment of X and Y bands to $\nu_{C_\alpha-H}$. The IR spectrum of **10** shows X and Y bands at 2750 and 2800 $cm^{-1}$, respectively. The X band disappears in **10a** (Table VI) and hence, it can be assigned to $\nu_{C_\alpha-H}$ at C-8 and C-13a. The value of $\varepsilon_Y$ in **10a** is approximately equal to one-third of the sum of $\varepsilon_X$ and $\varepsilon_Y$ in **10** (Table VI) and accordingly, the Y band in **10a** may be assigned to $\nu_{C_\alpha-H}$ at C-6. In the spectra of 8,13,13a-$D_3$ and 8,8-$D_2$ derivatives (**10b** and **10e**), the value of $\varepsilon_X$ decreases in proportion to the deuterium content (Table VI). This indicates that each $\nu_{C_\alpha-H}$ at C-8 and C-13a may contribute to the X band in nearly equally degree. Since the assignment of X and Y bands to the $\nu_{C_\alpha-H}$ in the crystal state became possible as in solution, configuration of the B/C ring can be decided by examination of the Bohlmann bands. In group I, both racemates and corresponding optically active compounds exhibit Bohlmann

TABLE VII. C-H Stretching Vibration ($\nu_{C-H}$) ($cm^{-1}$) of Bohlmann Bands in Tetrahydroprotoberberine-type Alkaloids

| | Sample | No. | $\nu_{C-H}$ in KBr | | $\nu_{C-H}$ in $CHCl_3$ | |
|---|---|---|---|---|---|---|
| I | *dl*-Tetrahydropalmatine | (**2**) | 2735 | 2790 | 2755 | 2795 |
| | *l*-Tetrahydropalmatine | (**2′**) | 2745 | 2790 | | |
| | *dl*-Tetrahydroberberine | (**3**) | 2745 | 2800 | 2750 | 2800 |
| | *l*-Tetrahydroberberine | (**3′**) | 2745 | 2795 | | |
| | *dl*-Tetrahydroprotoberberine | (**5**) | 2730 | 2790 | 2755 | 2800 |
| | *l*-Tetrahydroprotoberberine | (**5′**) | 2740 | 2820 | | |
| | *dl*-Corydaline | (**7**) | 2740 | 2775 | 2750 | 2800 |
| | *d*-Corydaline | (**7′**) | 2750 | 2800 | | |
| | *dl*-Thalictricavine | (**8**) | 2755 | 2800 | 2745 | 2800 |
| | *dl*-13-Methyltetrahydroprotoberberine | (**10**) | 2750 | 2800 | 2755 | 2800 |
| II | *dl*-Capaurine | (**11**) | — | — | 2750 | 2795 |
| | *l*-Capaurine | (**11′**) | 2745 | 2790 | | |
| | *dl*-O-Methylcapaurine | (**12**) | — | — | 2750 | 2795 |
| | *l*-O-Methylcapaurine | (**12′**) | 2740 | 2785 | | |
| | *dl*-O-Acetylcapaurine | (**13**) | 2745 | 2795 | 2755 | 2795 |
| | *l*-O-Acetylcapaurine | (**13′**) | 2740 | 2800 | | |
| | *dl*-Capaurimine | (**15**) | — | — | 2750 | 2800 |
| | *l*-Capaurimine | (**15′**) | — | — | | |
| | *dl*-Capaurimine-mono-*p*-bromobenzoate | (**16**) | — | — | 2750 | 2795 |
| | *l*-Capaurimine-mono-*p*-bromobenzoate | (**16′**) | — | — | | |
| III | *dl*-Mesocorydaline | (**19**) | — | — | 2745 | overlap |
| | *d*-Mesocorydaline | (**19′**) | — | — | | |

