$[\alpha]^{25}D$ − 54° (c 2.3, 80% AcOH), $[\alpha]^{25}D$ − 34° (c 1.1, DMF). From the mother liquor, a second crop (73 mg, mp 231–234°) was obtained. Amino acid analysis: Asp, 1.05; Glu, 1.0; Pro, 0.95; Gly, 1.1; Ile, 1.0; Leu, 1.0; Tyr, 0.90; Cys(Bzl), 1.9.

Anal. Calcd for $C_{57}H_{81}N_{12}O_{12}S_2Br$: C, 53.9; H, 6.4; N, 13.2; S, 5.1; Br, 6.3. Found: C, 54.0; H, 6.5; N, 13.1; S, 5.2; Br, 6.6.

Registry No. *o*-Nitrophenol, 88-75-5; benzyloxycarbonylglycine, 1138-80-3; benzyloxycarbonyl-L-alanine, 1142-20-7; benzyloxycarbonyl-L-valine, 1149-26-4; benzyloxycarbonyl-L-leucine, 2018-66-8; benzyloxycarbonyl-L-isoleucine, 3160-59-6; benzyloxycarbonyl-L-aspartic acid β-benzyl ester, 3479-47-8; benzyloxycarbonyl-L-glutamic acid γ-benzyl ester, 5680-86-4; benzyloxycarbonyl-L-asparagine, 35264-96-1; benzyloxycarbonyl-L-glutamine, 2650-64-8; N^{ϵ}-*tert*-butyloxycarbonyl-N^{α}-benzyloxycarbonyl-L-lysine, 2389-60-8; *N*-benzyloxycarbonyl-*S*-benzyl-L-cysteine, 3257-18-9; *N*-benzyloxycarbonyl-*O*-benzyl-L-serine, 20806-43-3; benzyloxycarbonyl-L-methionine, 1152-62-1; benzyloxycarbonyl-L-proline, 1148-11-4; benzyloxycarbonyl-L-phenylalanine, 1161-13-3; benzyloxycarbonyl-L-tryptophan, 7432-21-5; *N*-benzyloxycarbonyl-*O*-benzyl-L-tyrosine, 16677-29-5; *S,S'*-dibenzyloxytoceine (hydrobromide), 17772-77-9.

