Tetrahedron Letters No. 2, pp 187 - 190, 1974. Pergamon Press. Printed in Great Britain.

THE SYNTHESIS OF 3-SPIROOXINDOLE DERIVATIVES. TOTAL SYNTHESES OF dl-FORMOSANINE, dl-ISOFORMOSANINE, dl-MITRAPHYLLINE AND dl-ISOMITRAPHYLLINE

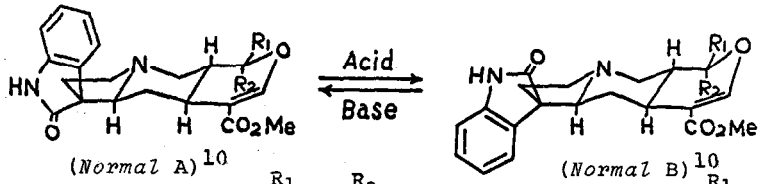
Yoshio Ban,* Naomasa Taga and Takeshi Oishi

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan

(Received in Japan 29 October 1973; received in UK for publication 3 December 1973)

After we published the intramolecular cyclization of the oxindole imino-ether,[1] Scott made a proposal claiming an important role of the oxindole alkaloid in the biosynthesis of various indole alkaloids.[2] Thus, attention was drawn to synthesize the pentacyclic oxindole alkaloids which are abundant in many stereo-isomeric forms in the botanical kingdom.[3] A total synthesis of dl-formosanine (1b, dl-uncarine B) and dl-isoformosanine(1a, dl-uncarine A)[4] was achieved by Windterfeldt according to an oxidative conversion of the indole to the oxindole at the final step,[5] which method had been applied to the conversion of natural ajimalicine into mitraphylline by Shavel[6] and Finch,[7] independently. We report a new total synthesis of dl-formosanine(1b), dl-isoformosanine(1a), dl-mitraphylline(2b) and dl-isomitraphylline(2a) starting from 2-hydroxytryptamine hydrochloride(4) in reference to our synthesis of rhynchophylline and isorhynchophylline.[8] The structures of these alkaloids[9] are delineated in Fig. I, in which their relationship as a pair of stereoisomers at 3-spiro position is shown by their ready interconversion and equilibration with acid or base.[10]

