STUDIES IN THE FORMATION OF OXINDOLES FROM THEIR INDOLOAZABICYCLO[3.3.1]NONANE COUNTERPARTS AND IMPLICATIONS FOR THE BIOGENESIS OF ALSTONISINE

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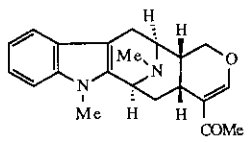
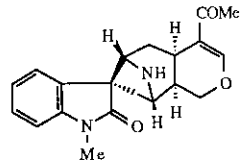
Abstract- Treatment of the N_a-H indoloazabicyclo[3.3.1]nonane **5** with *t*-BuOCl and hydrolysis of the intermediate chloroindolenine provided the oxindole **6** in 88% yield. In contrast, N_a-methyl analogues **9a-c** failed to rearrange to the corresponding oxindoles when reacted under the analogous conditions. Instead, the indolooctane-1,4-dione **11** and an isomer related to **12** were isolated from the oxidation of **9a**. The implications in regard to the biogenesis of alstonisine **2** are discussed.

During the course of work[1] directed towards the stereospecific synthesis of indole alkaloids isolated from *Alstonia* species,[2] it became of interest to study the interconversion of molecules related to alstonerine **1** and alstonisine **2**, as a possible means of synthetic entry into the latter oxindole alkaloid **2**.



(1)



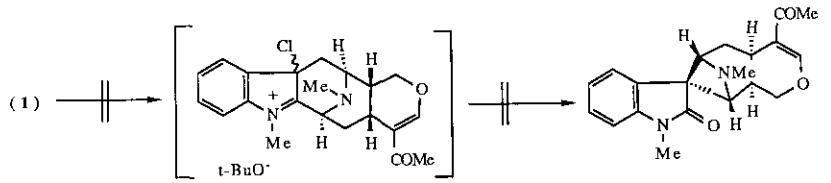
(2)†

† Footnote: For clarity, the relative stereochemistry of the four chiral methine protons has been depicted as shown, although for a full representation of the absolute stereochemistry of alstonisine, the indole portion should be perpendicular to the plane of the paper. (It should be noted that the original X-ray structure determination by Nordman[7a] depicts the wrong enantiomer, which had previously been assigned by a comparison with the configuration of ajmalicine).

This approach is based on the published conversion of tetrahydro-β-carboline alkaloids into their corresponding oxindole counterparts,[3] a pathway which might also be regarded as a part of their formal biogenesis.

Le Quesne *et al.*[4] had previously attempted to convert alstonerine **1** into N_b-methylalstonisine **4** by the action of *t*-BuOCl on **1**, but these efforts were unsuccessful.[5] No oxindole products were isolated in this sequence (Scheme 1).

Scheme 1



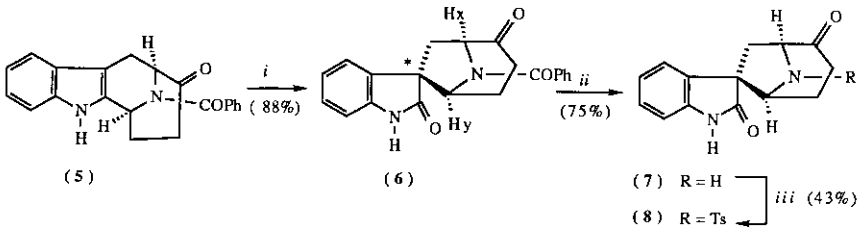
It was reported that oxidation of **1** may be more difficult to effect in the case of the N_a-methylated base in comparison to its N_a-H analogue.[5] The presence of the N_a-methyl group would dramatically reduce the reactivity of the indole at position-3 toward electrophiles and formation of the chloroindolenine **3** would be retarded (Scheme 1).

It was decided to study this oxidative transformation with **5**, a tetracyclic derivative closely related to **1** to observe the effect of an N_a-H or N_a-methyl group on the progress of oxindole formation. This would provide some insight into the biogenesis of **2**, and permit an evaluation of an indole-oxindole rearrangement pathway for the synthesis of **2**.