References and Footnotes

(1) This study was supported by a grant from the U. S. Public Health Service (NIH AM-12473).
(2) Overseas Research Scholar, sponsored by the Ministry of Education in Japan.
(3) M. Bodanszky, K. W. Funk, and M. L. Fink, *J. Org. Chem.*, **38**, 3565 (1973).
(4) M. Bodanszky and R. J. Bath, *Chem. Commun.*, 1259 (1969).
(5) M. Bodanszky, R. J. Bath, A. Chang, M. L. Fink, K. W. Funk, S. M. Greenwald, and Y. S. Klausner in "Chemistry and Biology of Peptides. Proceedings of the 3rd American Peptide Symposium," J. Meienhofer, Ed., Ann Arbor Science Publishers, Ann Arbor, Mich., 1972, p 203.
(6) M. Bodanszky and K. W. Funk, *J. Org. Chem.*, **38**, 1296 (1973).
(7) M. Bodanszky, M. L. Fink, K. W. Funk, C. Yang Lin, M. Kondo, and A. Bodanszky, *J. Amer. Chem. Soc.*, in press.
(8) M. Bodanszky and V. du Vigneaud, *Biochem. Prep.*, **9**, 110 (1962).
(9) M. Bodanszky, G. S. Denning, and V. du Vigneaud, *Biochem. Prep.*, **10**, 122 (1963).
(10) This partially protected form of reduced oxytocin was prepared from natural oxytocin by S. Gordon and V. du Vigneaud [*Proc. Soc. Exp. Biol. Med.*, **84**, 723 (1953)]. The name *S,S'*-dibenzyloxytoceine was proposed by V. du Vigneaud, P. S. Fitt, M. Bodanszky, and M. O'Connel [*ibid.*, **104**, 653 (1960)].
(11) M. Bodanszky and A. Bodanszky, *Chem. Commun.*, 591 (1967).
(12) M. Bodanszky in "Prebiotic and Biochemical Evolution," A. P. Kimball and J. Oro, Ed., North-Holland Publishing Co., Amsterdam, 1971, p 217.
(13) Prepared as described by M. Bodanszky and V. du Vigneaud, *J. Amer. Chem. Soc.*, **81**, 2504 (1959).
(14) D. P. Schwartz and M. J. Pallansch, *Anal. Chem.*, **30**, 219 (1958).
(15) R. H. Mazur, B. W. Ellis, and B. Cammarata, *J. Biol. Chem.*, **237**, 1619 (1962).
(16) S. G. Waley and J. Watson, *Biochem. J.*, **57**, 529 (1954).
(17) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).
(18) M. Bodanszky, *Acta Chim. Hung.* **10**, 335 (1957).
(19) The deprotection step and all subsequent operations were carried out in a centrifuge tube prepared from a 28 mm o.d. glass tube ending in a 24/40 standard tapered glass joint. The vessel formed in this way (*ca.* 40 ml) was provided with a drying tube containing cotton during the deprotection and with a 24/40 ground glass stopper during coupling reactions. A simple bench instrument (International Clinical Centrifuge, Model CL) was used for the separation of solids from the supernatant solutions. For evaporation of solvents, the tube was attached to all glass rotary evaporators. The intermediates were dried and weighed in the same tube in which also the next deprotection was performed. When purification by recrystallization became necessary, this too was done in the same vessel, without removing the peptide from it.
(20) The alkalinity of the mixture was checked by holding a piece of moist universal-indicator paper close above the surface of the solution.
(21) The weight corresponds to a polyhydrobromide; *cf.* footnote 23 in M. Bodanszky and V. du Vigneaud, *J. Amer. Chem. Soc.*, **81**, 5688 (1959).
(22) In preliminary experiments, *S,S'*-dibenzyloxytoceine hydrobromide was distributed in this solvent system in which it migrated with a *K* value of 4.0. Subsequently, however, the peptide separated from the system too readily and countercurrent distribution became impractical.
(23) H. C. Beyerman and R. A. In't Veld, *Recl. Trav. Chim. Pays-Bas*, **88**, 1019 (1969); *cf.* also H. C. Beyerman, C. A. M. Boers-Boonekamp, and H. Maassen van den Brink-Zimmermannova, *ibid.*, **87**, 257 (1968).

A Novel Regioselective Protoberberine Synthesis by Thermolysis

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Thermolytic intermolecular cycloaddition reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline (**7**) with 1-cyanocyclobutenes (**5a** and **5b**) gave two stereoisomers **15**, **17** and **20**, **21**, respectively. Isomer **15** was found to be converted to the more stable trans isomer **17** by heating or keeping aside for a long time.

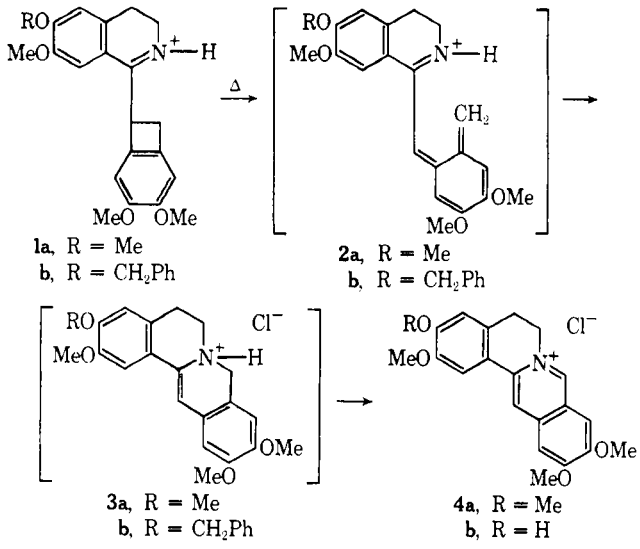
Recently we reported a novel synthesis of the protoberberine salts (**4**) through the intramolecular thermal rearrangement of the 1-(benzocyclobutenyl)-3,4-dihydroisoquinolines (**1**), in which *o*-quinodimethanes (**2**) and **3**[1] were postulated to be the intermediates (Chart I). It was thus of interest to examine the intermolecular condensation between the benzocyclobutenes (**5**) and the 3,4-dihydroisoquinoline (**7**),[2] the former of which would generate *o*-quinodimethane intermediates (**6**) thermally, thus leading to the formation of protoberberines (**8** and/or **9**) (Chart II).

