A NOVEL SKELETAL REARRANGEMENT OF AN INDOLIZIDINE ALKALOID, SWAINSONINE VIA AN AZIRIDINIUM INTERMEDIATE

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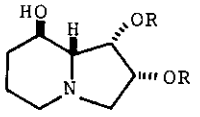
Abstract—Nucleophilic displacement reactions of mesylate 3, derived from swainsonine (1), gave the rearranged products 5 along with the swainsonine-type products 6 via an aziridinium intermediate 4.

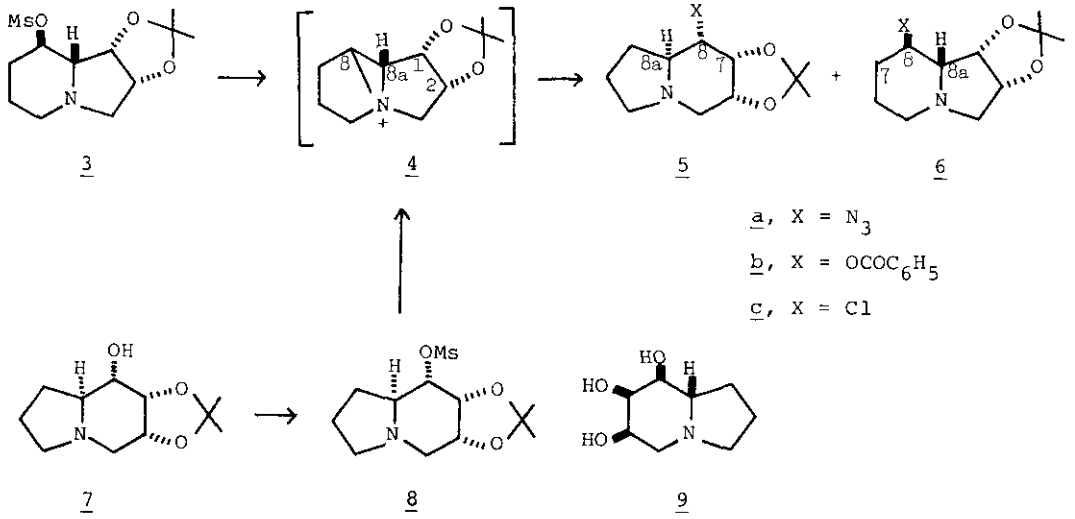
There has been considerable current interest in the medicinal chemistry of polyhydroxylated indolizidine alkaloids represented by swainsonine (1), because of their interesting biological activities.[1] As part of our program in this field,[2,3] we have been concerned with chemical modifications of swainsonine, in which we have encountered a novel skeletal rearrangement of the indolizidine ring of swainsonine. The present paper deals with this rearrangement.

With a view to obtaining the compounds having other functional groups in place of the hydroxy group at C-8 of swainsonine, we examined substitution reactions of mesyl derivative 3 (mp 90-92°C), derived from swainsonine acetonide 2[4] by mesylation (MsCl/pyridine, 5°C, 95 %). Treatment of 3 with NaN_3 (DMF, 100°C) gave a mixture of two products, which were easily separated by silica gel chromatography to give 5a (oil)[8] and 6a (oil)[8] in 60 % and 17 % yields, respectively. The structure of these products were assigned on the basis of the following ^1H NMR data of the methine (C-8) protons bearing the newly introduced azido groups. In the major product 5a, the C-8 proton was observed at δ3.25 with a cis coupling (5 Hz) to 7-H (δ4.41, t, J = 5 Hz) and a trans coupling (10 Hz) to 8a-H (δ2.43, dt, J = 7, 10 Hz), suggesting the structure 5a for this compound. In contrast, the minor product showed at δ3.58 the corresponding proton which was coupled to 7α-H (δ2.16, m), 7β-H (δ1.29, m), and 8a-H (δ1.63, dd, J = 4, 10 Hz) with coupling constants 4.5 (cis), 12 (trans), and 10 Hz (trans), respectively, being in agreement with the structure 6a.