bands (Table VII, Fig. 5). In the $\nu_{C_\alpha-D}$ region, the racemates of 8,8,13,13a-$D_4$, 8,13,13a-$D_3$, and 8,13a-$D_2$ derivatives in crystal state show the absorptions as in solution (Table VIII). These results indicate that the racemates and optically active compounds in group I exist in the B/C-*trans* form. In the crystal state, neither optically active compounds nor racemates of group III show Bohlmann bands which were present in solution (Table VII, Fig. 5). In 8,8,13,13a-$D_4$ derivative (**22a**), the absorption band at 2035 $cm^{-1}$ ($\nu_{C_\alpha-D}$) also disappears (Table VIII). Therefore the alkaloids of group III exist only in the B/C-*cis* form. In group II, *dl*-capaurine (**11**), *dl*-O-methylcapaurine (**12**), *dl*- and *l*-capaurimine (**15** and **15′**), and *dl*- and *l*-capaurimine mono-*p*-bromobenzoate (**16** and **16′**) do not exhibit Bohlmann bands and hence, they are thought to exist in the B/C-*cis* form. On the other hand, *l*-capaurine (**11′**), *l*-O-methylcapaurine (**12′**), and *dl*- and *l*-O-acetylcapaurine (**13** and **13′**) show Bohlmann bands and accordingly, they adopt the B/C-*trans* form. Though the intensity of the Bohlmann bands in **13** is weaker than that in **13′**, we could consider the former as the B/C-*trans* form

TABLE VIII. C-D Stretching Vibration ($\nu_{C-D}$) ($cm^{-1}$) of Deuterated Tetrahydroprotoberberine-type Alkaloids

| No. | in KBr | | in $CHCl_3$ | |
|---|---|---|---|---|
| **2b** | 2020 (s) | 2195[a] (m) | 2030 (s) | 2200 (w) |
| **2c** | 2020 (s) | 2190[a] (w) | 2040 (s) | 2170 (w) |
| **3b** | 2040 (s) | 2160[a] (m) | 2030 (s) | 2150 (m) |
| **3c** | 2030 (s) | 2160[a] (w) | 2040 (s) | 2200 (w) |
| **7b** | 2025 (s) | 2140[a] (s) | 2020 (s) | 2140 (s) |
| **19b** | 2060[a] (w) | 2120[a] (s) | 2040 (w) | 2140 (s) |
| **22a** | 2070[a]—2140 (s) | 2190[a] (s) | 2035 (m)<br>2070—2145 (s) | 2200 (s) |

s, strong; m, medium; w, weak

a) $\nu_{C-D}$ of equatorial-D and/or axial-D at C-13, $\nu_{C-D}$ of equatorial-D at C-8 or C-13a

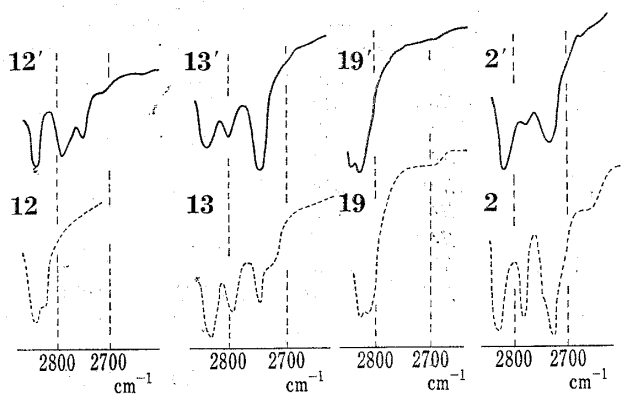



Fig. 5. IR Spectra (in KBr) of Tetrahydroprotoberberine-type Alkaloids in 2600—2850 $cm^{-1}$ Region

