

A NEW ENTRY INTO THE SYNTHESIS OF THE STRYCHNOS INDOLE ALKALOIDS  
CONTAINING 19,20-DOUBLE BOND VIA THE THIO-CLAISEN REARRANGEMENT

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Summary: A simple and selective route to the Strychnos framework containing 19,20-double bond has been developed employing the thio-Claisen rearrangement.

One of the major difficulties in the synthesis of the Strychnos-type indole alkaloids lies in the introduction of the 19,20-double bond with an appropriate stereochemistry<sup>1</sup>. We report here a thio-Claisen approach<sup>2</sup> leading to the selective formation of the Strychnos framework containing 19,20-double bond with the requisite stereochemistry.

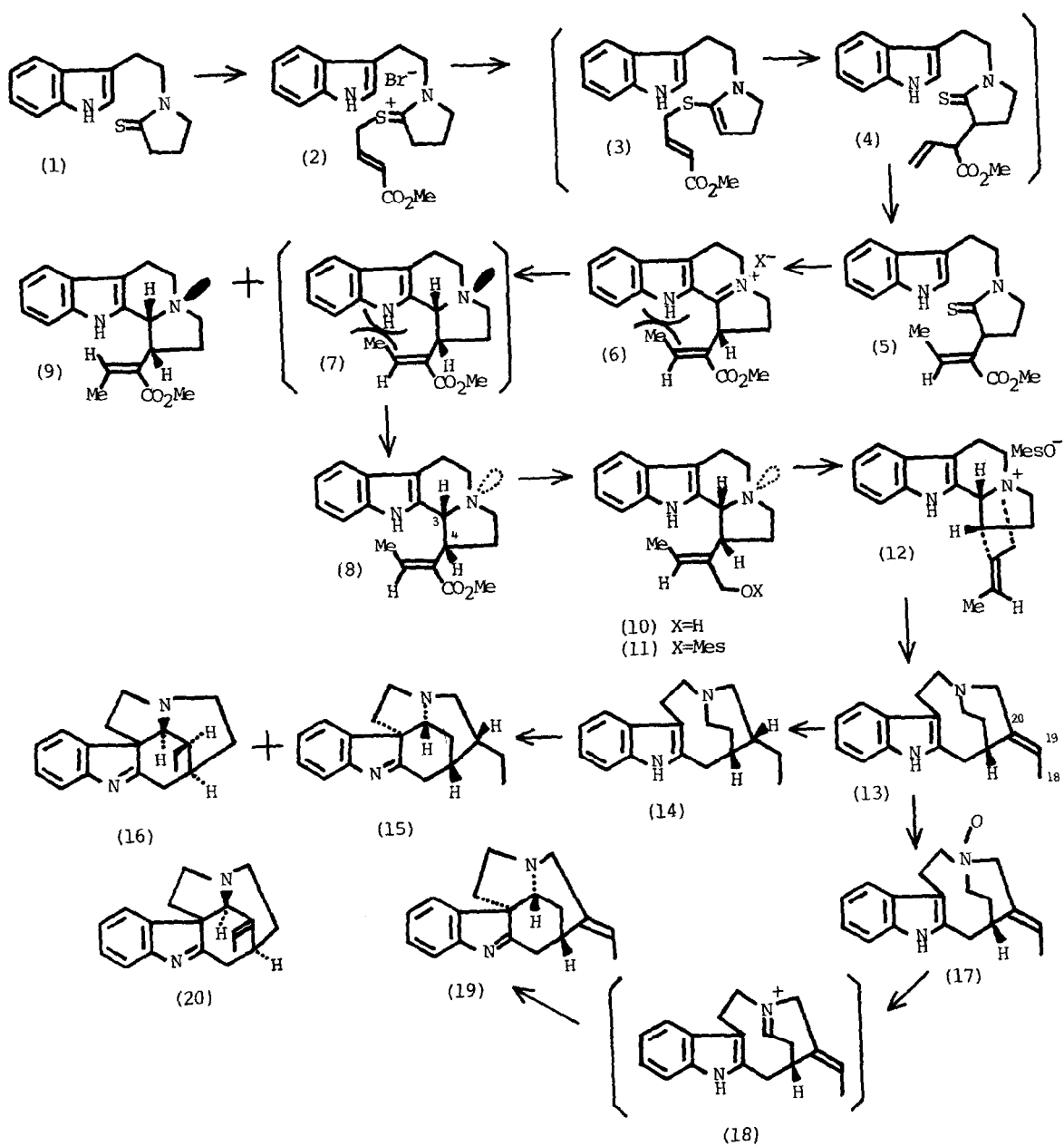
Thio-lactam(1)<sup>3,4</sup>, mp 131-133 °C, was reacted with methyl  $\gamma$ -bromocrotonate<sup>5</sup> in THF at room temperature to give quantitative yield of the sulfonium salt(2) which was then treated with sodium methoxide in THF at room temperature to induce concurrent ketene thioaminoacetal formation, [3.3]-sigmatropic rearrangement, and stereoselective double bond migration<sup>6</sup>, affording the  $\alpha,\beta$ -unsaturated(E) ester(5)<sup>7</sup>, mp 139.5-141.5 °C, in 83% yield. Cyclization<sup>8</sup> of the thio-lactam(5) with neat phosphorus oxychloride at reflux temperature gave the crude quaternary base(6) which on reduction with sodium borohydride gave 54% yield of the E-isomer(8), mp 124-126 °C, accompanied by 8% yield of the Z-isomer(9), mp 97-100 °C. These compounds were separated on a silica-gel column and were distinguished spectroscopically: namely, the former showed the Bohlmann bands in the IR spectrum and strongly deshielded 19-H(q, J=8 Hz,  $\delta$  6.92 ppm) and less deshielded 18-methyl(d, J=8 Hz,  $\delta$  1.92 ppm) in the NMR spectrum, while the latter showed no Bohlmann bands in the IR spectrum and less deshielded 19-H(q, J=8 Hz,  $\delta$  5.87 ppm), more deshielded 18-methyl(d, J=8 Hz,  $\delta$  1.83 ppm) and the characteristic

