STUDIES IN THE (+)-MORPHINAN SERIES VI[1]. DIMERS OF NATURAL (-)- AND UNNATURAL (+)-SINOMENINE

Jun-ichi Minamikawa, Ikuo Iijima and Arnold Brossi*

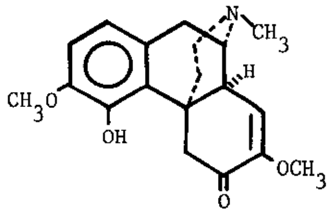
Section on Medicinal Chemistry, Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014, USA,

Thermal equilibration of either (+)-disinomenine or (+)-ψ-disinomenine, obtained by chemical oxidation of natural (-)-sinomenine, affords a 1:1 mixture of the two readily separable dimers. Synthesis of the (-)-enantiomers of the two dimers was accomplished from unnatural (+)-sinomenine. Physical data collected with both enantiomeric pairs show that they are chemically and optically pure. These crystalline dimers contain tightly bound solvents of crystallization and are not suited for X-ray analysis.

Chemical oxidation of natural (-)-sinomenine (1a) affords two dimers named (+)-disinomenine (water insoluble dihydrochloride) and (+)-ψ-disinomenine[2] (water soluble dihydrochloride). Goto et. al. postulated[3] that both are stereoisomers with restricted rotation around their 1,1' diphenyl axis, shown in their formulas 2a in Fig. 1.

Some of Goto's physical data for the two dimers, especially the optical rotations, differ considerably from values found in our laboratory. To clarify these discrepancies we decided to prepare the optical isomers 2b, namely (-)-disinomenine and (-)-ψ-disinomenine (Fig. 1).

Dedicated to Professor Dr. A. Butenandt at the occasion of his 75th birthday.



1a

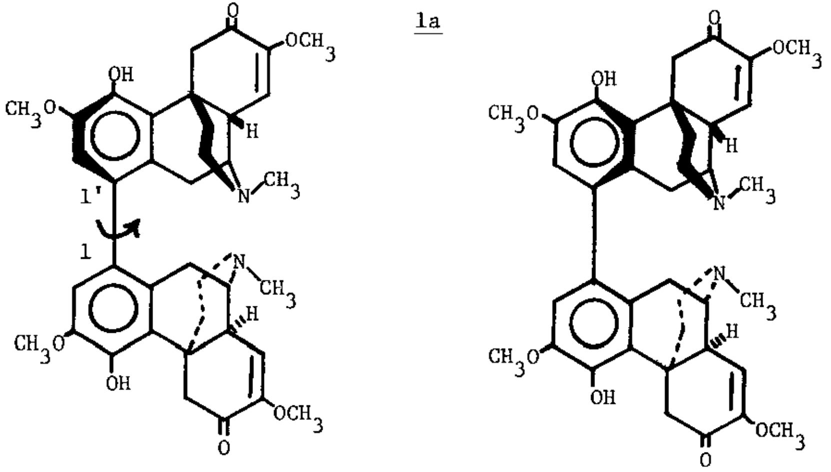


Fig. 1 2a (+)-Disinomenine and (+)-ψ-Disinomenine
2b Mirror images of 2a, (−)-Enantiomers.

The synthesis of unnatural (+)-sinomenine (1b = mirror image of 1a) was accomplished from the known diketone 3b[4] by O-methylation in methanol with HCl.[5] (Fig. 2). Separation of the methyl ether mixture on silica gel ($CHCl_3$-MeOH, 9:1) gave first isosinomenine (4b), which could be reconverted into 3b through acid hydrolysis.

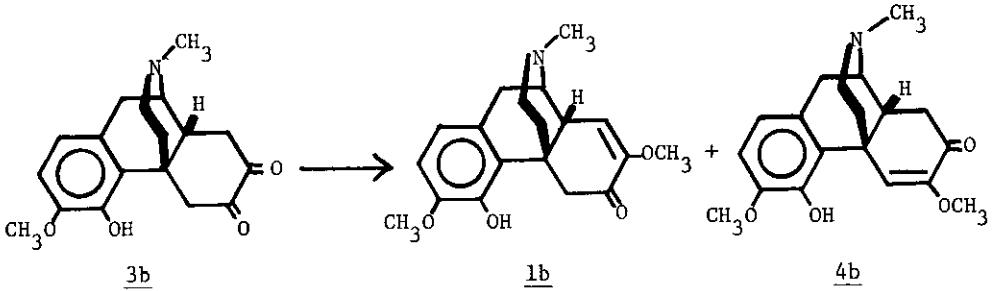


Fig. 2

The second product obtained was (+)-sinomenine (1b), isolated as its hydrochloride [mp 1b·HCl 229-233° (dec.); $[\alpha]_D^{20}$ + 84.2° (c 4.59, H_2O); tlc (SiO_2, $CHCl_3$-MeOH = 9:1), enantiomeric with 1a].