Thermolysis of an equimolar amount of **5a** and **7** in bromobenzene at 150–160° gave two compounds in 80.4% total yield. Both products had the required composition for the protoberberines **8a** and **9a**.

Each of the two stereoisomers could be dehydrogenated with iodine in boiling ethanol[3] to give the same quaternary protoberberine iodide (**10**) which showed a deshielded one-proton singlet due to the C-8 hydrogen at 9.47 ppm, in addition to the signals for a pair of coupled methylene protons, four methoxyl groups, and four singlet aromatic protons in the nmr spectrum. Treatment of the quaternary protoberberine iodide (**10**) with sodium hydroxide provided a lactam (**11**) showing no C-8 proton in the nmr spectrum (Chart III). These results unequivocally allowed the assignment of a C-13 substituted structure **8a** to each of the isomers.

Interestingly, the first compound was transformed into the second one under the following conditions: (a) when heated at 150–160° for 15 min without solvent or kept aside at room temperature for 2 months and (b) when treated by filtration through silica gel eluted with methylene chloride. The reverse process could not be observed under the same conditions, or even under more severe conditions such as prolonged heating or heating at higher temperature. When the thermolysis was carried out without solvent, the second isomer was obtained in 88.0% yield as a major product accompanied by a small amount of the first isomer. These observations indicate that the compounds are stereoisomeric and that the former could be a kinetically formed product, while the latter could be the more stable thermodynamically formed product. It

Chart I



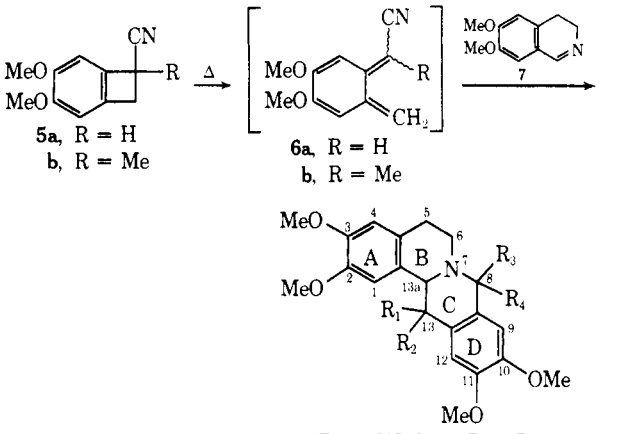
1a, R = Me
b, R = CH_2Ph

2a, R = Me
b, R = CH_2Ph

3a, R = Me
b, R = CH_2Ph

4a, R = Me
b, R = H

Chart II

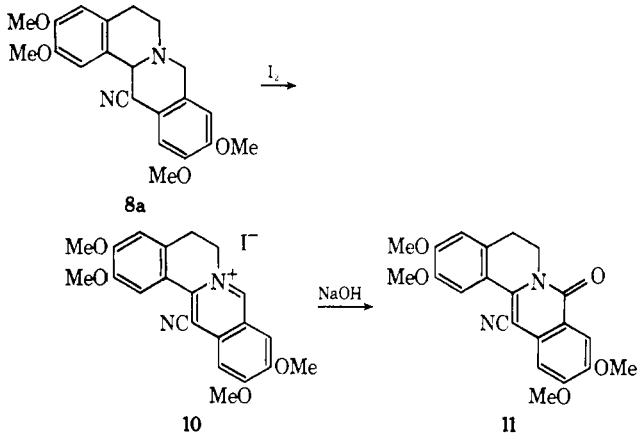


5a, R = H
b, R = Me

6a, R = H
b, R = Me

8a, R_1 = CN; $R_2 = R_3 = R_4$ = H
b, R_1 = CN; R_2 = Me; $R_3 = R_4$ = H
9a, $R_1 = R_2 = R_3$ = H; R_4 = CN
b, $R_1 = R_2$ = H; R_3 = Me; R_4 = CN

