Communications to the Editor

[Chem. Pharm. Bull. 31(5)1806—1808(1983)]

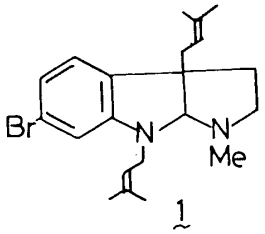
SYNTHESIS OF (±)-FLUSTRAMINE B, A MARINE ALKALOID

Tohru Hino,* Takao Tanaka, Kenji Matsuki, and Masako Nakagawa
Faculty of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Chiba-shi, 260, Japan

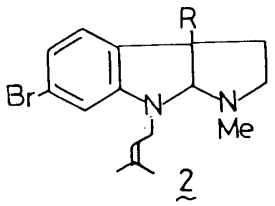
6-Bromo-N_b-methoxycarbonyltryptamine (7) was prepared from 5-nitropyrroloindole (4a) by a series of reactions: reduction, bromination, deamination, and ring opening. Prenylation of 7 with an excess dimethylallyl bromide gave the 3a,8-diprenylpyrroloindole (8). Hydrolysis of 8 followed by methylation with MeI-K_2CO_3-acetone provided (±)-flustramine B.

KEYWORDS—— flustramine B; bromination; prenylation; cyclic tautomer; tryptamine; 6-bromotryptamine; pyrroloindole

In recent years many brominated indole derivatives have been isolated from marine animals.[1] Among them flustramines[2] (flustramine B (1), flustramine A (2a), flustraminol B (2b) and others) isolated from Flustra foliacea (Bryozoa) have basic character and are known as marine alkaloids. These alkaloids are 6-bromopyrroloindole derivatives having one or two isoprene units at the 8- and/ or 3a-positions. We describe here the first synthesis of (±)-flustramine B (1) from tryptamine.