Dimerization of 1b was accomplished as follows: 450 mg 1b were dissolved in 15 ml aqueous EtOH (30%) and combined with 350 mg $AgNO_3$ in 10 ml H_2O at 0°. Saturated aqueous NaCl (10 ml) was added after 5 min, the precipitated AgCl was filtered, and the filtrate made alkaline with NH_4OH and extracted with $CHCl_3$. Preparative tlc (SiO_2, $CHCl_3$-MeOH = 9:1) separated the faster moving (-)-ψ-disinomenine (2b, 11%) from the slower moving (-)-disinomenine (2b, 44%). Both unnatural dimers 2b are, except for showing opposite optical behaviour, identical with the two (+)-dimers described below.

Both sinomenine dimers afford, when heated under vacuum at 235° for 5 min, a 1:1 mixture of both stereoisomers which can easily be separated, thus simplifying their preparation.

The following physical data were collected for the chemically and optically pure (+)-dimers (2a) crystallized from MeOH.

(+)-Disinomenine, plates mp 221-223° [lit.[3] 222°]; m/e 656 (M^+); $[\alpha]_D^{20}$ + 86.2° (1.28, $CHCl_3$) [lit.[3] $[\alpha]_D$ + 149.98°][a]; ir (ν_{max}, $CHCl_3$, cm^{-1}) 3520 (OH), 1690 (CO), 1635 (C=C) and 1605 (Ar); uv (λ_{max}, MeOH) 252 (ε,16700) and 280 nm (sh 8670); nmr (δ, $CDCl_3$) 6.32 (1H, s, ArH), 5.50 (1H, broad s, vinyl. H), 3.78 (3H, s, ArOMe), 3.55 (3H, s, C-7 OMe), 2.36 (3H, s, NMe); mp dihydrochloride > 250°, insoluble H_2O; CD and ORD spectrum of free base, Fig. 3.

Footnote a: Temperature, concentration and solvent not given.

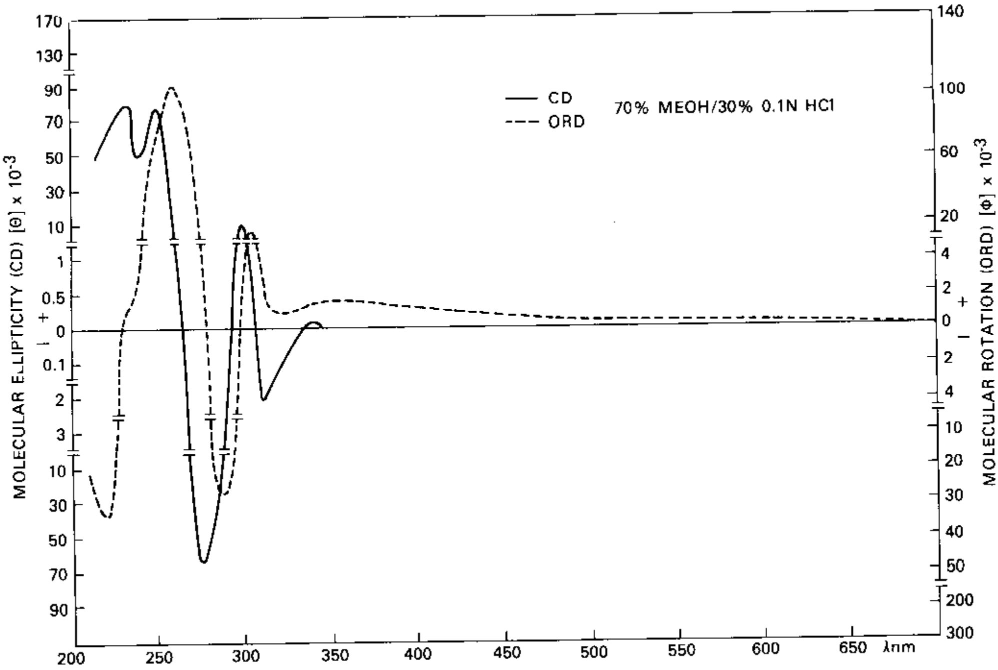


FIGURE 3. DISINOMENINE

(+)-ψ-Disinomenine, fine needles mp 209-210° [lit.[3] 227°]; m/e 656 (M^+); $[\alpha]_D^{20}$ + 50.8° (c 0.83, $CHCl_3$) [lit.[3] $[\alpha]_D$ + 30°][b]; ir (ν_{max}, $CHCl_3$, cm^{-1}) 3520 (OH), 1690 (CO), 1635 (C=C), 1605 (Ar); uv (λ_{max}, MeOH) 251 (ε, 13400) and 282 nm (sh 9020); nmr (δ, $CDCl_3$) 6.50 (1H, s, ArH), 5.32 (1H, broad s, vinyl.H) 3.82 (3H, s, ArOMe), 3.54 (3H, s, C-7 OMe) and 2.31 (3H, s, NMe); mp dihydrochloride > 250°, soluble H_2O, CD and ORD spectra of free base, Fig. 4.