Chart III



8a

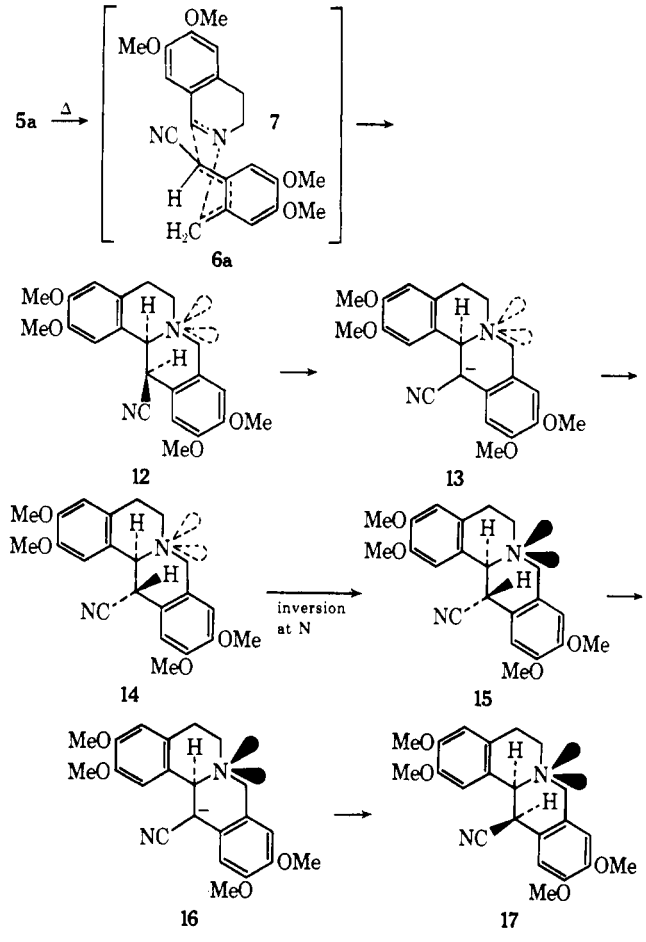
10

11

could be therefore concluded that the reaction afforded exclusively one of the possible adducts **8a** and that the reaction exhibited regioselectivity.

On the grounds of the above transformation, the stereochemistry of the adducts was deduced from the spectral data. Of the two stereoisomeric adducts **8a**, the less stable isomer was assigned the α-cyano isomer **15** (Chart IV) by a large coupling constant of 13-H and 13a-H, while the more stable isomer was assigned to the β-cyano isomer **17** by a small coupling constant of 13-H and 13a-H.

Chart IV



6a

12

13

14

15

16

17

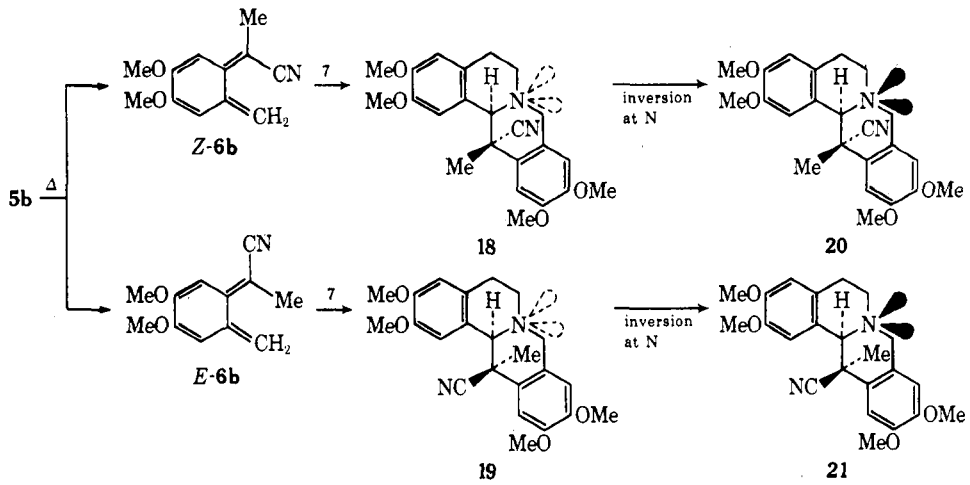
The formation of these products could be explained as follows: in the course of the reaction, the four-membered ring of the benzocyclobutene **5a** opens to form the more stable *E*-oriented *o*-quinodimethane (**6a**); subsequent synchronous cycloaddition to 3,4-dihydroisoquinoline (**7**) would give the adducts **8** in a regioselective manner.[4] Since it is known that a [$_\pi4 + _\pi2$] cycloaddition proceeds in an endocyclic and suprafacial manner in the concerted thermal reaction,[5] it could lead to the B/C cis-fused protoberberines.

