Pakistan J. Sci. Ind. Res., Vol. 26, No. 4, August 1983

OXIDATION STUDIES IN SOME STEROIDAL BASES (SOLASODINE, 3β-O-ACETYL SOLASODINE AND CONESSINE)

Part II.Periodic Acid as the Trans Hydroxylating Agent

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Periodic acid (KIO_4/H_2SO_4) oxidation of solasodine, 3β-O-acetyl solasodine and conessine, yielded the corresponding trans diols. It is noteworthy in this context that the reagent (KIO_4/H_2SO_4) is generally employed for the cleavage of vicinal cis diols and there is no reference in literature to the formation of diols from olefins through this reagent. Prolonged treatment of spirosolanes with acetic anhydride resulted in the formation of 22, 26-acetyl-epimino-cholest-22-en-derivatives through ring E cleavage. [1].

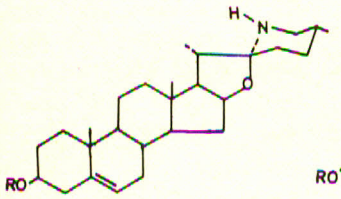
INTRODUCTION

In continuation of oxidative studies [1] in the steroidal alkaloid solasodine [2], various derivatives of solasodine, 3β-O-acetyl solasodine as well as another steroidal base conessine [3] have been obtained through their oxidation with KIO_4/H_2SO_4. It is notable in this context that all of these bases, possessing the steroidal skeleton with an olefinic function at C-5(6), when treated with the reagent gave the corresponding diols (I, V, VII) in good yields Similar results were observed when $NaIO_4$ was used in place of KIO_4. Formation of a diol from an olefinic double bond through its oxidation with KIO_4/H_2SO_4 appears to be the first example in literature. The ^{1}H-NMR studies suggested that these diols are trans, probably resulting from the hydrolysis of the epoxides [4] formed as an intermediate during the course of the reaction. The fact that the diols (I, V, VII) do not undergo further cleavage in presence of KIO_4/H_2SO_4 lends added support to their trans nature. Further work on determining the range of applicability of this reagent as a means of trans hydroxylation is being pursued with variable olefinic functions in steroidal as well as simpler olefinic bases.

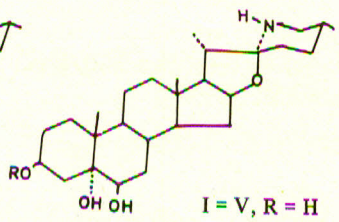
On periodic acid (KIO_4/H_2SO_4) oxidation solasodine yielded (25R) –5 α, 22 α N-spirosolan-3β–5 α, 6β-triol I, which showed M^+ at *m/e* 447.3335 ($C_{27}H_{45}NO_4$). ^{1}H-NMR spectrum (Table) indicated that the resulting diol is trans showing a multiplet at δ 3.9 for H-3 and a broad signal at δ 3.6 ($W_{h/2}$ = 7 cps) for H-6. The downfield appearance of H-3 may be explained to be due to 1,3 diaxial interaction between H-3 and C_5–OH , whereas H-6 resonates at slightly upfield being cis to C_5-OH [5]. Peaks at δ 1.2 and a broad multiplet between δ 2.25 – 2.5 disappeared on shaking with D_2O (NH and 3xOH). I formed monoacetyl derivative II on reaction with one mole of acetic anhydride for one hr at room temperature. The mass spectrum of II showed M^+ at *m/e* 489.34433 ($C_{29}H_{47}NO_5$) while the IR spectrum indicated the presence of one acetyl group showing a sharp carbonyl peak at 1735 cm^{-1} and a broad band at 3400 cm^{-1} for O-H and N-H stretchings. In the ^{1}H-NMR spectrum (Table) the broad resonances at δ 5.15 ($W_{h/2}$ = 23 cps) and δ 3.54, ($W_{h/2}$ = 7 cps) and a singlet at δ 2.03 have been assigned to H-3, H-6 and 3 β-acetoxy function respectively. The $W_{h/2}$ of H-3 (i.e. 23 cps) in II, supported the fact that H-3 is axial, because in I it was not possible to calculate the $W_{h/2}$ of this proton due to the occurrence of H-16 multiplet in the same region. This fact further confirmed the equatorial nature of H-6 having $W_{h/2}$ = 7 cps in both the compounds (I, II).