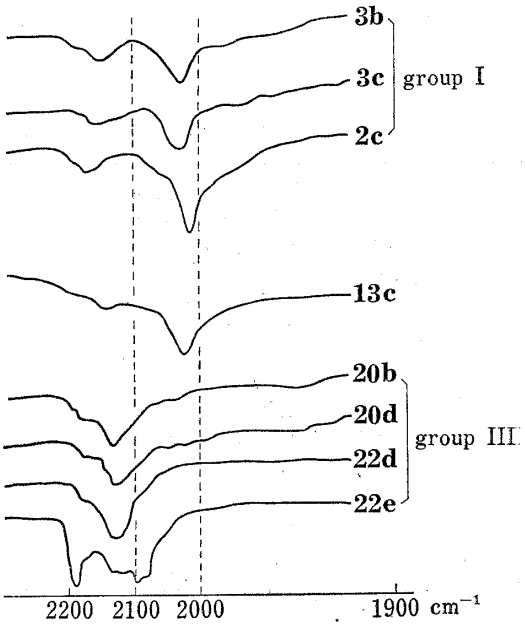



Fig. 6. C–D Stretching Vibration ($\nu_{C-D}$) of Deuterated Tetrahydroprotoberberine-type Alkaloids (in KBr)

because the absorption due to $\nu_{C_\alpha-D}$ in *dl*-(8,13a-$D_2$)-O-acetylcapaurine (**13c**) is closer to that of group I than to that of group III (Fig. 6).

In groups I and III, the preferred conformation present in solution is retained in the crystal state, that is, the group I compounds adopt the B/C-*trans* form and group III compounds the B/C-*cis* form. In the alkaloids of group II, in which the position of the equilibrium is shifted to the B/C-*trans* side rather than that of group III, the crystal contains only one of the configurations, and it seems interesting that in certain cases the configuration is different between optically active compound and racemate because little attention has been paid to this point in the past.

## Experimental

The melting points are not corrected. Silica gel $PF_{254}$ (E. Merck) was used for the preparative thin-layer chromatography (TLC). The IR spectra were obtained with a Hitachi EPI-G2 spectrometer measured in $CHCl_3$ solution at a concentration range of 0.1—0.03 mM using an expanded frequency scale of 1 $cm^{-1}$/0.19 mm. KRS cell with a path length of 0.5 mm was used. The apparent molecular absorptivity, $\varepsilon$, was estimated from Eq. 1

$$\varepsilon = \frac{1}{b, c} \log\left(\frac{T_0}{T}\right) \nu_{max} \qquad (1)$$

where $T_o$ and $T$ are the apparent intensities of the incident and transmitted radiation when the spectrometer is set at frequency $\nu$, $b$ is the cell length in cm, and $c$ is the concentration of the solute in mol/liter. The apparent integrated intensity, B, was calculated by means of measurement with the eye of the area occupied by the wave number-molecular absorptivity curve. The spectra in KBr tablet were measured using an expanded scale as above. The thickness of the tablet was 1 mm and 1—3 mg of the sample was mixed in 200 mg of KBr. The apparent molecular absorptivity, $\varepsilon$, was estimated from Eq. 1 where $b$ is the thickness of KBr tablet in cm and $c$ is the concentration of the alkaloid in mol/g. The mass spectra were measured on a JEOL-OIS instrument at an ionizing potential of 75 eV and ionizing current of approximately 200 A. Samples were introduced either through an all-glass inlet system. The PMR spectra were determined with a Varian A-60D spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard.

**Preparation of 13-Methyltetrahydroprotoberberine (10) and *meso*-13-Methyltetrahydroprotoberberine (22)**——The compounds **10** and **22** were prepared by reduction of 13-methyl-8-oxo-protoberberine (**23**)[11] with

11) I. Ninomiya, T. Naito, and H. Takasugi, *J. Chem. Soc., Perkin I*, **1975**, 1791.

$LiAlH_4$ and Zn dust-HCl as described for the deuterated compounds (**10a** and **22a**). The IR spectra of **10** and **22** were identical with those of the authentic samples.