As expected from the stereochemistry of a symmetry-allowed [$_\pi4_s + _\pi2_s$] cycloaddition of the *E*-oriented **6a** and **7**, the configuration of the cyano group at C-13 would have a trans relationship to the C-13a hydrogen as shown in **12**. However, large steric interference could be expected in this structure (**12**) by inspection of the appropriate model and **12** could convert to the more stable *cis*-quinolizidine intermediate **14** through the anion **13** derived from abstraction of the C-13 hydrogen. The energy barrier for inversion at the nitrogen in the quinolizidine system is known to be very small, of the order of a few calories. Therefore, the *cis*-quinolizidine (**14**) could be converted into the *trans*-quinolizidine (**15**), which was easily transformed to the thermodynamically stable product **17** *via* the anion **16**.

However, since a kinetically formed product showed no Bohlmann bands in its ir spectrum,[6] the structure **12** for the less stable isomer would not be perfectly ruled out from the ir and nmr spectral data described in the Experimental Section.

Thermolysis of the benzocyclobutene **5b** and the dihy-

Chart V



droisoquinoline 7 was next carried out. After purification by silica gel chromatography, two isomeric protoberberines, A and B (1.3:1), were obtained in 41.7 and 32.5% yield. The nmr spectra revealed that A and B were in a stereoisomeric relation, isomer A showing a C-8 methylene as a geminal coupled quartet centered at 4.07 ppm (J = 15 Hz) and a C-13a methine as a singlet at 3.09 ppm, while isomer B displayed a C-8 methylene as a singlet at 3.89 ppm and a C-13a methine as a singlet at 4.20 ppm. Since C-8 disubstituted compounds, such as **9a**, would not exhibit such spectra, the adducts obtained have a C-13 substituted structure **8b**, so that the reaction must exhibit the regioselectivity. However, the 13-disubstituted protoberberines (**8b**), in contrast to the 13-monosubstituted series **8a**, could not be interconverted under thermal conditions, which was consistent with the absence of a C-13 (enolizable) hydrogen in both products.

The stereochemistry of the adducts A and B from **5b** and **7** was deduced. The assignment of a configuration of the C-13 methyl group in both A and B was based upon a comparison of the nmr spectra. The adduct B, which exhibited a methyl singlet at 1.41 ppm relatively upfield, was assigned as β-methylprotoberberine (**20**). On the other hand, the adduct A, which exhibited a methyl singlet at 1.91 ppm, was confirmed as the α-methyl isomer **21**. The relative positions of the C-13 methyl resonances were thoroughly in accord with those recorded in the literature.[7,8]

Although the other signals supported the above stereochemical assignment, the C-13a-methine signal displayed an unusual chemical shift which is in conflict with the working rule.[9] The isomer B displayed it at 4.2 ppm, while the isomer A showed it upfield at 3.90 ppm together with the methoxy signals. However, inspection of models allowed the assumption that the paramagnetic shift of the C-13a methine was caused by the anisotropy of the C-13 cyano group, such a situation being allowed only in the B/C trans isomer B for stereochemical reasons. On this assumption, together with the observation of no A $\rightleftarrows$ B interconversion, the four-membered ring in **6b** which carries two bulky groups would open without selectivity to form two *o*-quinodimethanes (*Z*-**6b**, *E*-**6b**); the subsequent synchronous endo [$_{\pi}4_s + _{\pi}2_s$] cycloaddition of **7** to each would be regioselective, giving two B/C cis diastereoisomers **18** and **19**, in which the inversion occurred at N-7 in the more hindered isomers to be converted into the less hindered B/C trans stereoisomers **20** and **21** (Chart V). Moreover, the isomer A exhibited no Bohlmann bonds, and the nmr spectral data of this provided the formula **19** as another possible structure for the isomer A.

In conclusion, the above experiments suggest the following conclusions: (a) the cycloadditions described above proceed in a highly regioselective manner; (b) the observed stereochemical relationships of the adducts are in keeping with the operation of a symmetry-controlled [$_{\pi}4_s + _{\pi}2_s$] process; and (c) regioselectivity of benzocyclobutene ring opening can be expected only in the case of a four-membered ring substituted with one bulky group.