Footnote b: Temperature, concentration and solvent not given.

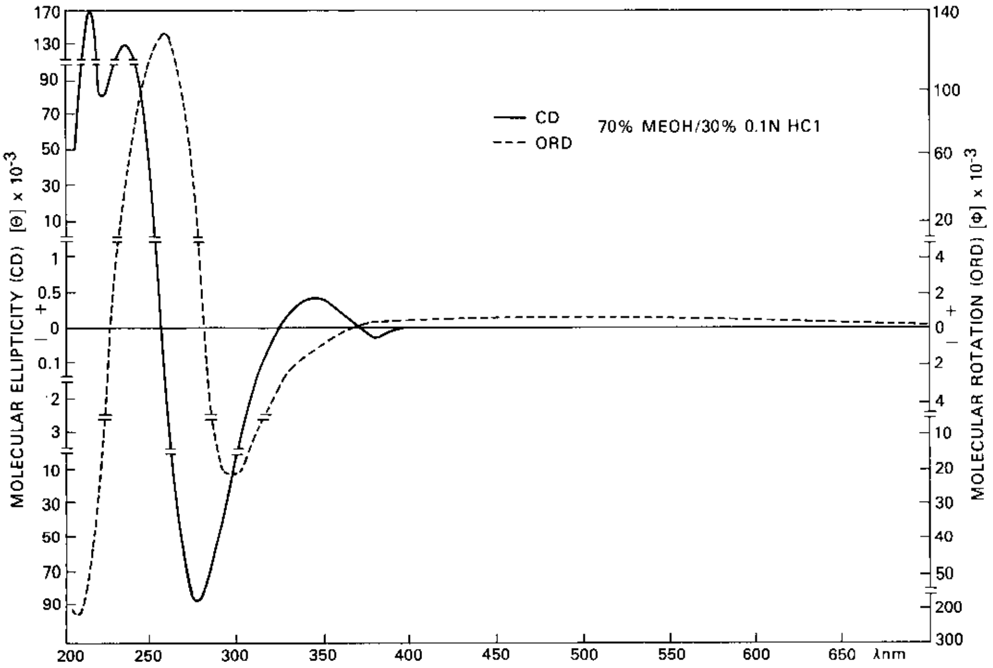


FIGURE 4. φ-DISINOMENINE

The formation of a 1:1 mixture of two dimers from a single dimer by thermal equilibration proves that both are stereoisomers. Steric hinderance is imposed by the bulky and opposing ethano bridges in the two confronting sinomenine moieties. The methine derived from bisquaternary salts of their corresponding bisdihydro dimers by Hofmann elimination are idential.[3] An additional factor hindering free rotation around the diphenyl linkage might be derive from their strong affinity for solvents. These dimers crystallize with solvent which cannot be removed or exchanged without changes in the crystal integrity. A good crystal of (+)-disinomenine, suitable for an X-ray analysis has, therefore, not been obtained as yet. It is not possible at this moment to decide whether structure 2a on the left in Fig. 1, with the ethano bridge of the lower sinomenine moiety above the corresponding unit of the upper half (confronting bridges), represents (+)-disinomenine or its ψ-dimer.

We would like to thank Dr. V. Toome, Physical Chemistry Department, Hoffmann-La Roche Inc., Nutley, New Jersey, for having measured and reported the CD and ORD spectra of the two (+)-dimers. We also would like to thank Dr. A. E. Jacobson from our Section for having initiated the analgesic and antitumor screening, of the two (+)- and (-)-dimers; all were found inactive. The interest of Dr. J. V. Silverton, National Heart, Lung and Blood Institute, NIH, in attempting to make an X-ray analysis of (+)-disinomenine, is also appreciated.

References:

1. Paper V, I. Iijima, J. Minamikawa, A. E. Jacobson, A. Brossi, and K. C. Rice, J. Med. Chem., 21, 398 (1978).
2. K. W. Bentley in "The Alkaloids", ed. by R. F. Manske, Academic Press, New York, Vol. XIII, 1971, p. 58.
3. K. Goto, "Sinomenine, an Optical Antipode of Morphine Alkaloids", Kitasato Institute, Tokyo, Japan, 1964.
4. Y. K. Sawa, N. Tsuji, K. Okabe, and T. Miyamoto, Tetrahedron, 21, 1121 (1965).
5. K. Okabe, K. Hayashi, and Y. Sawa, Chem. Pharm. Bull. Japan, 16, 1611 (1968).

Received, 26th September, 1978