**Preparation of 10a and 22a**——A solution of **23** (540 mg) and $LiAlD_4$ (100 mg) in dry ether (100 ml) was refluxed for 1 hr and the mixture was heated further for 1.5 hr after the addition of $LiAlD_4$ (50 mg). The residual reagent was decomposed with $H_2O$. The solution was made strongly alkaline and extracted with ether. The dried ether solution was evaporated under a reduced pressure and the residue, dissolved in MeOD (10 ml) and 35% DCl (1.5 ml), was heated with zinc dust (500 mg) for 4.5 hr on a steam bath. The zinc dust were filtered off, the filtrate was diluted with $H_2O$, and concentrated to a small volume under a reduced pressure. The solution was made alkaline and extracted with $CH_2Cl_2$. The dried $CH_2Cl_2$ solution was evaporated and the residue indicated two spots on TLC. The mixture was separated by the preparative TLC on silica gel with benzene–ether (9: 1) to afford **10a** (120 mg), mp 49—50° (petro ether–ether) and **22a** (35 mg), mp 80—82° (ether–MeOH). The deuterated products were identified by TLC and analysed by PMR and mass spectra. The values of deuterium content are given in the text.

**Preparation of 10d and 22d**——Compounds **10d** and **22d** were prepared by $LiAlH_4$ and Zn-DCl reduction of **23** as in the same way for **10a** and **22a**.

**Preparation of 10e**——Dihydro derivative obtained by the reduction of **23** (200 mg) with $LiAlD_4$ (60 mg) as described above was dissolved in MeOH and excess $NaBH_4$ was added, and the solution was heated on a steam bath for 1 hr. The residual reagent was decomposed with an acid and the solution was made strongly alkaline and extracted with $CH_2Cl_2$. The dried $CH_2Cl_2$ solution was evaporated and the residue was purified by preparative TLC on silica gel with benzene–ether (9: 1) to afford **10e** (80 mg) as an oil. The product was identified by TLC and analysed by PMR and mass spectra.

**Preparation of Deuterated Tetrahydroprotoberberines**——The deuterated products were prepared by reduction with a suitable deuterated reducing agent. In detail, the following pathways were followed. The deuterated products were identified by TLC and analysed by PMR and mass spectra. The values of deuterium content are given in the text.

protoberberine chloride $\xrightarrow{NaBD_4 \text{ in MeOD}}$ 8,13,13a-$D_3$ derivative (**3b**)

13-methyl protoberberine chlorides $\xrightarrow{Zn \text{ in (DCl–MeOD)}}$ 8,13,13a-$D_3$ derivatives (**8b**, **9b**, **20b**, **21b**)

protoberberine chlorides $\xrightarrow{NaBD_4 \text{ in } Me_2SO}$ 8,13a-$D_2$ derivatives (**2c**, **3c**, **4c**, **11c**)

protoberberine chloride $\xrightarrow[2)\ NaBD_4 \text{ in MeOD}]{1)\ LiAlH_4 \text{ in THF}}$ 13,13a-$D_2$ derivative (**3d**)

13-methyl protoberberine chlorides $\xrightarrow[2)\ Zn \text{ in (DCl–MeOD)}]{1)\ LiAlH_4 \text{ in THF}}$ 13,13a-$D_2$ derivatives (**8d**, **20d**)

8-oxoprotoberberine $\xrightarrow[2)\ NaBH_4 \text{ in MeOH}]{1)\ LiAlD_4 \text{ in THF}}$ 8,8-$D_2$ derivative (**3e**)

protoberberine chloride $\xrightarrow[2)\ NaBH_4 \text{ in MeOH–}Me_2SO]{1)\ LiAlD_4 \text{ in THF}}$ 13a-D derivative (**3f**)

**Preparation of *l*-O-Methylcapaurine (12)**——To a solution of *l*-capaurine (170 mg) in EtOH (20 ml) ether solution of $CH_2N_2$ generated from nitrosomethylurea (10 g) was added and the mixture was allowed to stand at room temperature for 4 days. After concentration of the reaction mixture, the residue was dissolved in $CH_2Cl_2$, washed with 5% NaOH solution, and dried over $MgSO_4$. After evaporation of the solvent, the residue was recrystallized from MeOH to give 120 mg of *l*-O-methylcapaurine as colorless needles, mp 149—150°, which were identified with an authentic sample of *dl*-O-methylcapaurine by TLC and IR spectrum ($CHCl_3$).