3-H of cis C/D configuration<sup>9</sup> (d, J=6 Hz,  $\delta$  4.37 ppm), in the NMR spectrum. Formation of the Z-isomer(9) may be explained in terms of the steric congestion of the quaternary base(6) which induced partial isomerization of the double bond under the reaction conditions. On the reduction, stereoselective hydride delivery occurred from the less hindered face of both the E- and Z-isomers giving the corresponding C/D-cis tertiary amines (7) and (9) with cis 3-H/4-H configuration. Of these, the former underwent spontaneous inversion at the tertiary nitrogen to relieve the steric congestion affording the trans-C/D amine(8) with less hindered configuration.

Although the reduction of the ester group of (8) was found to be difficult<sup>10</sup>, the desired allylic alcohol(10), mp 172-177 °C, could be obtained in 85% yield by using diisobutylaluminum hydride in benzene solution at 0 °C. Methanesulfonation of (10) afforded the unstable mesylate(11) which underwent spontaneous intramolecular alkylation to give the pentacyclic quaternary base(12) during work-up. Treatment of (12) with sodium metal in liquid ammonia<sup>11</sup> furnished the known nine-membered amine(13)<sup>1,13</sup>, mp 146-149 °C (lit<sup>13</sup>. 125-150 °C), NMR(CDCl<sub>3</sub>+CD<sub>3</sub>OD)  $\delta$  1.69(3H, d, J=7 Hz), 5.49(1H, br q, J=7 Hz) ppm, in 81% yield from (10). Since this compound has been converted into the Strychnos alkaloids, tubifoline (15) and tubifolidine(15, 19,20-dihydro), and the Aspidospermatidine alkaloid, tubotaiwine(16), via catalytic hydrogenation<sup>13</sup>, followed by platinum mediated oxidative cyclization<sup>1,14</sup>, the present synthesis also constitutes an alternative route to these saturated alkaloids.