1

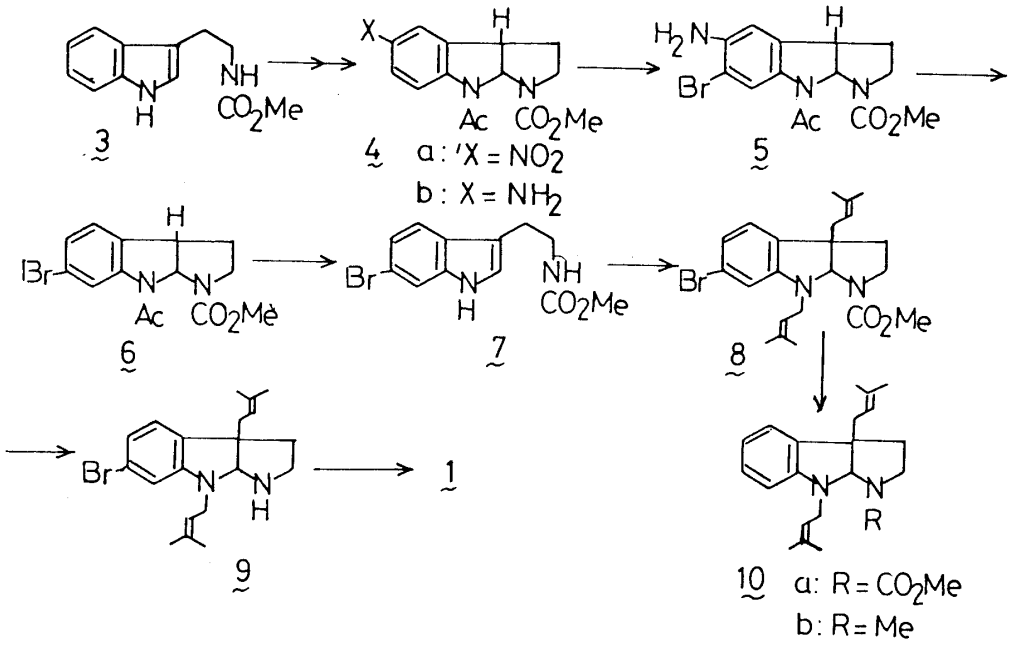


2

a : R = $-C(CH_3)_2-CH=CH_2$

b : R = OH

To synthesize these flustramines, 6-bromotryptamine is the crucial intermediate. As no convenient method to introduce a bromine atom directly to the 6-position of tryptamine is available at present, we have chosen as the starting material 5-nitropyrroloindole (4a), which is readily obtained from N_b-methoxycarbonyltryptamine (3) via the corresponding cyclic tautomer.[3] The bromination of the 5-amino derivative (4b) obtained by the catalytic reduction of 4a with NBS in dimethylformamide[4] gave 5-amino-6-bromo derivative (5)[5] in 27% yield. The deamination of 5 with an excess of isoamylnitrite[6] in tetrahydrofuran gave the 6-bromo derivative (6), mp 149.5-150.5°C,[7] in 60% yield from 4a without purification of the intermediates (4b, and 5). The structure of 6 was confirmed by its spectral data,[8] in particular, the position of the bromine atom was established by the NMR signal of the 7-proton



which appeared as a fine doublet at 8.27 ppm. Ring opening of 6 with 10% sulfuric acid-methanol at room temperature provided 6-bromotryptamine (7), mp 143-144.5°C,[7,9] in excellent yield. Thus a convenient method for the preparation of 6-bromotryptamine from tryptamine was established.

Prenylation of 7 with an excess (10 equivalents) of dimethylallyl bromide in acetate buffer (pH 2.7)[10] at room temperature gave the diprenylated pyrroloindole (8)[11] in 71% yield as an oil. In contrast to the prenylation of 3, in which 5 equivalents of dimethylallyl bromide were used to obtain 10a in 75% yield,[12] the prenylation of 7 afforded 8 in poor yield, showing the effect of the 6-bromine atom on the enamine character of the indole ring. The $LiAlH_4$ reduction of 8 in boiling dioxane gave the debrominated flustramine B (10b)[13] in excellent yield, but not 1. Hydrolysis of 8 with boiling 10% NaOH-EtOH for 100 h gave 9 in 39% yield. Methylation of 9 with CH_3I (1.0 eq)-K_2CO_3-acetone at room temperature successfully gave (±)-flustramine B (1) in 18% yield along with recovered 9 in 57% yield. The spectral data [NMR, IR(in $CHCl_3$), UV] of the synthetic sample were interchangeable with those of the natural product.

ACKNOWLEDGEMENTS We are grateful to Prof. C.Christophersen, University of Copenhagen, for spectral data on the natural product. Financial support from The Ministry of Education, Science, and Culture (Grant-in-Aid for Scientific Research) is also acknowledged.

REFERENCES AND NOTES

1) A.Sato and W.Fenical, Tetrahedron Lett., 24, 481 (1983); P.Djura and D.J. Faulkner, J.Org.Chem., 45, 735 (1980); P.Djura, D.B.Stierle, B.Sullivan, D.J. Faulkner, E.Arnold, and J.Clardy, J.Org.Chem., 45, 1435 (1980).

2) J.S.Carle and C.Christophersen, J.Am.Chem.Soc., 101, 4012 (1979); J.Org. Chem., 45, 1586 (1980); 46, 3440 (1981); P.Wulff, J.S.Carle, and C.Christophersen, J.Chem.Soc. Perkin Trans. 1, 1981, 2985; Comp.Biochem.Physiol., 71B, 523 (1982).

3) T.Hino and M.Taniguchi, J.Am.Chem.Soc., 100, 5564 (1978); T.Hino, M.Taniguchi, A.Gonsho, and M.Nakagawa, Heterocycles, 12, 1027 (1979); T.Hino, M.Taniguchi, and M.Nakagawa, Heterocycles, 15, 187 (1981); M.Taniguchi and T.Hino, Tetrahedron, 37, 1485 (1981); T.Hino, M.Taniguchi, I.Yamamoto, K.Yamaguchi, and M.Nakagawa, Tetrahedron Lett., 22, 2565 (1981); M.Taniguchi, A.Gonsho, M. Nakagawa, and T.Hino, Chem.Pharm.Bull., 31, in press.