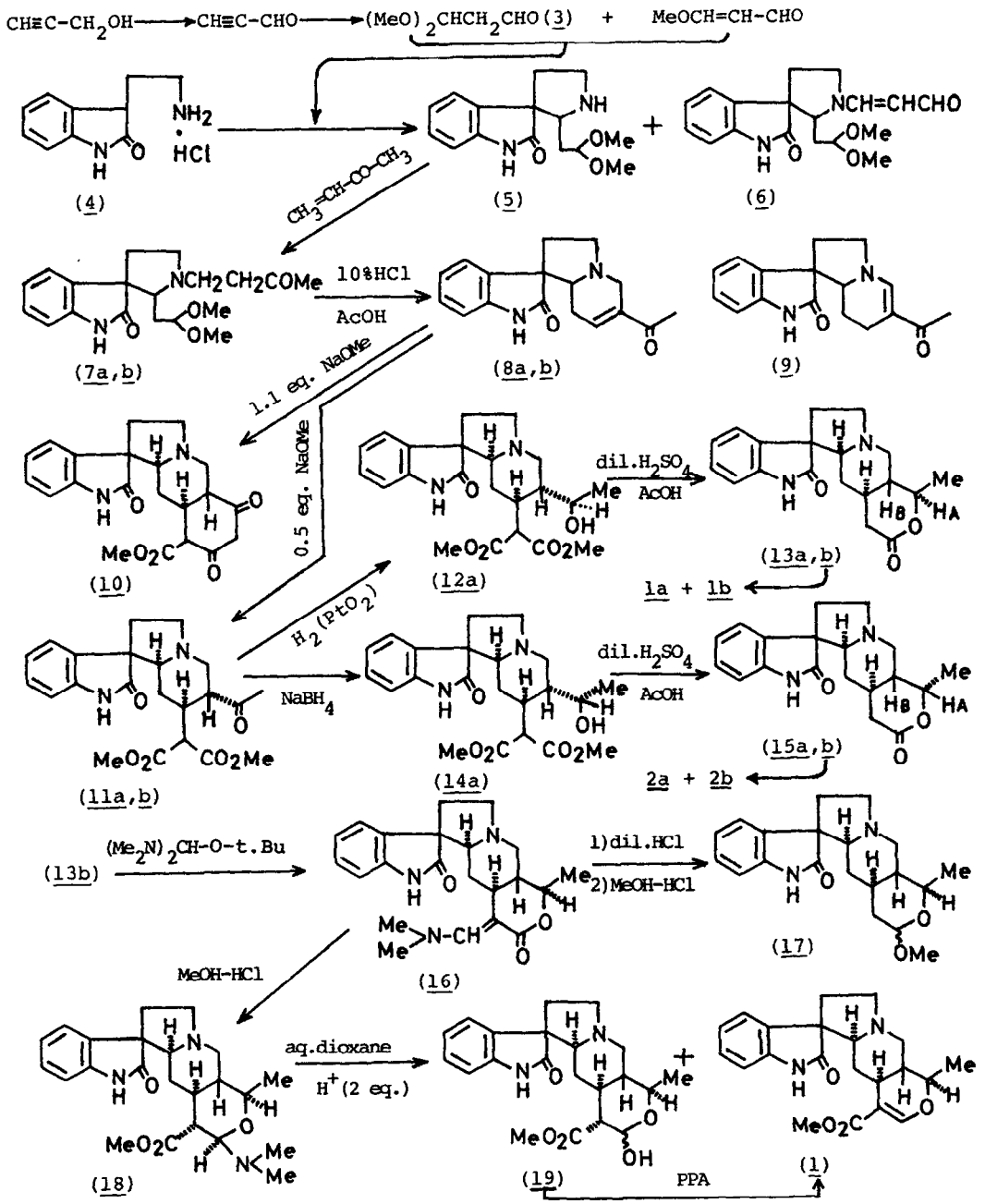
Fig. I



(*Normal* A)[10] (*Normal* B)[10]

	R_1	R_2		R_1	R_2
Isoformosanine(1a)	Me	H	Formosanine(1b)	Me	H
Isomitraphylline(2a)	H	Me	Mitraphylline(2b)	H	Me

3,3-Dimethoxypropionaldehyde[(3), b.p.$_{7}$40-41][11] which was adopted as a starting material and prepared from propargyl alcohol via propiol aldehyde[12] was found to be contaminated with 11% of 3-methoxyacrolein based upon NMR spectral



data. A solution of 3(1.2 eq.) and 4(1 eq.) in aqueous methanol containing NaOH(1.25 eq.) was kept at room temperature for 2 days to give 5 as pale yellow

oil in 72% yield along with 6(m.p. 185-187°) as a by-product(16% yield), in which separation was easy because of the insolubility of 6 in many organic solvents. The compound(5) was condensed with methyl vinyl ketone in dry benzene at room temperature overnight to provide 7 as two 3-spiroisomers, which without purification, was treated with 10%HCl-AcOH(1:1) at 100° to give 8a(m.p. 145°, 31% yield from 5) and 8b(m.p. 167°, 65% yield) after silica gel chromatography. Both of these isomers lacked the absorption around 300 nm, which excluded the possibility of 9. The Michael condensation of 8a with dimethyl malonate in methanol containing 1.1 eq. of NaOMe gave the diketoester(10, m.p. 194-196°). When treated with 0.5 eq. of NaOMe in methanol, however, 8a afforded 11a[m.p. 151-152°(dp.), 57% yield] and 8b gave 11b[m.p. 207-208°(dp.), 78% yield], in which the configuration at C-15 and C-20 should be thermodynamycally stable *trans*.

The compound(11a) was hydrogenated with Adams' catalyst in methanol to give 12a[m.p. 166-167°, M^+=416; NMR($CDCl_3$) δ 1.21(3H,d.), 3.60(3H,s.) and 3.68(3H,s.); ca. 100% yield], which was refluxed with dil.H_2SO_4 in AcOH to afford the two isomeric lactones[(13a), m.p. 265-267°, 27% yield, and (13b), m.p. 268°, 41% yield]. Both of the products indicated M^+=326 and the proton signals at δ 1.24 (3H,d.,C_{19}-CH_3) and 4.10(1H,m.,H_A, J_{AB}=8 Hz),[13] whose coupling constant(J_{AB}) suggested that the configuration at C_{20}-H_B and C_{19}-H_A should be *trans*(axial-axial). On reduction of 11a with $NaBH_4$ in methanol at -5∼-10° was obtained 14a[m.p. 160-162°(dp.), M^+=416, NMR($CDCl_3$) δ1.23(3H,d.), 3.61(3H,s.) and 3.69(3H,s.); 87% yield] as a sole product, which was heated with dil.H_2SO_4 in AcOH to afford the two isomeric lactones[(15a), m.p. 257-258°, 13% yield; and (15b), m.p. 254°, 47% yield], both of which indicated M^+=326 and the signals at δ 1.18(3H,d.) and 4.60 (1H,m.H , J_{AB}=4 Hz).[13] The coupling constant(J_{AB}) revealed the *cis*-relationship between H_A and H_B(equatorial-axial). The result of these remarkable stereoselectivities is noteworthy, but the cause is not clear.