Experimental Section

Thermolysis of 5a and 7 without Solvent. A mixture of 500 mg (2.65 mmol) of **5a** and 505 mg (2.65 mmol) of **7** was heated at 150–160° for 45 min under an atmosphere of nitrogen. The reaction mixture was crystallized from 95% ethanol to give 884 mg (88.0%) of 13β-cyano-2,3,10,11-tetramethoxy-13aαH-tetrahydroprotoberberine (**17**) as pale yellow needles: mp 218–219°; ir ($CHCl_3$) 2850–2750 (Bohlmann bands), 2245 cm^{-1} (CN); nmr ($CDCl_3$) δ 2.50–2.90 (2 H, m, C_5-methylene), 3.02–3.38 (2 H, m, C_6-methylene), 3.72 and 4.09 (2 H, AB q, J = 14 Hz, C_8-methylene), 3.86 (1 H, d, J = 3 Hz, C_{13}-methine), 3.90 (12 H, s, 4 OMe), 4.27 (1 H, d, J = 3 Hz, C_{13a}-methine), 4.21 (1 H, s, $\frac{1}{2}H_2O$, disappeared with D_2O), 6.60, 6.64, 6.66, and 6.78 (4 H, each s, 4 ArH); uv (MeOH) λ 290 (sh), 282 nm (sh); mass spectrum m/e 380 (M^+).

Anal. Calcd for $C_{22}H_{24}O_4N_2 \cdot \frac{1}{2}H_2O$: C, 67.85; H, 6.47; N, 7.19. Found: C, 67.73; H, 6.38; N, 6.90.

Thermolysis of 5a and 7 in Bromobenzene. A mixture of 500 mg (2.65 mmol) of **5a** and 505 mg (2.65 mmol) of **7** in 20 ml of bromobenzene was heated at 150–160° for 3 hr under an atmosphere of nitrogen. The solvent was removed under reduced pressure to leave a pale brown resin which was crystallized from 95% ethanol to give 758 mg (75.4%) of 13α-cyano-2,3,10,11-tetramethoxy-13aαH-tetrahydroprotoberberine (**15**) as pale yellow needles: mp 160–161°; ir ($CHCl_3$) 2245 cm^{-1} (CN); nmr ($CDCl_3$) δ 2.70–3.30 (4 H, br s, C_5- and C_6-methylene), 3.89 (6 H, s, 2 OMe), 3.90, 3.94 (6 H, each s, 2 OMe), 4.02 (2 H, AB q, J = 12 Hz, internal chemical shift 42 Hz), 4.10 (2 H, AB q, J = 13 Hz, internal chemical shift 18 Hz), 6.58, 6.62, 6.89, and 7.27 (4 H, each s, 4 ArH); uv (MeOH) λ 290 (sh), 285, 282 nm (sh); mass spectrum m/e 380 (M^+).

Anal. Calcd for $C_{22}H_{24}O_4N_2$: C, 69.45; H, 6.36; N, 7.36. Found: C, 69.77; H, 6.53; N, 7.54.

From the above mother liquor 51 mg (5.0%) of **17** was obtained after recrystallization from 95% ethanol.

Conversion of 15 into 17. A. Thermal Treatment. **15** (50 mg) was heated at 150–160° under an atmosphere of nitrogen for 15 min to give a light brown oil which was found to be a mixture of **15** and **17** in 1:1 ratio by nmr determination and tlc. Further treatment converted **15** into **17** completely.

B. Chromatographic Treatment. **15** (50 mg) was filtered through 2 g of silica gel with methylene chloride to leave 10.7 mg of **17** (conversion ratio, 21.4%) and 36.7 mg of the starting material.

C. Direct Conversion. The nmr spectrum was measured after storage at room temperature for 2 months to show 54% conversion.