**Preparation of *l*-O-Acetylcapaurine (13)**——A solution of 200 mg of *l*-capaurine dissolved in $Ac_2O$ (1 ml) and pyridine (0.1 ml) was left to stand at room temperature for 3 hr. Water was added to the mixture, the solution was made alkaline with NaOH solution, and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ solution was evaporated and the residue was recrystallized from MeOH to afford 150 mg of **13** as colorless needles, mp 137—139°. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1760 (C=O, broad), IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1762 (C=O, sharp). PMR $\delta$: 2.30 (3H, s, $COCH_3$), 3.82 and 3.85 (12H, s, $4\times OCH_3$), 6.62 (1H, s, 4-H), 6.80 (2H, s, 11-H and 12-H). Mass Spectrum *m/e*: 413 ($M^+$), 371, 248, 206, 164, 149.

**Preparation of *l*-Capaurine *p*-Bromobenzoate (14)**——Compound (**14**) was prepared from *l*-capaurine (150 mg) and *p*-bromobenzoyl chloride (190 mg) as described below for *l*-capaurimine. Purification of the product by preparative TLC on silica gel gave **14** (90 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1740 (C=O, broad). PMR $\delta$: 3.82, 3.83, and 3.91 (each 3H, s, $3\times$OMe), 6.72 (1H, s, 4-H), 6.77 (2H, s, 11-H, and 12-H), 7.72 (2H, d, $J$= 8.5 Hz, Ar-H), 8.13 (2H, d, $J$=8.5 Hz, Ar-H). Mass Spectrum *m/e*: 555 ($M^+$).

**Preparation of *l*-O,O-Diacetylcapaurimine (17)**——*l*-Capaurimine (220 mg) was acetylated as described above. Preparative TLC on silica gel afforded 180 mg of *l*-O-diacetylcapaurimine as an oil. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1760 (C=O, broad). PMR $\delta$: 2.29 and 2.32 (each 3H, s, $OCOCH_3$), 3.79, 3.81, and 3.85 (each 3H, s, $3\times OCH_3$), 6.61 (1H, s, 4-H), 6.87 (2H, s, 11-H and 12-H). Mass Spectrum *m/e*: 441 ($M^+$).

**Preparation of *l*-Capaurimine Mono- and Di-*p*-bromobenzoate (16 and 18)**——A solution of *l*-capaurimine (200 mg) and *p*-bromobenzoyl chloride (240 mg) dissolved in pyridine (1 ml) was allowed to stand at room temperature for 3 hr. After evaporation of pyridine, the residue was dissolved in $CH_2Cl_2$, washed with 5% NaOH solution, and dried over $MgSO_4$. Evaporation of the solvent left an oil which indicated two spots on TLC. Preparative TLC on silica gel of the oil afforded 50 mg of mono-*p*-bromobenzoate (**16**) as pale plates (from MeOH), mp 177—178° (from MeOH) (reported, mp 177—178°)[5b] and 120 mg of di-*p*-bromobenzoate (**18**) as yellowish oil. **18**; IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1735 (C=O, broad). PMR $\delta$: 3.73, 3.77, and 3.86 (each 3H, s, $3\times OCH_3$), 6.67 (1H, s, 4-H), 6.87 (2H, ABq, $J$=8.8 Hz, 11-H and 12-H), 7.50—8.17 (8H, Ar-H). Mass Spectrum *m/e*: 723 ($M^+$), 540, 391, 357, 358, 208, 206.

**Optically Active Tetrahydroprotoberberines**——The optically active form of **1** was prepared according to the Späth's procedure[12] *l*-form $[\alpha]_D^{23}$ −270° ($c$=0.37, $CHCl_3$). The active forms of **3** and **7** are natural products. The active form of **5** was prepared by K. Tagahara.[13] **5**; *l*-form $[\alpha]_D^{23}$ −380° ($c$=0.48, $CHCl_3$). The active form of **19** was obtained by resolution with D-10-camphorsulfonic acid *d*-form $[\alpha]_D^{23}$ +190° ($c$=0.23, $CHCl_3$).

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12) E. Späth and W. Leithe, *Chem. Ber.*, **63**, 3007 (1930).
13) K. Tagahara, unpublished data.