I when treated with excess of acetic anhydride at room temperature for 24 hr. yielded III, the mass spectrum of which showed M^+ at *m/e* 615.37775 ($C_{35}H_{53}NO_8$) and other fragments at *m/e* 572, 166 (BP) and 83. Its IR spectrum is indicative of amide (1660 cm^{-1}), acetate (1735 cm^{-1}), C = C (1630 cm^{-1}) and hydroxy (3450 cm^{-1}) functions. Its UV spectrum showed characteristic λ_{max} at 235 nm . Its ^{1}H-NMR spectrum further confirmed its structure showing a 4-protons multiplet extending from δ 4.7 – 5.2 for H-3, H-6, H-16 and H-23 and peaks at δ 2.0, 2.03, 2.06 and 2.16 indicating the presence of four acetyl groups. I on further oxidation with potassium permanganate/acetic acid in cold formed diketo product (25R) – 5 α-hydroxy-5 α, 22 α N-spirosolan-3, 6-dione IV, which showed M^+ at *m/e* 443.3016 ($C_{27}H_{41}NO_4$). The IR spectrum of IV showed strong carbonyl stretchings at 1710 cm^{-1} and 1725 cm^{-1}; N-H and O-H stretching at 3400 cm^{-1}.

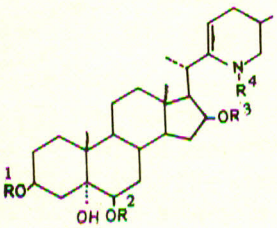
3 β-O-acetyl solasodine on periodic acid oxidation under the reaction conditions followed in the case of solasodine gave V; its m.p., TLC and spectral data confirmed its identity with I, showing that the acetyl group was hydrolysed during the reaction. It showed M^+ at *m/e*



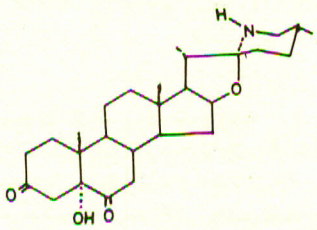
R = H, Solasodine
R = Ac, 3β-O-acetyl solasodine



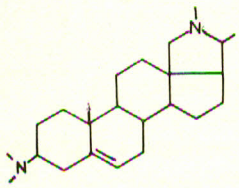
I = V, R = H
II, R = Ac



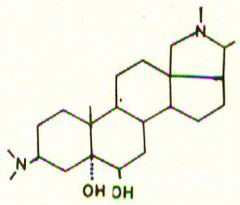
III = VI;
$R^1=R^2=R^3=R^4$ =Ac



IV



Conessine

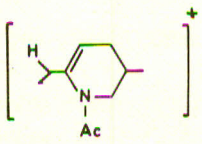


VII

447.3335 ($C_{27}H_{45}NO_4$), while the IR spectrum revealed the absence of carbonyl stretching, at 1730 cm^{-1} of the acetyl group. The formation of V was further confirmed by its acetylation with excess of acetic anhydride which afforded VI, the mass spectrum of which showed M^+ at 615.7775 ($C_{35}H_{53}NO_8$). VI was found identical with III.

The same reaction when carried out with conessine, led to the formation of trans diol VII which was characterized through ^{1}H-NMR studies (Table).

It was observed in the course of these studies [1], that the compounds which possess azaoxaspirane function undergo cleavage of ring E on their prolonged treatment with excess of acetic anhydride resulting in the formation of 22-26-acetyl epimino-cholest-22-en derivatives as the major product exhibiting a common base peak at *m/e* 166 in each case.



Acetylation of solasodine under similar reaction conditions also yielded the corresponding 22–26-acetyl-epimino derivative as the major product thus confirming these observations.

Table. ^{1}H-Spectral data.