1, R = H

2, R,R = $C(CH_3)_2$



3 4 5 6

a, X = N_3

b, X = $OCOC_6H_5$

c, X = Cl

7 8 9

These products were presumed to be formed via an aziridinium intermediate 4, which was attacked by the azide anion at the 8 or 8a carbons to give 5a and 6a, respectively.[5] The preferential formation of 5a may be interepreted in terms of a steric hindrance of the 1,2-acetonide protecting group in the intermediate 4. It also appears that the approaches of the azide nucleophile to C-8 or C-8a from the opposite side of the aziridinium nitrogen established the configurations of the azido groups.

For corroboration of the above reaction mechanism leading to 5a and 6a, we treated 3 with sodium benzoate (DMF, 100°C) to yield, after silica gel chromatography, the benzoyl derivatives 5b (oil, 68 %)[8] and 6b (mp 81-83°C, 15 %).[8] Deprotection of the major product 5b by methanolysis with MeONa (MeOH, r.t.), followed by acid treatment (75 % aqueous TFA, r.t.) of the resulting product 7 (mp 88-89°C, 62 %), provided triol 9 (mp 175-177°C, 66 %)[8] which was identified with the compound synthesized from D-mannose as described in the preceding paper.[2] The same treatments of the minor product 6b gave the compound identical with the starting

swainsonine itself. These results thus provided a corroborative evidence for the reaction mechanism described above.[6,7] Furthermore, more definitive evidence was obtained as follows. Mesylate 8 (unstable oil), derived from 7 by mesylation (MsCl/pyridine, 5°C, 100 %), was treated with sodium benzoate under the same conditions used for the reaction of 3 to give 5b and 6b (40 %) in the same ratio as that from 3. These products, especially the ring-contracted product 5b, clearly proved the intermediacy of the aziridinium ion 4 in this displacement reaction.

When 3 was treated with LiCl (DMSO, 70°C), the chloro derivative 5c (oil) was obtained as a single product (100 %).[8] It is probable that, in this reaction, two products (5c and probably 6c) were initially formed and the swainsonine-type product 6c was further converted, via the aziridinium ion 4, to the thermodynamically stable rearranged product 5c during the reaction. Treatment of the product 5c with NaN_3 in the same manner as that used for the reaction of 3 gave, also via 4, the same ratio of 5a and 6a (93 %) as in the case of 3.

The present work outlined a novel rearrangement of swainsonine, which permits the preparation of various derivatives of indolizidine alkaloids. Details for these derivatives and their biological activities will be reported in due course.

REFERENCES AND NOTES

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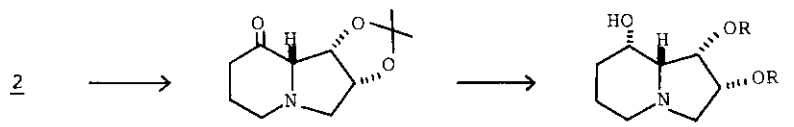
(b) Immunostimulating activity: T.Kino, N.Inamura, K.Nakahara, S.Kiyoto, T.Goto, H.Terano, M.Kohsaka, H.Aoki, and H.Imanaka, J. Antibiot., 38, 936 (1985).
2. H.Setoi, H.Takeno, and M.Hashimoto, J. Org. Chem., 50, 3948 (1985).
3. H.Setoi, H.Takeno, and M.Hashimoto, Tetrahedron Lett., 26, 4617 (1985).
4. H.J.Schneider, F.S.Ungemach, H.P.Broquist, and T.M.Harris, Tetrahedron, 39, 29 (1983).
5. For a similar type of rearrangement, see e.g. S.Archer, T.R.Lewis, M.R.Bell, and J.W.Schulenberg, J. Am. Chem. Soc., 83, 2386 (1961).
6. Reaction of 2 under the Mitsunobu reaction conditions also gave 5b (82 %) and 6b (11 %) (O.Mitsunobu, Synthesis, 1 (1981) and references cited therein).

