INDOLOQUINOLIZIDINE N-OXIDES AND POLONOVSKI REARRANGEMENT

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Abstract—— The structures of two (±)-indoloquinolizidine N-oxides 3a and 3b were determined unequivocally. Their Polonovski rearrangements gave 4, 5, and 1 with acetic anhydride in acetic acid and gave a complex molecule 12 with acetic anhydride.

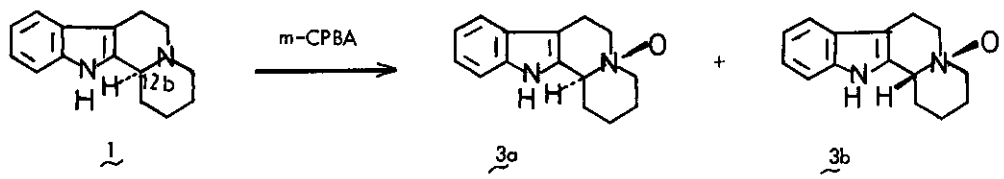
Recent achievements in the synthesis of vinblastine and related compounds have shown the utility of the Polonovski rearrangement in organic synthesis [1]. There has been considerable interest in the mechanism of the Polonovski reaction and several schemes have been proposed [2]. Little is known about the stereochemical requirements for the generation of an iminium intermediate from cyclic amine N-oxides. While Polonovski elimination occurred trans in a cis-fused quinolozidine N-oxide [3], cis elimination for lupanine N-oxide has been reported [4]. The abundant, naturally occurring N-oxides of indole alkaloids [5] may be regarded as possible precursors to the corresponding 2-acylindole alkaloids. In connection with our studies [6] of the oxidation of indoloquinolizidine 1 to the corresponding 2-acylindole derivative 2, we have now synthesized indoloquinolizidine N-oxides and established the stereochemistry of the two isomers. Furthermore, the Polonovski reaction of the trans and cis N-oxides has been investigated.

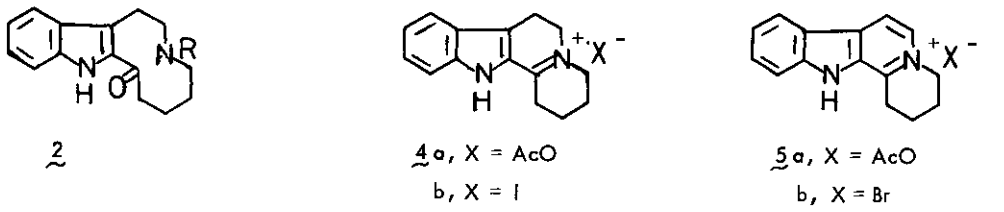
Treatment of (±)-indoloquinolizidine 1 with m-chloroperbenzoic acid (m-CPBA) (1.1 mole equivalents) in chloroform at 15-20°C [7] for 15 hr produced two products 3a and 3b which were isolated by ion exchange column chromatography (Amberlite CG-400, N^+OH^- form). Evaporation of the solvent (30-50% MeOH-H_2O) gave a mixture of diastereoisomers of 3a and 3b (97%) which were separated by fractional crystallizations followed by column chromatography (Al_2O_3) of the mother liquor to give 3a, mp 210.5-211.5°C [8] as the less soluble isomer in 57% yield, and 3b, mp 212-213.5°C [8] as the more soluble isomer in 24% yield. Both were isomers of quinolizidine N-oxide 3 on the basis of elemental analysis as well as mass spectra [8], and showed the characteristic indole chromophore in their UV spectra. Inspection of their