The lactone(13b) was heated with $(Me_2N)_2CH$-O-tert.Bu[14] in DMF at 100° to give 16(M^+=381, UV λ_{max}^{MeOH} 302 nm) in 64% yield, which was hydrolyzed and decarboxylated by refluxing with dil.HCl, followed by treatment with MeOH-HCl to furnish 17(M^+= 342). On heating 16 with MeOH-HCl was obtained the aminoester[(18), M^+=413; NMR ($CDCl_3$) δ 1.18(3H,d.), 2.32(6H,s.) 3.53(3H,s.) and 4.02(1H,d.,J=10 Hz)], di-hydro-

chloride of which was heated in aqueous dioxane for 20 hr. to give the hemiacetal [(19), M^+=386] and the objective compound [(1), M^+=368]. The former (19) was converted into the latter (1) on treatment with PPA in DME. Accordingly, these operations with 13b were continuously made in one vessel without isolation of any intermediate to stereoselectively afford dl-isoformosanine [(1a), m.p. 222-224°, 19% yield] and dl-formosanine [(1b), m.p. 225-226°, 35% yield], both (M^+=368) of which were identified with authentic specimens of the natural alkaloids on direct comparisons of the IR ($CHCl_3$) spectra and Rf values of tlc, respectively. Similarly, 15b furnished dl-isomitraphylline [(2a), m.p. 217-220°, 16% yield] and dl-mitraphylline [(2b), m.p. 223-224°, 27% yield], which (M^+=368) were identical with the natural alkaloids, respectively, on comparisons of the IR spectra ($CHCl_3$) and Rf values on tlc.

Acknowledgement: We thank Professor Em. S. Sugasawa, University of Tokyo, for his valuable suggestion, Professor S. Sakai, Chiba University, Professor T. Nozoye, Meiji Pharmaceutical College, for their generous donation of authentic specimens of the natural alkaloids, and the Ministry of Education for the Grant-in-Aid.

References and Notes

1. T. Oishi, M. Nagai and Y. Ban, Tetrahedron Letters, 491 (1968).
2. a) A. I. Scott, Accounts Chem. Res., 3, 151 (1970). b) A. I. Scott and A. A. Qureshi, J. Am. Chem. Soc., 91, 5874 (1969).
3. a) M. Shamma and K. F. Foley, J. Org. Chem., 32, 4141 (1967). b) M. Shamma, R. J. Shine, I. Kompiś, T. Sticzay, F. Morsingh, J. Poisson, J.-L. Pousset, J. Am. Chem. Soc., 89, 1739 (1967). c) Formosanine and isoformosanine are the alkaloids of *Uncaria kawakamii* and *Ouroparia formosana*, and mitraphylline and isomitraphylline were isolated from the *Mitragina* species. [J. E. Saxton, "The Alkaloids, Chemistry and Physiology, Vol. VIII", edited by R. H. F. Manske (Academic Press, New York), p. 51 (1965)].
4. A. F. Beecham, N. K. Hart, S. R. Johns and J. A. Lamberton, Chem. Comm., 535 (1967).
5. E. Winterfeldt, A. J. Gaskell, T. Korth, H.-E. Radunz and M. Walkowiak, Chem. Ber., 102, 3558 (1969).
6. J. Shavel and H. Zinnes, J. Am. Chem. Soc, 84, 1320 (1962).
7. N. Finch and W. I. Taylor, ibid., 84, 1318 (1962).
8. Y. Ban, M. Seto and T. Oishi, Tetrahedron Letters, 2113 (1972).
9. J. C. Seaton, M. D. Nair, O. E. Edwards and L. Marion, Can. J. Chem., 38, 1035 (1960).
10. *Normal* A (Formula Nos. accompanied by a): Oxindole CO below C/D plane. *Normal* B (Formula Nos. accocmpanied by b): Oxindole CO above C/D plane.
11. A. P. Skoldinow, A. P. Arendank and T. M. Godzhello, J. Org. Chem. USSR, 6, 421 (1970).
12. Organic Syntheses, Coll. Vol. 4, 813 (1963) [John Wiley & Sons, Inc. New York].
13. These coupling constants were obtained by decoupling on irradiation at C_{19}-CH_3 frequencies.
14. H. Bredereck et al., Chem. Ber., 101, 41 (1968).