Treatment of the unsaturated amine(13) with m-chloroperbenzoic acid(1.5 equiv.) in methylene chloride at 0 °C afforded the N-oxide(17), in practically pure state, which was then exposed to trifluoroacetic anhydride in methylene chloride(-78 °C to room temperature) to induce the Polonovsky-Potier reaction<sup>15</sup>. Interestingly the product isolated possessed only the Strychnos framework(19)<sup>12</sup>, mp 79-82 °C (lit<sup>13</sup>. 80-84 °C),  $\delta$ (CDCl<sub>3</sub>) 1.64(3H, d, J=7 Hz), 5.37(1H, q, J=7 Hz) ppm, and the formation of the alternative Aspidospermatidine framework(20) could not be detected. The same selectivity has been reported by Crawley and Harley-Mason who have obtained only (19) from (13) on the platinum mediated oxidative cyclization<sup>16</sup>.

The present procedure represents a simple and selective entry to the Strychnos type alkaloids containing the 19,20-double bond and further efforts to utilize this procedure for the Strychnos alkaloid synthesis are underway.



## REFERENCES

1. Harley-Mason and his co-worker have developed an ingenious method for the introduction of the 19,20-double bond in the Strychnos-type alkaloids, however it lacks controlling the stereochemistry: see, G.C. Crawley and J. Harley-Mason, J. C. S. Chem. Comm., 1971, 685.
2. We have established the thio-Claisen approach for the synthesis of the Iboga-type and the Aspidosperma-type indole alkaloids: see, S. Takano, M. Hirama, T. Araki, and K. Ogasawara, J. Am. Chem. Soc., 1976, 98, 7084.
3. This compound was prepared by condensation of tryptamine and  $\gamma$ -butyrolactone, followed by treatment of the lactam produced with phosphorus pentasulfide.
4. All new compounds isolated gave satisfactory analytical (combustion and/or high-resolution MS) and spectral (IR, NMR, and MS) data.
5. K. Ziegler, A. Späth, E. Schaaf, W. Schumann, and E. Winkelmann, Ann., 1942, 551, 80.
6. Cf. S. Takano, E. Yoshida, M. Hirama, and K. Ogasawara, J. C. S. Chem. Comm., 1976, 776.
7. IR: (Nujol) Max 3355, 1690  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  1.83(3H, d,  $J=7$  Hz), 1.9-2.37(2H, m), 2.9-3.36(2H, br t,  $J=8$  Hz), 3.4-3.8(2H, m), 3.7(3H, s), 3.87-4.3(3H, m), 6.9-7.9(6H, m), 8.67(1H, s);  $^{13}\text{C-NMR}(\text{CDCl}_3)$   $\delta$  14.501(q), 21.722(t), 25.010(t), 49.081(t), 51.547(q), 52.604(d), 54.130(t), 111.315(d), 112.137(s), 118.651(d), 119.238(d), 121.883(d), 122.352(d), 127.284(s), 132.624(s), 136.265(s), 140.492(d), 166.615(s), 201.138(s).
8. Cf. S. Yamada and A.M.F. Omar, Chem. Pharm. Bull., 1964, 12, 249.
9. E. Wenkert, S. Garratt, and K.G. Dave, Can. J. Chem., 1964, 42, 489.
10. Reduction using  $\text{LiAlH}_4$  under various conditions yielded a complex mixture of the products including the saturated pentacyclic amines formed through concomitant reduction of the double bond and reductive cyclization between the ester group and the indole nitrogen.
11. Cf. J. Harley-Mason, Atta-ur-Rahman, and J.A. Beisler, J. C. S. Chem. Comm., 1966, 743.
12. This compound was first obtained by Smith and Wröbel<sup>13</sup> from the Strychnos alkaloid, akuammicine, in the degradation study and then was synthesized by Harley-Mason and his co-worker<sup>1</sup>.
13. G.F. Smith and J.T. Wröbel, J. Chem. Soc., 1960, 792.
14. D. Schumann and H. Schmid, Helv. Chim. Acta., 1963, 46, 1996.
15. Cf. L. Chevolot, H.-P. Husson, and P. Potier, Tetrahedron, 1975, 31, 2491.
16. We also obtained (19) exclusively from (13) employing the platinum mediated oxidative cyclization<sup>14</sup>.

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