THE ABSOLUTE CONFIGURATION OF (+)-THALICTRICAVINE

Kinuko Iwasa and Mark Cushman*

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

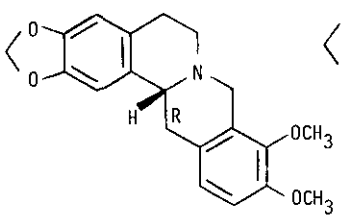
Abstract. (+)-Thalictricavine (7) and (+)-canadine (1) have been synthesized from an optically resolved (+)-13-carboxy-7,8,13,14-tetrahydro-8-oxoprotoberberine 15. This establishes the absolute configuration of (+)-thalictricavine (7) as 13S, 14R.

The absolute configurations of the tetrahydroprotoberberines[1] [e.g. (+)-canadine (1)], 13-hydroxy-tetrahydroprotoberberines[2] [e.g. (-)-ophiocarpine (2) and (-)-epiophiocarpine (3)], and 8-methyl-tetrahydroprotoberberines[3] [(+)-coralydine (4) and (+)-O-methylcorytenchirine (5)] are known from chemical correlations, rotational data, or x-ray crystallography. The naturally occurring (+)-cis-13-methyltetrahydroprotoberberines (6-14) are believed to have the absolute configurations portrayed here on the basis of rotational data[4] or circular dichroism[5] with the assumption that the axial 13-methyl groups do not make a significant contribution to the molecular rotation.

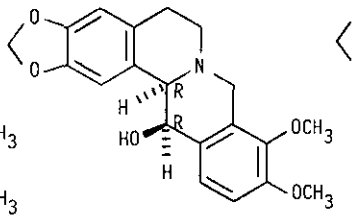
We recently executed a total synthesis of (±)-thalictricavine (7) and (±)-canadine (1) from a common intermediate (±)-15[6]. This work suggests that the absolute configuration of (+)-thalictricavine (7) could be determined by correlation with (+)-canadine (1) of known absolute configuration provided the intermediate 15 could be resolved and methods could be found for its conversion to optically active compounds 7 and 1.

The (±)-13-carboxy-8-oxotetrahydroprotoberberine 15 afforded a crystalline salt, mp 164-171°C, $[\alpha]_D$ +168° (c = 0.11, $CHCl_3$) when treated with (-)-strychnine in acetone. One recrystallization from acetone afforded optically pure material, $[\alpha]_D$ +174° (c = 0.086, $CHCl_3$). The free acid (+)-15, mp 242-243°C, $[\alpha]_D$ +412° (c = 0.08, $CHCl_3$) yielded an optically impure (+)-lactam 16, mp 214-215°C, $[\alpha]_D$ +48° (c = 0.11, $CHCl_3$) when heated at 240-244°C for 5 min.[7] Lithium aluminum hydride reduction of 16 gave (±)-canadine (1), mp 167-168°C, and optically impure (+)-canadine of mp 118-157°C, $[\alpha]_D$ +86° (c = 0.086, $CHCl_3$). This established the absolute configuration of (+)-15. The (+)-methyl ester 17, mp 176-177°C, $[\alpha]_D$ +398° (c = 0.082, $CHCl_3$) was obtained by treatment of (+)-15 with diazomethane. Lithium aluminum hydride reduction of (+)-17 provided the amino alcohol (+)-18, mp 199-200°C, $[\alpha]_D$ +278° (c = 0.07, $CHCl_3$). Reduction of the mesylate of (+)-18 with lithium aluminum hydride afforded (+)-thalictricavine (7), mp 149-150°C, $[\alpha]_D$ +312° (c = 0.056, $CHCl_3$), lit.[8] $[\alpha]_D^{23}$ +291.9° (c = 0.555, $CHCl_3$), whose infrared spectrum ($CHCl_3$) was identical with that of authentic (±)-thalictricavine. The absolute configuration of (+)-thalictricavine is therefore 13S, 14R as shown in structure 7.

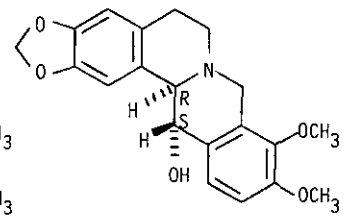
Certain cis- and trans-13-methyltetrahydroprotoberberines are converted to benzo[c]phenanthridines [e.g. (+)-corynoline (19) and (+)-14-epicorynoline (20)] via the protopines [e.g. corycavine (21)] in the plant and the tissue culture.[9] Elucidation of the stereochemistry of (+)-cis-tetrahydroprotoberberines is important in considering the mechanisms of this biosynthetic conversion.