Dehydrogenation of 15 with Iodine. To a solution of 200 mg (0.526 mmol) of **15** in 80 ml of ethanol was added 533 mg (2.1 mmol) of iodine and the mixture was heated under reflux for 60 min. Ethanol was evaporated and the excess of iodine was decomposed by dropwise addition of 10% sodium thiosulfate solution. An insoluble substance was filtered off and washed with benzene. Recrystallization from ethanol left 137.0 mg (51.5%) of 13-cyano-2,3,10,11-tetramethoxyprotoberberine iodide (**10**) as yellow granules: mp 240–241°; ir (KBr) 2230 cm^{-1} (CN); nmr (CF_3CO_2H) δ 3.35 (2 H, t, J = 6 Hz, C_5-methylene), 4.10, 4.14, 4.20, 4.32 (12 H, each s, 4 OMe), 4.91 (2 H, t, J = 6 Hz, C_6-methylene), 7.13, 7.75, 7.78, 8.16 (4 H, each s, 4 ArH), 9.47 (1 H, s, C_8-methine); uv (MeOH) λ 365 (sh), 322 (sh), 302, 277 nm (sh).

Anal. Calcd for $C_{22}H_{21}O_4N_2I$: C, 52.42; H, 4.20. Found: C, 52.84; H, 4.26.

Dehydrogenation of 17 with Iodine. To a solution of 50 mg (0.132 mmol) of **17** in 20 ml of ethanol was added 133 mg (0.52 mmol) of iodine, and the mixture was treated as above to give 30.4 mg (45.7%) of the iodide **10**.

Treatment of 10 with Sodium Hydroxide. To a chilled (0°) suspension of 100 mg (0.20 mmol) of **10** in 10 ml of ethanol was added in small portions 159 mg (4.0 mmol) of sodium hydroxide. After stirring for 24 hr, the ethanol was evaporated. The residue was mixed with water and taken up in chloroform. The organic layer was separated, and, after the usual work-up, a yellow, crystalline mass (66.2 mg) was obtained. Filtration of the above compound (39.9 mg) was carried out through silica gel (4.8 g) with methylene chloride to leave 31.6 mg (61.0%) of 13-cyano-2,3,10,11-tetramethoxy-8-oxoprotoberberine (**11**) as pale yellow granules after recrystallization from a mixture of chloroform and hexane: mp 261–262°; ir ($CHCl_3$) 2210 (CN), 1640 cm^{-1} (NC=O); nmr ($CDCl_3$) δ 2.94 (2 H, t, J = 6 Hz, C_5-methylene), 4.00, 4.03 (6 H, each s, 2 OMe), 4.31 (2 H, t, J = 6 Hz, C_6-methylene), 6.79, 7.10, 7.70, 7.90 (4 H, each s, 4 ArH); uv (MeOH) λ 353, 258 nm (sh); mass spectrum m/e 392 (M^+), 377 (M^+ – Me).

Anal. Calcd for $C_{22}H_{20}O_5N_2$: N, 7.14. Found: N, 7.00.

Thermolysis of 5b and 7 without Solvent. A mixture of 101.5 mg (0.5 mmol) of **5b** and 95.5 mg (0.5 mmol) of **7** was heated at 150–160° for 60 min under an atmosphere of nitrogen. The reaction mixture was chromatographed on silica gel (10 g) with methylene chloride to afford 64.0 mg (32.5%) of 13α-cyano-2,3,10,11-tetramethoxy-13β-methyl-13aα*H*-tetrahydroprotoberberine (**20**) as colorless prisms (from ethanol): mp 157–158°; ir ($CHCl_3$) 2850–2750 (Bohlmann bands), 2230 cm^{-1} (CN); nmr ($CDCl_3$) δ 1.41 (3 H, s, C_{13}-Me), 2.44–3.28 (4 H, m, C_5- and C_6-methylene), 3.89 (2 H, s, C_8-methylene), 3.90, 3.91 (6 H, each s, 2 OMe), 3.94 (6 H, s, 2 OMe), 4.20 (1 H, s, C_{13a}-methine), 6.54, 6.62, 6.99, 7.54 (4 H, each s, 4 ArH); uv (MeOH) λ 290 (sh), 285, 282 nm (sh); mass spectrum m/e 394 (M^+), 203 ($M^+ - C_{11}H_{13}O_2N$), 191 ($M^+ - C_{12}H_{13}O_2N$).

Anal. Calcd for $C_{23}H_{26}O_4N_2$: C, 70.03; H, 6.64; N, 7.10. Found: C, 69.79; H, 6.61; N, 7.01.

