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NITROGEN INVERSION IN SOLASODINE N-METHYL AND N-FORMYL DERIVATIVES

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O-Acetyl-N-methylsolasodine A (III) and B (IV), O-Acetyl-N-formylsolasodine A (V) and B (VI) are prepared. III and IV are interconvertible under acidic condition or at high temperature. Procedure of recrystallization of the mixture of III and IV precipitates III alone. V are reduced to N-methylsolasodine B (XI), while VI are reduced to a mixture of N-methylsolasodine A (X) and B (XI). These isomers are described as a result of nitrogen inversion.

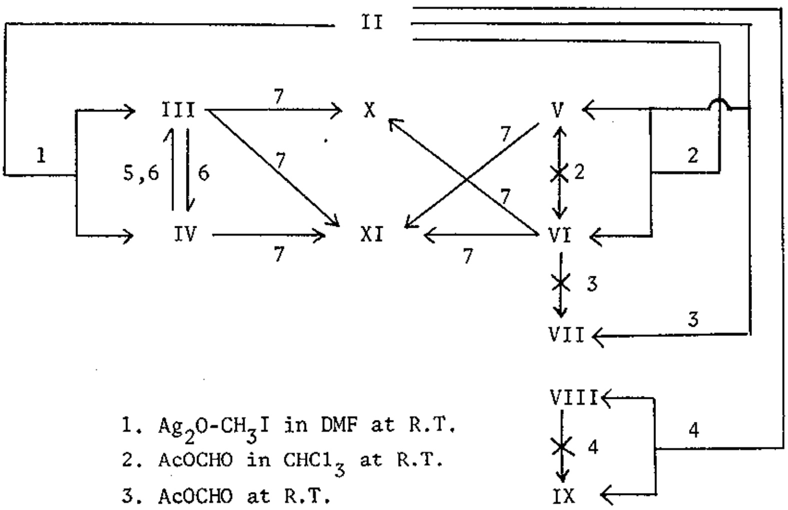
The nitrogen atom of solasodine, a common Solanum steroidal alkaloid, is in a sterically crowded envirnoment and this gives rise to differences in reactivity between N-chlorosuccinimide and N-bromosuccinimide with solasodine (I).$^{1)}$

In this communication we like to report on a kind of nitrogen inversion *observed in solasodine N-methyl and N-formyl* derivatives (III-VI) and reasonably explained as a result of the steric requirements around the nitrogen. Upon treatment with silver oxide and methyliodide in dimethylformamide, O-acetylsolasodine (II) produces a chromatographically homogeneous mixture of O-acetyl-N-methylsolasodine A (III) and B (IV) in 90% yield. III and IV are differentiated by NMR spectrometry [III (in C_5D_5N): 2.48 ppm, 3H, s, N-CH_3; 2.07, 3H, s, $OCOCH_3$; 1.19, 3H, d, J=7 Hz, C_{25}-CH_3; 1.01, 3H, s, C_{10}-CH_3; 0.84, 3H, s, 2.07, s, $OCOCH_3$; 1.15, 3H, d, J=7 Hz, C_{25}-CH_3; 1.01 3H, s, C_{10}-CH_3; 0.99, 3H, d, J=7 Hz, C_{20}-CH_3; 0.88, s, C_{13}-CH_3]. After recrystallization of the mixture of III and IV from MeOH, EtOH, Me_2CO, AcOEt or C_6H_6, every crop of crystalline material is identified to O-acetyl-N-methylsolasodine A (III), while the gummy residue of the mother solution contains O-acetyl-N-methylsolasodine B (IV) mainly. III returns to the mixture of III and IV on refluxing in xylene, standing on in a $CDCl_3$ solution leaving in $CDCl_3$-CD_3COOD, melting (at 170-180°) or heating at 130-170° in dimethylsulfoxide.

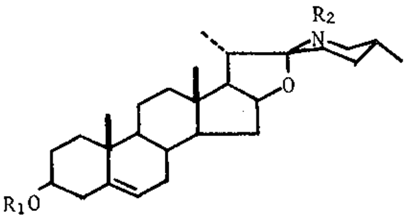
On the other hand, solasodine is known to give two kinds of the N-formyl derivatives, which have been assigned as cis and trans isomers in regard to the N$\overline{\cdots}$C bond of the N-formyl moiety.2) Upon treatment with acetic-formic anhydride in chloroform at room temperature, O-acetylsolasodine (II) yields O-acetyl-N-formylsolasodine A (V), mp 200-201°, $C_{30}H_{45}O_4N$, NMR ($CDCl_3$) ppm: 8.42 (1H, s, N-CHO), 5.36 (1H, d, J=5 Hz, C_6-H), 4.6 (1H, m, C_3-H), 4.3 (1H, m, C_{16}-H), 4.22 (1H, q, J_1=12 Hz, J_2=3, C_{26}-H), 2.20 (1H, q, J_1=12, J_2=8, C_{26}-H), 2.00 (3H, s, $OCOCH_3$), 1.14 (3H, d, J=7 Hz, C_{25}-CH_3), 1.00 (3H, s, C_{10}-CH_3), 0.89 (3H, d, J=7 Hz, C_{20}-CH_3), 0.79 (3H, s, C_{13}-CH_3) and O-acetyl-