4) R.H.Mitchell, Y-H.Lai, and R.V.Williams, J.Org.Chem., 44, 4733 (1979).

5) mp 193-195°C. λ_{max}(EtOH): 266 and 323 nm. m/z : 355, 353(M^+, 37), 313,311 (M-CH_2CO, 100). NMR($CDCl_3$) δ: 2.51(s, 3H, Ac), 3.72(s, 3H, OMe), 3.95(t, 1H, J=6 Hz, 3a-H), 6.18(d, 1H, J=6 Hz, 8a-H), 6.61(s, 1H, 4-H), 8.17(s, 1H, 7-H).

6) J.I.G.Cadogan and G.A.Molina, J.Chem.Soc.,Perkin Trans. 1, 1973, 541.

7) Satisfactory analytical data were obtained on the compounds whose mps are given in the text.

8) λ_{max}(EtOH) nm(ε): 216(29600), 248(11600), 284(2760), 291(2710). m/z : 340, 338(M^+, 12), 298, 296(M-CH_2CO, 100). NMR($CDCl_3$) δ: 2.13(m, 2H, 3-H_2), 2.55(s, 3H, Ac), 2.89, 3.84(m, 2H, 2-H_2), 3.73(s, 3H, OMe), 4.02(t, 3H, J=7 Hz, 3a-H), 6.23(d, 1H, J=7 Hz, 8a-H), 7.04(dd, 1H, J=8 and 1 Hz, 4-H), 7.23 (dd, 1H, J=8 and 2 Hz, 5-H), 8.27(d, 1H, J=2 Hz, 7-H).

9) λ_{max}(EtOH) nm(ε) : 229(28200), 280^{sh}(3960), 287(4420), 296(4020). m/z : 298, 296(M^+, 35), 223, 221(M-H_2NCO_2Me, 63), 210, 208(100). NMR($CDCl_3$) δ : 2.94(t, 2H, J=7 Hz, CH_2), 3.49(m, 2H, CH_2N), 3.66(s, 3H, OMe), 4.74(br, 1H, NH), 7.01(d, 1H, J=2 Hz, 2-H), 7.22(dd, 1H, J=8 and 2 Hz, 5-H), 7.46(d, 1H, J=8 Hz, 4-H), 7.52(d, 1H, J=2 Hz, 7-H), 8.05(br, 1H, Ind-NH).

10) G.Casnati, M.Francioni, A.Guareschi, and A.Pochini, Tetrahedron Lett., 1969, 2485; V.Bocchi, G.Casnati, and R.Marchelli, Tetrahedron, 34, 929 (1978).

11) λ_{max}(EtOH): 261 and 316 nm. m/z : 434, 432(M^+, 18), 365, 363(M-69, 100). NMR($CDCl_3$) δ: 1.56, 1.67, 1.70, 1.74(each s, each 3H, CH_3), 1.99(m, 2H, 3-H_2), 2.35(d, 2H, J=7 Hz, CH_2-C=C), 3.03, 4.01(m, each 1H, 2-H_2), 3.71(s, 3H, OMe), 3.89(m, 2H, NCH_2C=C), 5.00(m, 1H, CCH=C), 5.11(m, 1H, CCH=C), 5.35(s, 1H, 8a-H), 6.44(d, 1H, J=1 Hz, 7-H), 6.73(dd, 1H, J=8 and 1 Hz, 5-H), 6.80(d, 1H, J=8 Hz, 4-H).

12) M.Nakagawa, K.Matsuki, and T.Hino, Tetrahedron Lett., 24, in press.

13) Debromoflustramine B has been synthesized by another route; Private communication from Prof. Christophersen.

(Received April 3, 1983)