Proton	Solasodine	I	II	III	VII
19	1.02,s, 3H	1.19,s, 3H	1.2,s, 3H	1.15,s, 3H	1.0,s, 3H
18	0.82,s, 3H	0.81,s, 3H	0.82,s, 3H	0.91,s, 3H	–
21	0.94,d, 3H	0.95,d, 3H	0.94,d, 3H	1.08,d, 3H	1.06,d, 3H
27	0.85,d, 3H	0.86,d, 3H	0.85,d, 3H	0.86,d, 3H	–
3	3.5,m, 1H $W_{h/2}$ = 23cps	3.9,m, 1H	5.15,m, 1H $W_{h/2}$ = 23cps	4.7–5.2[a]	2.9,m, 1H
6	5.34,m, 1H	3.6,m, 1H $W_{h/2}$ = 7cps	3.54,m, 1H $W_{h/2}$ = 7cps	4.7–5.2[a]	3.53 $W_{h/2}$ =7cps
16	4.28,m, 1H	4.26,m, 1H	4.25,m, 1H	4.7–5.2[a]	–
26	2.62,m, 2H	2.62,m, 2H	2.63,m, 2H	3.0,m, 1H,ax. 3.45,m,1H,eq.	–
23	–	–	–	4.7–5.2[a]	–
Acetyl			2.03,s, 3H	2.0,2.03,2.06,2.16 (3xOAc and N-Ac)	
–N-Me					2.2
$-N(Me)_2$					2.31

(a) H-3, H-6, H-16 and H-23 appeared as 5 protons broad multiplet. All values are in δ (ppm) relative to TMS = 0.

EXPERIMENTAL

For general experimental detail see Part I [1].

Periodic acid oxidation of solasodine – (25R) - 5 α, 22 α N-spirosolan-3β, 5α, 6β-triol I. To 0.3 g of solasodine, a solution of potassium periodate (0.198 g) in 10 % sulfuric acid (7.5 ml) was added and kept at room temperature overnight in the dark. The reaction mixture was then filtered and the darkish insoluble matter was washed with 10 % acetic acid. The filterate and washings were freed of traces of iodine by shaking with ethyl acetate. The colourless aqueous layer was basified with ammonia and extracted out with ethyl acetate. The crystalline residue left on working up the ethyl acetate extract in the usual manner and removal of the solvent yielded I, which formed fine needles, on crystallisation from ethyl acetate – methanol (1:1), m.p. 246–48°, (o.25 g; yield 77.1 %). It is readily soluble in chloroform and methanol, soluble in ethyl acetate, sparingly soluble in benzene and insoluble in petroleum ether and ether. IRν_{max} KBr (cm^{-1}): 1620, 3400 broad and strong band; UVλ_{max} (nm): 207, 222: Mass *(m/e)* 447.3335 (37 %) M+ (calculated for $C_{27}H_{45}NO_4$: 447.3348), 432, 429, 414, 396, 376, 138, 114 (100 %), 71.

Acetylation of I – (25R)-5α, 22α, N-spirosolan-3β, 5α, 6β-triol-3-acetate II. To a solution of I (90 mg) in pyridine (1 ml), acetic anhydride (0.023 ml ; 1 mol.) was added and the reaction mixture was kept at room temperature for 1 hr. On working up the product in the usual manner the acetyl derivative II, crystallized out from methanol in fine needles m.p. 258–59°. It is insoluble in petroleum ether, sparingly soluble in ether and benzene and soluble in ethyl acetate, chloroform and methanol. IRν_{max} KBr (cm^{-1}) : 1620, 1735, 3400: UVλ_{max}(nm) : 210, 220: Mass (*m/e*) : 489.3443 (3 %) M^+ (calculated for $C_{29}H_{47}NO_5$: 489.3454), 474, 459, 446, 429, 390, 138 (100 %), 114,99.