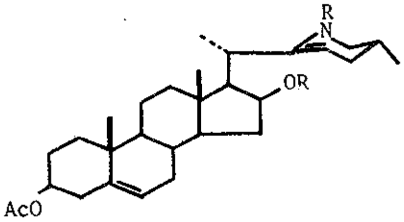
N-formylsolasodine B (VI), mp 194-197°, $C_{30}H_{45}O_4N$, NMR ($CDCl_3$) ppm: 8.62 (1H, s, N-CHO), 5.37 (1H, d, J=5 Hz, C_6-H), 4.6 (1H, m, C_3-H), 4.26 (1H, m, C_{16}-H), 3.88 (1H, q, J_1=12, J_2=3, C_{26}-H), 3.10 (1H, q, J_1=12, J_2=8, C_{26}-H), 2.00 (3H, s, $OCOCH_3$), 1.11 (3H, d, J=7, C_{25}-CH_3), 1.02 (3H, s, C_{10}-CH_3), 0.91 (3H, d, J=7, C_{20}-CH_3), 0.82 (3H, s, C_{13}-CH_3). Under direct contact with acetic-formic anhydride, O-acetylsolasodine (II) gives, along with V, 3-O-acetyl-16-O,N-diformylpseudosolasodine (VII), mp 174-176°, $C_{31}H_{45}O_5N$, NMR ($CDCl_3$) ppm: 8.73 (1H, s, N-CHO), 7.85 (1H, s, O-CHO), 5.35 (1H, unresolved d, J=5 Hz, C_6-H), 4.95 (1H, unresolved, C_{23}-H), 4.6 (1H, m, C_3-H), 2.01 (3H, s, $OCOCH_3$), 1.96 (3H, d, J=7 Hz, C_{25}-CH_3), 1.03 (3H, s, C_{10}-CH_3), 0.93 (3H, d, J=7 Hz, C_{20}-CH_3), 0.90 (3H, s, C_{13}-CH_3), instead of VI. This result is similar to that of acetylation. O-Acetylsolasodine (II) affords O,N-diacetyl derivative (VIII) and 3,16-O,N-triacetylpseudosolasodine (IX) under usual acetylation. Because formamide A (V) and B (VI) return to O-acetylsolasodine upon irradiation with a high pressure mercury lamp in isopropanol, V and VI are concluded as isomers due to the formyl moiety. V and VI are not interconvertible even under the same condition of the formylation, neither does formamide B (VI) go to formenamide (VII). When V and VI are treated with $LiAlH_4$ in tetrahydrofuran at room temperature for 2 weeks, V gives N-methylsolasodine B (XI), while VI gives N-methylsolasodine A (X) and B (XI). On the other hand, under the same treatment III gives a mixture of X and XI, while the gummy preparation of IV gives XI with traces of III.

These results are summarized as depicted in the scheme. For this kind of the isomerism three possibilities are supposed: 1) Ring inversion$^{3)}$, 2)



1. Ag_2O-CH_3I in DMF at R.T.
2. AcOCHO in $CHCl_3$ at R.T.
3. AcOCHO at R.T.
4. Ac_2O in C_5H_5N at R.T.
5. recryst. from MeOH, EtOH, Me_2CO, AcOEt or C_6H_6
6. in $CDCl_3$ for 2 days, in $CDCl_3$-CD_3COOD for few min., refluxing in xylene, melting at 170-180°, or heating at 130-170° in DMSO
7. $LiAlH_4$ in THF at R.T. for 2 weeks





I : R_1=R_2=H

II : R_1=Ac; R_2=H

III,IV: R_1=Ac; R_2=Me

V,VI : R_1=Ac; R_2=CHO

VIII : R_1=R_2=Ac

X,XI : R_1=H; R_2=CHO

VII : R=CHO

IX : R=Ac

Rotatory isomerism of C=N bond4), 3) Nitrogen inversion5). The first possibility is rejected because the same vicinal coupling constants (3 and 8 Hz) are observed between C_{26}-2H and C_{25}-H in the NMR spectra of V and VI. The second possibility is, also, cancelled because formate A (V) is reduced to N-methylsolasodine B (XI), selectively and this possibility is not expected in N-methylderivatives (III, IV, X, XI). An effort to assign these compounds to axial and equatorial derivatives each another is being made, but this isomerism is concluded to be due to nitrogen inversion. The energy barrier between III and IV or V and VI is too high for piperidine N-derivatives.5) An examination of molecular models suggests that the 16(22)-oxide ring of these derivatives is somewhat flexible and certain conformation of the oxide ring seems to result to decrease the steric bulkiness around the nitrogen in N-methyl (equatorial and axial) or N-formyl (equatorial and axial) solasodine derivatives.

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