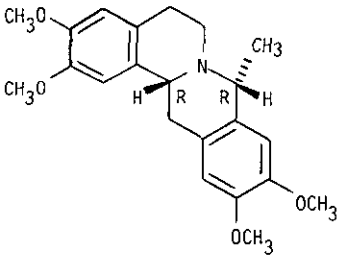
1



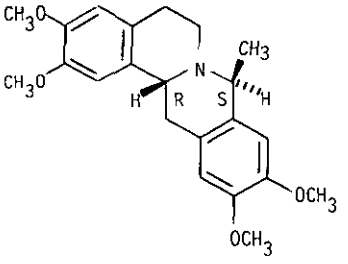
2



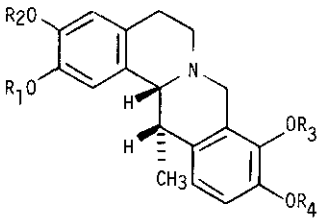
3



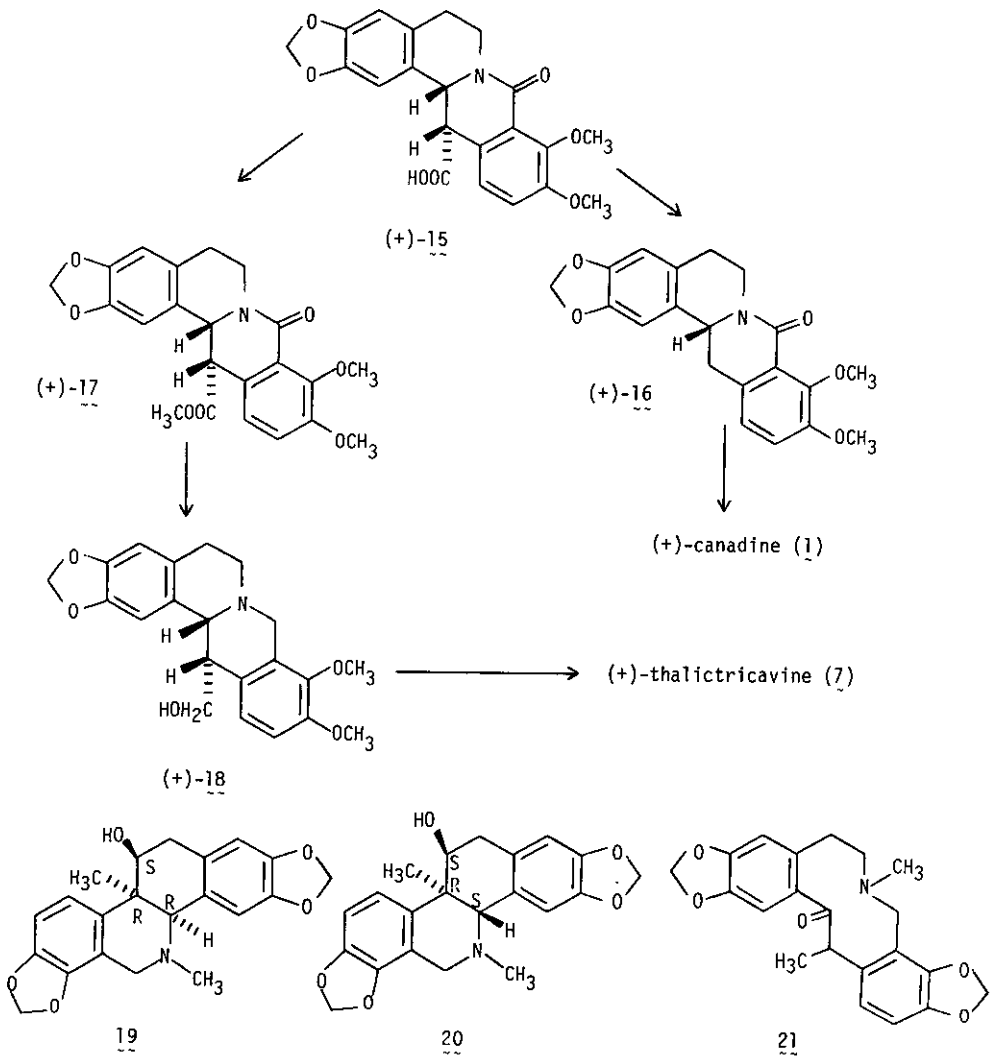
4



5



6	$R_1 = R_2 = CH_3$, $R_3 + R_4 = CH_2$	cavidine
7	$R_1 + R_2 = CH_2$, $R_3 = R_4 = CH_3$	thalictricavine
8	$R_1 = H$, $R_2 = CH_3$, $R_3 + R_4 = CH_2$	apocavidine
9	$R_1 + R_2 = CH_2$, $R_3 = CH_3$, $R_4 = H$	epiapocavidine
10	$R_1 + R_2 = R_3 + R_4 = CH_2$	tetrahydrocorysamine
11	$R_1 = R_3 = R_4 = CH_3$, $R_2 = H$	corybulbine
12	$R_1 = H$, $R_2 = R_3 = R_4 = CH_3$	isocorybulbine
13	$R_1 = R_3 = CH_3$, $R_2 = R_4 = H$	corydalidzine
14	$R_1 = R_2 = R_3 = R_4 = CH_3$	corydaline



Acknowledgment. This investigation was supported by Grant CA19204, awarded by the National Cancer Institute, NIH.

REFERENCES

1. H. Corrodiand and E. Hardegger, Helv. Chim. Acta., 1956, 39, 889.
2. M. Ohta, H. Tani, and S. Morozumi, Chem. Pharm. Bull., 1964, 12, 1072.
3. H. Bruderer, J. Metzger, and A. Brossi, Helv. Chim. Acta., 1975, 58, 1719; H. Bruderer, J. Metzger, A. Brossi, and J.J. Daly, Helv. Chim. Acta., 1976, 59, 2793.
4. P.W. Jeffs, Experientia, 1965, 21, 690.
5. G. Snatzke, J. Hrbek, Jr., L. Hruban, A. Horeau, and F. Šantavý, Tetrahedron, 1970, 26, 5013.
6. M. Cushman and F.W. Dekow, J. Org. Chem., 1979, 44, 407.
7. M. Cushman, J. Gentry, and F.W. Dekow, J. Org. Chem., 1977, 42, 1111.
8. R.H.F. Manske, J. Amer. Chem. Soc., 1953, 75, 4928.
9. N. Takao, K. Iwasa, M. Kamigauchi, and M. Sugiura, Chem. Pharm. Bull. (Tokyo), 1976, 24, 2859.

Received, 17th February, 1981