In this regard, the tetracyclic ketone **5** was synthesized by the procedure of Hobson[6] and subsequently reacted with 2 equivalents of *t*-BuOCl in CH_2Cl_2 (Scheme 2). The intermediate chloroindolenine[3] was not isolated but was subjected to hydrolysis in a mixture (1:1) of methanol and aqueous acetic acid (10%).

The oxindole **6** was isolated from this reaction in 88% yield, accompanied by a small amount of starting material **5** (12%). The ^1H and ^{13}C nmr spectra of **6** were complex because of the presence of rotamers, a phenomenon determined by a saturation transfer experiment involving methine protons H_x and H_y. In order to determine, unambiguously, whether this mixture was composed of two rotamers or two

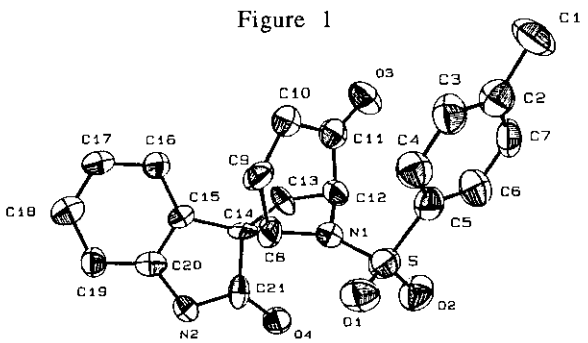
Scheme 2



Reagents: *i*, *t*-BuOCl, CH_2Cl_2 then MeOH/aq. AcOH/reflux; *ii*, 6N HCl/AcOH/MeOH/reflux; *iii*, TsCl/py

diastereomers, the N_b-benzoyl group was removed to simplify the spectra. Treatment of **6** with aqueous acid gave **7** (R = H) as a single pure oxindole in 75% yield. The carbon skeleton of this oxindole was confirmed by 2D-COSY nmr, but the relative stereochemistry of the quaternary carbon (*) could not be established unequivocally. Suitable crystals of **7** (R = H) could not be obtained for a crystal structure, consequently the amine was converted into the tosylamide **8** (R = Ts), crystals of which could be grown from ethanol. The tosyl group is unique for its stereochemistry precluded the formation of rotamers, while providing suitable material for X-ray analysis (Figure 1).

Figure 1



(8)

Figure 1 ORTEP drawing of **8**. Thermal ellipsoids are drawn at 50% probability level. The hydrogen atoms have been omitted for clarity. **8** crystallizes in the triclinic space group $P\bar{1}$ with unit cell dimensions a = 7.775 (2) Å, b = 10.788 (2) Å, c = 11.707 (2) Å, α = 108.39 (2)°, β = 92.28 (2)°, γ = 93.74 (2)°, V = 927.9 (4) $Å^3$, and d_{calc} = 1.412 g/cm^3 for Z = 2. Reflections within a 2θ range of $4° \leq 2\theta \leq 40°$ were collected with 3 check reflections every 120 minutes, yielding 1293 unique reflections of which 1079 were coded observed, $I > 3\sigma(I)$. The structure was refined to R = 0.078.

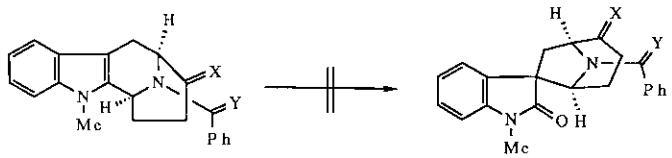
The crystallographic data were collected by θ-2θ scans at 22°C on a Picker four-circle autodiffractometer with PCXTAL.* All heavy atoms were located by direct methods using SHELXS-86.** Hydrogen atom positions were calculated based on ideal geometries. Refinement of the structure was accomplished using SHELX-76.*** All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were allowed to ride on the corresponding carbon atom and refined isotropically with a common temperature factor. The atom coordinates and anisotropic temperature factors, bond lengths, bond angles, and tables of calculated and observed structure factors are available on request.

* Locally written software.
** Sheldrick, G. M. "Shelxs-86, A Program for Crystal Structure Solution," University of Cambridge; Cambridge England, 1986.
*** Sheldrick, G. M. "Shelx-76, A Program for Crystal Structure Determination," University of Cambridge: Cambridge England, 1976.