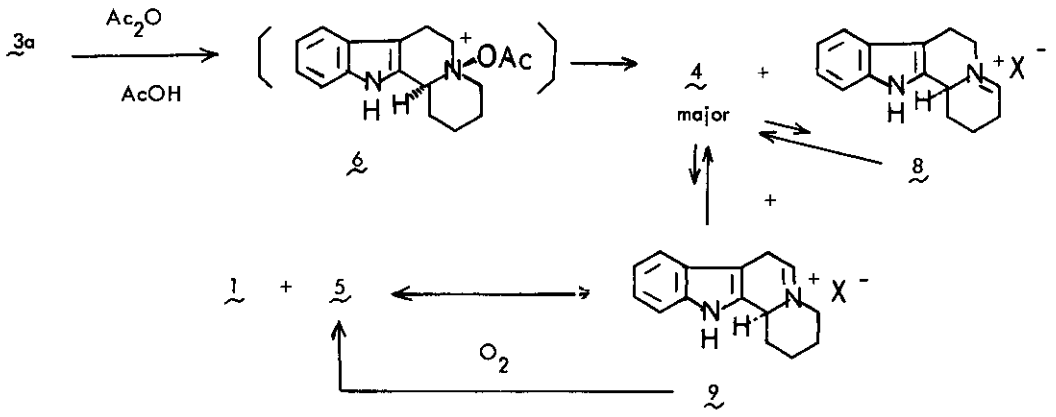
^{1}HNMR spectra gave clues about the stereochemistry of the C/D - ring junction and the major isomer 3a was assigned as trans on the basis of a signal at δ 4.14 (CD_3OD), 4.80 (CF_3CO_2H) with larger coupling constants (half-width ca 20 Hz) consistent with the axial orientation of the proton at C_{12b}, while in 3b this signal has a smaller coupling constant (half-width ca 10 Hz), suggesting that the cis isomer 3b prefers cis steroidal conformation [5, 9]. This was further confirmed by a single-crystal x-ray crystallographic structure determination of 3a, which confirmed the trans relationship regarding the C/D - ring junction as represented in Figure 1 [10a]. The trans isomer 3a crystallizes in the monoclinic space group $P2_1/c$ with a = 10.437 (4) Å, b = 11.592 (3) Å, c = 12.028 (3) Å, β = 93.5 (1)° and z = 4. 1900 independent intensities were measured on a Nicolet P3F automatic diffractometer using CuKα radiation with a graphite monochromator on the incident beam. The structure was solved using the symbolic addition procedure for centrosymmetric crystals [10b]. It was refined by full-matrix methods using all 1900 reflections. Hydrogen atoms were located in difference maps and their positional parameters were included in the final cycles of refinement. The final R-factor (agreement between observed and calculated structure factors) was 8.0%.

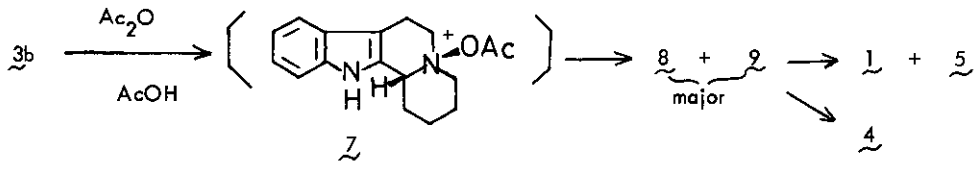
With trans and cis N-oxides 3 readily available, their Polonowski rearrangements were investigated. On refluxing the trans isomer 3a with Ac_2O (8 mole equivalents) in acetic acid for 20 min followed by ion exchange column chromatography (Amberlite CG-50, COOH form, 0.5 N ~ 20% AcOH), indoloquinolizidinium acetate 4a was obtained in 58% yield, together with 5a (7%) and 1 (5%). On the other hand, the analogous reaction of the cis isomer 3b provided 4a (31%), 5a (16%), and 1 (16%). The structures of 4a and 5a were confirmed by converting them to their crystalline iodide 4b [11] and bromide 5b [12], respectively. However, the yield of 4a increased to 67% while the yields of 5a (4%) and 1 (0.2%) decreased when 3a was refluxed with $(F_3CCO)_2O$ (8 mole equivalents) in CF_3CO_2H for 25 min. Similar results were obtained after refluxing 3b for 120 min under similar conditions, providing 4a (70%), 5a (7%), and 1 (0.7%). Treatment of either 3a or 3b with $(CF_3CO)_2O$ (3 mole equivalents) in methylene chloride at room temperature for 3 hr afforded 4a in 50% yield. In any case, the desired 2-acylindole derivative 2 was not obtained.

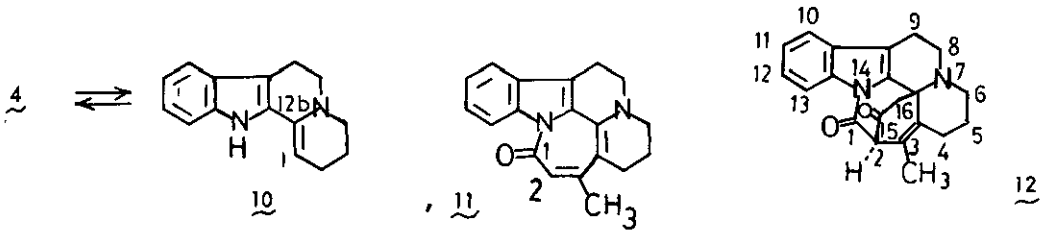
From a consideration of the above results, it may be concluded that the reactions proceed probably by trans elimination of acetic acid from the acyloxy ammonium ion intermediate (6 and 7) to give iminium ions 4, 8 [13], and 9. The trans N-oxide 3a would be expected to give 4 as the major product in addition to 8 and 9, which are, however, not stable and readily undergo isomerization to the more stable isomer 4. Two minor products, 1 and 5, are obtained in almost comparable amounts, probably formed by disproportionation of 9, although a part of 5 might arise from air oxidation of 9. In the case of $(CF_3CO)_2O$ in