Furthermore, 82.2 mg (41.7%) of 13β-cyano-2,3,10,11-tetramethoxy-13α-methyl-13aα*H*-tetrahydroprotoberberine (**21**) was obtained as colorless prisms (from ethanol): mp 201–202°; ir ($CHCl_3$) 2230 cm^{-1} (CN); nmr ($CDCl_3$) δ 1.91 (3 H, s, C_{13}-Me), 2.67–3.51 (4 H, m, C_5- and C_6-methylene), 3.90 and 4.25 (2 H, AB q, J = 15 Hz, C_8-methylene), 3.90 (13 H, s, 4 OMe and C_{13a}-methine), 6.57 (1 H, s, ArH), 6.70 (2 H, s, 2 ArH), 6.94 (1 H, s, ArH); uv (MeOH) λ 290 (sh), 282 nm (sh); mass spectrum m/e 394 (M^+), 203 ($M^+ - C_{11}H_{13}O_2N$), 191 ($M^+ - C_{12}H_{13}O_2N$).

Anal. Calcd for $C_{23}H_{26}O_4N_2$: C, 70.03; H, 6.64; N, 7.10. Found: C, 69.76; H, 6.72; N, 7.38. In this case the starting material **5b** (25.7 mg) was recovered.

Thermolysis of 5b and 7 in Bromobenzene. A mixture of 101.5 mg (0.5 mmol) of **5b** and 95.5 mg (0.5 mmol) of **7** in 4 ml of bromobenzene was heated at 150–160° for 3 hr under an atmosphere of nitrogen. The solvent was removed under reduced pressure to leave a light brown oil, which was chromatographed on silica gel (10 g) as above to afford 37.0 mg (18.8%) of **20** and 47.2 mg (24.0%) of **21**, accompanied by the starting material **5b** (37.5 mg) and **7** (48.5 mg).

Thermal Treatment of 21 and 20. Compounds **21** (15.7 mg) and **20** (13.5 mg) were each heated at 150–160° for 90 min without solvent under an atmosphere of nitrogen. The isolated compound in each case showed no detectable change at all (tlc, ir, and nmr).

Acknowledgments. We wish to acknowledge the contributions of the reviewers in helping us to assign the structures of the compounds from **5a** and **7**. We thank Miss R. Kato, Miss C. Yoshida, Miss F. Yoshinaka, Mr. T. Ouchi, and Miss A. Ujiie, Pharmaceutical Institute, Tohoku University, for spectral measurements and microanalyses.

Registry No. 5a, 35202-54-1; **5b**, 40360-52-9; **7**, 3382-18-1; **10**, 42855-11-8; **11**, 21606-55-3; **15**, 42855-13-0; **17**, 42855-14-1; **20**, 42855-15-2; **21**, 42855-16-3.

References and Notes

(1) (a) T. Kametani, K. Ogasawara, and T. Takahashi, *Chem. Commun.*, 675 (1972); *Tetrahedron*, **29**, 73 (1973); (b) T. Kametani, Y. Hirai, F. Satoh, K. Ogasawara, and K. Fukumoto, *Chem. Pharm. Bull.*, **21**, 907 (1973).
(2) K. D. Paull, R. R. Engle, L. Twannoh, H. B. Wood, Jr., and J. S. Driscoll, *J. Pharm. Sci.*, **61**, 1481 (1972).
(3) T. Kametani and I. Noguchi, *J. Chem. Soc. C*, 2036 (1969).
(4) *Cf.* (a) W. Opplzer, *J. Amer. Chem. Soc.*, **93**, 3833, 3834 (1971); (b) W. Oppolzer, *Angew. Chem.*, **84**, 1108 (1972).
(5) *Cf.* R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970.
(6) F. Bohlmann, *Angew. Chem.*, **69**, 641 (1957); *Chem. Ber.*, **91**, 2157 (1958).
(7) (a) P. W. Jeffs, *Experientia*, **21**, 690 (1965); P. W. Jeffs, "The Alkaloids," Vol. IX, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1967, p 41; (b) S. Naruto and H. Kaneko, *J. Pharm. Soc. Jap.*, **92**, 1017 (1972).
(8) (a) M. Shamma, C. D. Jones, and J. A. Weiss, *Tetrahedron*, **25**, 4347 (1969); (b) M. Shamma and C. D. Jones, *J. Amer. Chem. Soc.*, **92**, 4942 (1970).
(9) M. Uskoković, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Amer. Chem. Soc.*, **86**, 3364 (1964).