Comparison of the ORTEP diagram of **8** with the structure reported for alstonisine[4,7] clearly indicates that the relative stereochemistry at the quaternary carbon (*) in the two oxindoles is reversed. Presumably, the reaction of *t*-BuOCl with **5** must have occurred from the least hindered (bottom) face since the top (β) face of the indole is sterically congested due to the three carbon bridge (see **5**). Hydrolysis of the intermediate chloroindolenine and rearrangement evidently occurred from the top face *via* an Sn2 "type" displacement[3,8] to afford oxindole **6** with the stereochemistry depicted in Figure 1.

Although oxindole formation in the N_a-H series had been successfully executed, in view of the earlier reports of LeQuesne *et al.*[4,5] it was of interest to attempt the oxidation with the corresponding N_a-methyl derivatives **9a-c**. Treatment of the N_a-methyl analogues **9a-c** of the indoloazabicyclo[3,3,1]nonane with *t*-BuOCl, followed by hydrolysis, in general gave a complex mixture of products. Moreover, none of the desired oxindoles were observed or isolated.

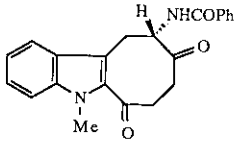
Scheme 3



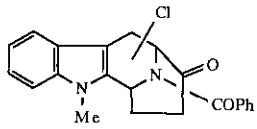
(9) a ; X = Y = O
b ; X = O, Y = H_2
c ; X = Y = H_2

(10)

For example, when **9a** was reacted under the same experimental conditions analogous to those employed for the oxidation of **5**, cleavage of the azabicyclo[3.3.1]nonane skeleton occurred to provide indolooctane-1,4-dione **11**. This material was accompanied by the chloro derivative **12** [ms (CI) 379 (M^++1), (100%) 381 (M^++3) (35.9%)], the structure of which has not been unambiguously determined.



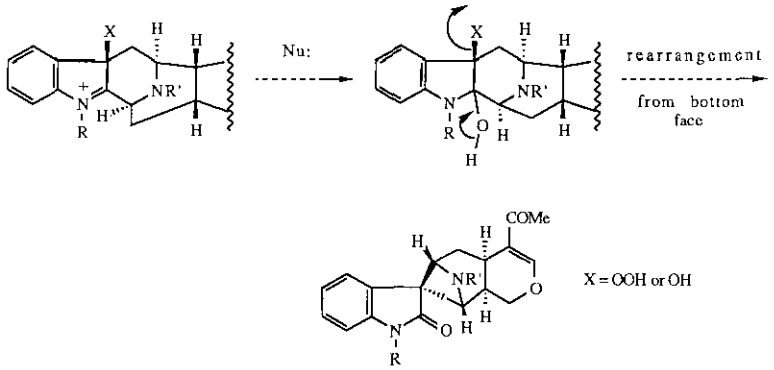
(11)



(12)

Conclusion The unsuccessful attempt to convert the N_a-methyl indoloazabicyclo[3.3.1]nonane **9** into the oxindole **10**, in contrast to conversion of **5** into oxindole **6** (88% yield) implies that the oxidation of indole to oxindole must precede that of N_a-methylation in the biogenesis of alstonisine. Moreover, the formation of the oxindole **6** (*via* **5**) with the incorrect absolute configuration at the spirocenter suggests that the oxidative transformation of indole to oxindole in the biogenesis of alstonisine must be enzymatically controlled. In the biogenesis of **2**, presumably, attack of an electrophile must occur from the more hindered (β) face, followed by rearrangement of the carbon-carbon bond from the bottom face of the indole system to provide the spirocenter found in **2** (see Scheme 4). This is exactly opposite to that observed in the laboratory (**5**→**6**) with *t*-BuOCl. Further work is underway in this area and will be reported in due course.