m-CPBA
12b
1
3a
3b


2
4a, X = AcO
b, X = I
5a, X = AcO
b, X = Br


3a
Ac2O
AcOH
6
4
major
8
1 + 5
O2
9


3b
Ac2O
AcOH
7
8 + 9
major
1 + 5
4


4
12b
10
11
12

CF_3CO_2H, the isomerization of 8 and 9 must be facilitated by the strong acid, CF_3CO_2H, to give a high yield of 4. However, 4 could also arise partially from cis-elimination in $(CF_3CO)_2O/CF_3CO_2H$ in the case of cis N-oxide 3b. On the other hand, when 3a was refluxed in Ac_2O without AcOH for 10 min, a new compound 12, mp 163.5-164.5°C, was obtained in 31% yield besides 1 (2%) and 5a (6%), which was also formed by direct treatment of 4a with Ac_2O under similar conditions. Structural assignment of 12 was provided by elemental analysis and the spectral data [14] (UV, IR, ^1H- and ^{13}C-NMR, mass). The signal at 1.91 ppm (d, 3H, J = 2 Hz, CH_3-C=C-C-H), 2.80 (d, 1H, J = 18 Hz, C_{16}-H), 3.04 (d, 1H, J = 18 Hz, C_{16}-H), 4.08 (s, 1H, C_2-H) and 8.42 (m, 1H, C_{13}-H) were newly observed in ^1HNMR (200 MHz) spectrum of 12. The presence of two carbonyl groups in 12 and one sp^3 quaternary carbon was indicated by appearance of the signals at 202.47, 160.61, and 57.87 ppm in the ^{13}CNMR (200 MHz) spectrum. On the basis of IR and UV as well as the NMR spectra, one of the carbonyls was shown forming the amide at the indole nitrogen. The stereochemistry of 12 was unambiguously determined by a single crystal x-ray analysis. The results are shown in Figure 2. 12 crystallizes in the monoclinic space group $P2_1/c$ with a = 11.469 (3) Å, b = 12.988 (4) Å, c = 13.659 (5) Å, β = 125.28 (2)° and z = 4. 2787 unique reflections having $F_o > 2\sigma(F_o)$ were measured on a Rigaku Denki AFC-5 diffractometer using graphite-monochromated CuKα radiation out to a $2\theta_{max} = 150°$. The structure was solved by direct methods using the RASA-11 program package [15] provided with the diffractometer. The structure was refined by block-diagonal least-squares methods to an R-factor of 6.9%.

Formation of 12 seems to involve initial acetylation at Na-nitrogen and C_1-carbon via 10 to give a diacetyl intermediate followed by cyclization and dehydration to give 11. Further acetylation of 11 at the 2-position and subsequent cyclization would lead to the formation of 12. The iminium species 4 may be stabilized by the indole moiety and thus prevent further conversion of 4 to 2-acylindole under these conditions, but 4 showed an enamine reactivity towards an acylating agent at the position-1 to give 12.

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REFERENCES AND NOTES

1. a) N. Langlois, F. Gueritte, Y. Langlois, P. Potier, J Am.Chem.Soc., 98, 7017 (1976); b)

P. Potier, N. Langlois, F. Gueritte, J.Chem.Soc., Chem.Commun., 670 (1975) ; c) J. P. Kutney, A. H. Ratcliffe, A. M. Treasurywala, S. Wunderly, Heterocycles, 3, 639 (1975).

2. a) N. Boekelheide, D. L. Harrington, Chem.& Ind., 1432 (1955) ; b) R. Huisgen, F. Bayerlein, W. Heydkamp, Chem.Ber., 92, 3223 (1959) ; c) J. C. Craig, F. P. Dwyer, A. N. Glazer, E. C. Horning, J.Am.Chem.Soc., 83, 1871 (1961) ; d) Y. Hayashi, Y. Nagano, S. Hongyo, K. Teramura, Tetrahedron Lett., 1299 (1974) ; e) for reviews see G. A. Russel, G. J. Mikol, "Mechanism of Molecular Migrations", B. S. Thyagarajan Ed., Vol. 1, p 176 (1968) Interscience and M. Ikeda, Y. Tamura, Yuki Gosei Kagaku Kyokai Shi, 38, 10 (1980).