(25R)-22, 26-acetyl-epimino-cholest-22-en-3β, 5 α, 6 β, 16β-tetraol-3, 6, 16-triacetate III. To a solution of I (80 mg) in pyridine (0.5 ml), was added excess of acetic anhydride and the reaction mixture was kept at room temperature for 36 hr. On working up the product in the usual way III was obtained mp 150–52°. It is insoluble in petroleum ether, sparingly soluble in ether and benzene and soluble in ethyl acetate, chloroform and methanol. IRν_{max} KBr (cm^{-1}) : 1630, 1660, 1735 (broad and strong band), 3450; UVλ_{max}(nm): 210, 235; Mass (*m/e*) 615.3777 (18 %) M^+ (calculated for $C_{35}H_{53}NO_8$: 615.3770), 600, 585, 572, 555, 540, 529, 512, 166 (100 %), 83, 55.

Oxidation of I with potassium permanganate in acetic acid – (25R)-5α-hydroxy-5α, 22α N-spirosolan-3, 6-dione IV. To a solution of 70 mg of I in 7 ml of 20 % acetic acid, 80 mg potassium permanganate in 10 ml water was added dropwise at 0°. The reaction mixture was stirred for 2 hr. at 10–15° and extracted out with ethyl acetate for removal of any impurities at acidic pH. The aqueous layer was ammoniated and the liberated base extracted out with ethyl acetate. The petroleum ether soluble fraction of the residue, obtained on working up the ethyl acetate extract in the usual manner, showed chromatographically pure uv inactive spot on tlc. It crystallized out from methanol-benzene (1 : 1) in fine needles melting at 180–82° and characterized as IV. IRν_{max} $CHCl_3$ (cm^{-1}): 1595, 1710, 1725, 3400 strong and broad band: UVλ_{max} (nm): 215, 230: Mass (*m/e*): 443.3016 (3 %) M^+ (calculated for $C_{27}H_{41}NO_4$: 443.3035), 428, 410, 415, 138, 114, 70, 55, 43 (100 %).

Oxidation of 3β-O-acetyl-solasodine with potassium periodiate – (25R)-5α, 22α N-spirosolan-3β, 5α, 6β-triol V. 90 mg of potassium periodate in 3.7 ml of 10 % sulfuric acid, was added to 150 mg of 3β-O-acetyl solasodine at room temperature and kept in the dark for 24 hr. The reaction mixture, on working up as in case of I, yielded V which formed aggregates of needles on crystallisation from methanol, m.p. 247–8°. It was identical with I, from its mixed TLC, m.p. and comparison of spectral data. Furthermore, its tetra-acetate derivative VI which was prepared in exactly the same manner as described for that of I, was also identical with III.

Periodic acid oxidation of conessine – 5α, 6β-dihydroxy conessine VII. To 0.1 g of conessine a solution of potassium periodate (0.05 g) in 10 % sulfuric acid (4 ml) was added and kept at room temperature overnight in the dark. The reaction mixture was worked up in the same manner as in case of I, when VII was obtained in fine needles, which on recrystallization from ethyl acetate melted at 275–6° (0.085 g, yield 82.5 %). It is soluble in chloroform, ethyl acetate, methanol and insoluble in benzene, ether, petroleum ether. IRν_{max} KBr (cm^{-1}): 1040, 1370, 3400: UV λ_{max} (nm): 210; Mass (*m/e*): 390.3233 (29 %) M^+ (Calculated for $C_{24}H_{42}N_2O_2$: 390.3246) 375, 330, 84 (100 %), and 71.

Acknowledgement. One of us (Shaheen Faizi) wishes to express her gratitudes to Hamdard Foundation for providing a research scholarship during the course of this work.

REFERENCES

1. Salimuzzaman Siddiqui, Bina S. Siddiqui, Shaheen Faizi (preceding paper).
2. H. Rochelmeyer, Chen, *Arch. Pharm.*, 277, 329 (1939).
3. R. Haines, *Trans. Med. Soc. Bombay*, 4, 28 (1958).
4. P. William Coker; E. Robert Lane Jr. (Dow Chemical Co.), U.S. 4, 120, 877 (Cl. 260–348.23: CO7D301/12), 17 Oct. (1978), CA 90: 54802.
5. Stereochemistry, *Fundamentals and Methods*, Edited by Henri B. Kagan, (George Thieme Publishers Stuttgart, 1977), Vol. I, p. 100.