Scheme 4



(2) R = Me, R' = H

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Proton nmr spectra were recorded on a Bruker 250MHz or 9E 500 MHz nmr spectrometer. Ir spectra were taken on a Matteson Polaris instrument while mass spectral data were obtained on a Hewlett Packard 5895 GC-mass spectrometer. Microanalyses were performed on an F and M Scientific Corp. model 185 carbon,

hydrogen, and nitrogen analyzer. Analytical TLC plates employed were Kieselgel 60 F_{254} plates on plastic. All reactions were performed in an atmosphere of dry nitrogen.

(1α, 5α, 6α)-Spiro[8-azabicyclo[3.2.1.]octane-6,3'-[3H]indole]-2,2'(1'H)-dione(6). Freshly prepared *t*-BuOCl[9] (0.72g, 0.79ml, 6.60mmol; 2 equiv.) was added dropwise to a cooled (0°C), stirred solution of the tetracyclic ketone **5**[6] (1.09g, 3.30mmol) which had been dissolved in CH_2Cl_2 (30ml), accompanied by freshly distilled Et_3N (0.37g, 0.51ml, 3.68mmol; 1.1 equiv.) After the mixture was warmed to ambient temperature, it was allowed to stir for 1.5h. The solvent was removed under reduced pressure and the resulting white foam was heated at reflux in a mixture (1:1) of MeOH/10% aq. AcOH for 1h. The solvent was removed under reduced pressure and the residue was taken up into EtOAc and washed with aq. $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure. The residue was chromatographed[10] on silica gel (eluent, 3:1 $Et_2O/CHCl_3$) to yield **5** (0.14g, 12%) and **6** (1.0g, 88%). **6**: mp 262-263°C (EtOAc); the ^1H and ^{13}C nmr spectra indicate the presence of 2 rotamers in a ratio of ca. 1:1. δ_H ($CDCl_3$, 500MHz) 2.04-2.86(6H, m), 4.18(0.5H, d, J 5.6Hz), 4.50(0.5H, d, J 7.9Hz), 5.04(0.5, d, J 5.6Hz), 5.30(0.5H, d, J 2.9Hz), 6.85-7.60(9H, m), 9.32(0.5H, s), 9.43(0.5H, s); δ_C ($CDCl_3$) 21.42(t), 32.70(t), 32.97(t), 37.42(t), 38.12(t), 54.19(s), 55.43(s), 57.87(d), 62.26(d), 62.72(d), 66.38(d), 110.56(d), 110.76(d), 122.29(d), 122.55(d), 123.98(d), 124.27(d), 127.11(s), 127.31(d), 127.62(d), 128.24(d), 128.47(d), 129.23(d), 130.33(d), 130.42(d), 132.64(s), 135.34(s), 141.71(s), 142.30(s), 169.08(s), 170.74(s), 181.73(s), 181.97(s), 203,90(s), 205.57(s); ir υ_{max}(KBr) 3400, 1730, 1705, and 1640 cm^{-1}; ms (CI) 347(M^++1); Anal. calcd for $C_{21}H_{18}N_2O_3$:C, 72.80; H, 5,24; N, 8.09. Found:C, 72.42; H, 5.28; N, 7.87.

(1α, 5α, 6α)-8-Benzoylspiro[8-azabicyclo[3.2.1.]octane-6,3'-[3H]indole]-2,2'(1 'H)-dione (7). The oxindole **6** (230mg, 0.66mmol) was heated to reflux in a mixture (4:1:1) of 6N HCl/AcOH/MeOH (30ml, total volume) for 40h. The solvent was removed under reduced pressure and the residue partitioned between CH_2Cl_2 and conc. NaOH(aq). The organic layer was separated, dried(Na_2SO_4) and the solvent removed under reduced pressure to yield a gum which was chromatographed[10] on silica gel (eluent 9:1 $CHCl_3$/MeOH) to provide the amine **7** (120mg, 75%): mp 171-173°C (EtOAc); δ_H ($CDCl_3$; 500MHz) 1.92-2.15(3H, m), 2.51-2.62(3H, m), 3.53(1H, d, J 6.6Hz), 3.9(1H, d, J 8.7Hz), 6.95(1H, d, 8.7Hz),8.95(1H, br s); δ_C ($CDCl_3$) 24.82(t), 32.42(t), 40.35(t), 58.18(s), 63.26(d), 66.64(d), 110.40(d), 122.68(d), 123.96(d), 128.46(d), 141.47(s), 184.30(s),

207.24(s); ir υ_{max} (KBr) 3400-3100, 1720-1680, 1610; ms (CI) 243 (M^++1): Anal. calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 14.11; N, 11.56. Found: C, 69.11; H, 14.01; N, 11.57.