3. R. T. Lalonde, E. Auer, C. F. Wong, V. P. Muralidharan, J.Am.Chem.Soc., 93, 2501 (1971).

4. P Baranowski, M. Wiewiorowski, L. Lompa-Krzymien, Ann.Soc.Chim.Polonorum, 40, 73 (1966) ; C.A., 65, 2320 (1966).

5. L. Merlini, G. Nasini, J.D. Phillipson, Tetrahedron, 28, 5971 (1972).

6. M. Nakagawa, Y. Okajima, K. Kobayashi, T. Asaka, T. Hino, Heterocycles, 3, 799 (1975).

7. The ratio of the trans and cis isomers in the oxidation of 1 varies with the reaction temperature. 3a/3b : 2.1 at 30 ~ 32° ; 2.3 at 1 ~ 2°, 15 ~ 20°, and 25° ; 3.6 at -30 ~ -40° ; 11.1 at -60 ~ -70°C. This temperature effect will be discussed in a full detail.

8. The melting points were taken after drying for 7 hr at 50°C over P_2O_5. The picrates (3a : mp 183-184.5°C. 3b : mp 162-164°C) gave a satisfactory elemental analysis. R_f value (Al_2O_3, 5% MeOH-CH_2Cl_2) are 0.45 and 0.29 for 3a and 3b, respectively. 3a : νmax (KBr) 955 cm^{-1} (N→O) ; δ (CD_3OD) 1.20-3.00 (4 x CH_2), 3.00-3.60 (2 x CH_2), 4.14 (triplet like, C_{12b}-H) ; m/z (%) 242 (5) M^+, 226 (71) M^+-O, 225 (100) M^+-OH. 3b ; ν max (KBr) 970 cm^{-1} (N→O) ; δ (CD_3OD) 1.00-1.85, 1.85-3.90 (6 x CH_2), 4.5 (broad s, C_{12b}-H) ; m/z (%) 242 (2) M^+, 226 (72) M^+-O, 225 (100) M^+-OH.

9. T. Fujii, M. Nohara, M. Mitsukuchi, M. Ohba, K. Shikata, S. Yoshifuji, S. Ikegami, Chem.Pharm. Bull., (Tokyo), 23, 144 (1975).

10. a) The results of the x-ray analysis on 3a are illustrated in the stereodiagram based on experimentally determined coordinates (C. K. Johnson (1965) ORTEP Report ORNL 3794, Oak Ridge National Lab., Tennessee). The N-O bond length is 1.388 (4) Å. The molecules of 3a make intermolecular hydrogen bonds with molecules of methanol which were found to cocrystallize with it.

b) J. Karle, I. L. Karle, Acta Cryst., 21, 849 (1966).

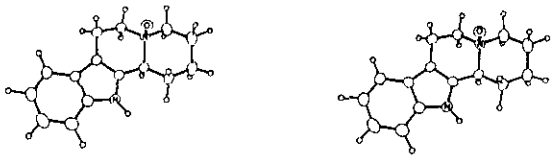

Figure 1 Stereodiagram of trans-Indoloquinolizidine N-oxide 3a

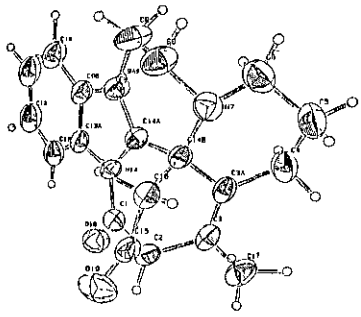

Figure 2

Stereoview of 12

11. M. Nakagawa, M. Kikuchi, M. Obi, M. Tonozuka, K. Kobayashi, T. Hino, Y. Ban, Chem.Pharm. Bull., (Tokyo), 23, 304 (1975).

12. L. H. Grove, G. A. Swan, J.Chem.Soc., 650 (1952).

13. Evidence for the formation of an iminium ion such as 8 has been obtained by the isolation of dihydromancunine and related compounds. S. Sakai, N. Shinma, Chem.Pharm.Bull., 25, 842 (1977); idem., ibid., 26, 2596 (1978).

14. High resolution mass (m/z 332.15522) and elemental analysis of 12 supported the molecular formula of $C_{21}H_{20}O_2N_2$: λmax (EtOH) nm 250, 270sh, 307 ; λmax (EtOH-HCl) 248, 267sh, 297, 305 ; ν max (KBr) cm^{-1} 1735, 1695.

15. P. Main, M. M. Woolfson, L. Lessinger, G. Germain, J. P. Declerq, MULTAN 74 ; A System of Computer Programs for the Automatic Solution of Crystal Structures from x-ray Diffraction Data. University of York, England, and Louvain-la-Neuve, Belgium, 1974. The ORTEP drawings : C.K. Johnson, ORTEP, Report ORNL-3794, Oak Ridge National Lab., Tennessee, 1965.

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