7. The C-8 epimer 12 (mp 101-103°C)[8] of swainsonine was prepared from 2 in 18 % yield by a sequence of reactions (1. DMSO/DCC; 2. $NaBH_4$; 3. 75 % aqueous TFA).



2 → 10 → 11, R,R = $C(CH_3)_2$; 12, R = H

8. The selected spectral data. 5a: IR(film) 2090 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.54 (m, 1 H), 1.76-1.92 (m, 2 H), 2.15 (m, 1 H), 2.20 (dd, J = 9, 15 Hz, 1 H), 2.29 (q, J = 8.5 Hz, 1 H), 2.43 (dt, J = 7, 10 Hz, 1 H), 2.97 (ddd, J = 8.5, 7, 4 Hz, 1 H), 3.08 (dd, J = 6.5, 11 Hz, 1 H), 3.25 (dd, J = 10, 5 Hz, 1 H), 4.34 (ddd, J = 5, 6.5, 9 Hz, 1 H), 4.41 (t, J = 5 Hz, 1 H). 6a: IR (film) 2090 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.29 (m, 1 H), 1.63 (dd, J = 4, 10 Hz, 1 H), 1.66-1.76 (m, 2 H), 1.87 (dt, J = 3, 11 Hz, 1 H), 2.13 (m, 1 H), 2.16 (dd, J = 4, 11 Hz, 1 H), 3.01 (dt, J = 3, 11 Hz, 1 H), 3.14 (d, J = 11 Hz, 1 H), 3.58 (ddd, J = 4.5, 10, 12 Hz, 1 H), 4.60(dd, J = 4, 6 Hz, 1 H), 4.66 (dd, J = 4, 6 Hz, 1 H). 5b: ^1H NMR ($CDCl_3$) δ1.2-1.5 (m, 1 H), 1.6-2.0 (m, 3 H), 2.1-2.4 (m, 2 H), 2.68 (m, 1 H), 3.00 (m, 1 H), 3.12 (dd, J = 6, 11 Hz, 1 H), 4.41 (m, 1 H), 4.81 (t, J = 4 Hz, 1 H), 5.05 (dd, J = 4, 12 Hz, 1 H). 6b: ^1H NMR ($CDCl_3$) δ1.30 (m, 1 H), 1.6-2.3 (m, 5 H), 2.40 (m, 1 H), 3.02 (m, 1 H), 3.18 (d, J = 11 Hz, 1 H), 4.5-4.7 (m, 2 H), 5.10 (dt, J = 4, 10 Hz, 1 H). 5c: ^1H NMR ($CDCl_3$) δ1.1-1.7 (m, 4 H), 1.87 (m, 1 H), 2.17 (dd, J = 5, 11 Hz, 1 H), 2.33 (m, 1 H), 3.05 (m, 1 H), 3.28 (dd, J = 7, 11 Hz, 1 H), 4.08 (ddd, J = 5, 7, 10 Hz, 1 H), 4.59 (dd, J = 6, 10 Hz, 1 H), 4.70 (dd, J = 5, 6 Hz, 1 H). 9: ^1H NMR (D_2O) δ1.3-2.1 (m, 4 H), 2.92 (dd, J = 5, 10 Hz, 1 H), 2.99 (m, 1 H), 3.43 (dd, J = 3, 10 Hz, 1 H), 3.83 (ddd, J = 3, 5, 10 Hz, 1 H), 4.03 (t, J = 3 Hz, 1 H), 12: ^1H NMR (pyridine-d_5 and D_2O) δ 1.2-1.4 (m, 2 H), 1.85 (dd, J = 2, 5 Hz, 1 H), 1.88 (dt, J = 3, 10 Hz, 1 H), 1.98 (m, 1 H), 2.27 (m, 1 H), 2.28 (dd, J = 6, 10 Hz, 1 H), 3.04 (dt, J = 10, 2.5 Hz, 1 H), 3.25 (dd, J = 10, 2 Hz, 1 H), 4.38 (dt, J = 2, 6 Hz, 1 H), 4.42-4.45 (m, 2 H).

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