(1α, 5α, 6α)-8-*p*-Toluenesulphonylspiro[8-azabicyclo[3.2.1.]octane-6,3'-[3H]indole-2,2'(1'H)-dione (8). Tosyl chloride (24.6mg, 1.29mmol; 2 equiv.) was added to a cooled (0°C) solution of 7 (156mg, 0.644mmol) in dry pyridine (5ml). The mixture was placed in the refrigerator for 18h , after which it was diluted with CH_2Cl_2 and poured into aq.HCl(2N). The organic layer was washed with brine, dried (Na_2SO_4) and the solvent was removed under pressure to yield **8** as a white solid (110mg, 43%): mp 255-256°C (EtOH); δ_H (d^6-DMSO) 1.80-2.25 (4H, m), 2.42 (3H, s), 2.65 (1H, dd, J 7.6, 13.8Hz), 2.85-2.98 (1H, m) 3.95 (1H, d, J 7.6Hz), 4.18 (1H, d, 4.2Hz), 6.88 (1H, d, J 6.9Hz), 7.00 (1H, t, J 6.9Hz), 7.28 (1H, t, J 6.9Hz), 7.42 (2H, d, J 6.9Hz), 7.86 (1H, d, J 6.9Hz), 10.40 (1H, br s); ir υ_{max} (KBr) 3360, 3230, 1720, 1692, 1320, and 1148cm^{-1}; ms (EI, 70eV) 396 (M^+, 7.2%), 251 (100%), 241 (10.3%); Anal. calcd for $C_{21}H_{20}N_2O_4S$: C, 63.62; H, 5.08; N,7.06. Found C, 63.12; H, 5.09; N, 7.02.

Reaction of 9a with *t*-BuOCl. The N_a-methyltetracyclic ketone **9a** (954mg, 2.77mmol) and *t*-BuOCl[9] (331mg, 363µl, 3.05mmol; 1.1 equiv.) were reacted together as described for the preparation of **6** with the exception that Et_3N was not employed.‡ Hydrolysis was followed by work-up and chromatography on silica gel (eluent 4:1 $CHCl_3$/EtOAc) to afford **11** as the major product (336mg, 34%): mp 203-204°C (EtOH); δ_H ($CDCl_3$) 2.72-3.12 (3H, m), 3.60-3.76 (1H, m), 3.80-4.10 (2H, m), 3.97 (3H, s), 5.28 (1H, m), 6.82-7.51 (9H, m); δ_C ($CDCl_3$) 28.31(t), 32.72(q), 39.07(t), 40.42(t), 60.04(d), 110.28(d), 120.22(s), 120.87(d), 126.90(d), 127.02(d), 127.52(s), 128.47(d), 131.61(d), 132.22(s), 134.05(s), 139.24(s), 167.02(s), 191.05(s), 204.96(s), ;ir υ_{max} 3350, 1710, and 1630; ms (EI, 70eV) 360(M^+, 38.5%), 239(100%). Anal. calcd for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.11; H, 5.63; N, 7.84.

‡ Reaction with the inclusion of NEt_3 did not affect the course of the process.

Reaction of 9b with *t*-BuOCl. The *t*-BuOCl (197mg, 217µl, 18.2mmol; 3 equiv.) and **9b** (200mg, 0.605mmol) were reacted in the fashion described above. Following hydrolysis, analysis by tlc indicated the presence of many products from which no oxindole was observed or isolated.

Reaction of 9c with *t*-BuOCl. The *t*-BuOCl (154mg,170µl, 1.42mmol; 3 equiv.) and **9c**

(150mg, 0.47mmol) were reacted in the fashion described above. Following hydrolysis, analysis by tlc indicated the presence of a complex mixture of products from which no oxindole was observed or isolated.

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