Synthesis of $3\beta$-Acetoxy-7-$a$-aza-B-homo-22-$a$-spirost-5(6)-en-7-one

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Diosgenin, 7-$a$-Aza-B-homo Analogue

Chromic acid oxidation of diosgenin acetate yielded 7-ketodiosgeninacetate. Oximation of the ketone followed by Beckmann rearrangement of oxime afforded the title compound.

The modification and enhancement of biological activity \[1,2\] of steroidal drugs containing nitrogen atom represent one of the most fruitful developments in medicinal chemistry. Voluminous literature \[3\] is available on azasteroids. However, a limited work is reported \[4-8\] about the preparation of aza derivatives corresponding to steroidal sapogenins. This prompted us to make an attempt in this direction. We chose the naturally occurring synthon diosgenin as our starting material. Our efforts were directed toward the introduction of a nitrogen atom in the B ring of the parent molecule.

The spectral data for lactam 5 are in agreement with the formulated structure. Thus, the UV spectrum of the lactam showed band at 242 nm ($\log e 4.05$) which is in accordance with the value reported in literature \[11\] for such compounds. The IR spectrum of the lactam showed peaks at 3556 cm$^{-1}$ due to the presence of N-H group. The IR bands at 1734 and 1700 cm$^{-1}$ may be explained to be due to the presence of acetate carbonyl and carbonyl group at C-7 in ring B. Characteristic IR
bands for a spirostan [12] moiety were observed at 970, 910, 890, 850 cm$^{-1}$. The structure 7-oxo-7a-aza was indicated by $^{1}$HMR spectrum of the lactam, which showed (i) a signal at $\delta$ 8.20 for proton in NH group, (ii) a singlet at $\delta$ 6.56 integrating for a single C-6 olefinic proton adjacent to the carbonyl group. The alternate structure for lactam, viz., 7a-oxo-7-aza may be excluded on the basis of the argument that such a structure would require the presence of a multiplet corresponding to the vinylic proton at C-6. A multiplet at $\delta$ 4.70 for one proton may be attributed to the methine proton at C-16. A doublet at $\delta$ 3.50 of the area of two protons may be assigned to the methylene protons at C-26. A singlet at $\delta$ 2.16 is due to the methyl group protons of acetate function. The mass spectrum of the lactam showed M$^+$ peak at m/e 485. It also exhibited peaks at m/e 426 M−(CH$_3$+CONH$_2$), 425 (M−AcOH), 370, 354, 294, 139 and 115. Scheme II outlines the manner in which the formation of these fragment ions can be explained. Thus all the spectral data are compatible with the proposed structure of lactam 5.
This is the first report about the introduction of nitrogen atom in the B-ring of steroidal sapogenins involving the Beckmann rearrangement.

Experimental

All the melting points were determined on Fisher Johns melting point apparatus and are uncorrected. The ultraviolet spectrum was recorded on a Beckman DU spectrophotometer. Infrared spectra were run on Perkin-Elmer 137 and 521 spectrophotometers. 1HMR spectrum was measured on Varian A 60-D spectrometer in CDCl3 using TMS as an internal standard. Mass spectrum was recorded on Hitachi RMU-6E mass spectrometer.

**Diosgenin acetate (2)**

A mixture of diosgenin (1) (10 g, 24.10 mmol), acetic anhydride (5 ml) and pyridine (5 ml) were allowed to stand overnight at room temperature (25 °C). The reaction mixture was poured onto crushed ice. The resulting white precipitate was extracted with ether. The ethereal layer was washed successively with water, dilute HCl, water and dried (MgSO4). Distillation of ether yielded brown residue (10 g). Column chromatography of the crude residue (10 g). Column chromatography of the crude product on silica gel using CCl4 as eluant yielded pure 3ß-acetoxy diosgenin acetate (2) (9.9 g, 90%) which crystallized from acetone as colorless needles, m.p. 190–191 °C (lit. [13] m.p. 189–190 °C).

**7-Ketodiosgenin acetate (3)**

Chromium trioxide (4.09 g, 40.9 mmol) in 50% acetic acid (10 ml) was added, during 1 h, to a vigorously stirred solution of diosgenin acetate (2) (6 g, 13.14 mmol) in acetic acid (250 ml) maintained at 50–52 °C. It was stirred for additional 2.5 h at the aforesaid temperature. Zinc dust (5 g) was introduced into the reaction mixture. After vigorous shaking, the suspension was filtered. From the filtrate solvent was distilled off at reduced pressure until about 50 ml of the liquid was left. The residual liquid was extracted with ether. The ethereal layer was washed with dilute NaOH solution (1%), water and dried (MgSO4). A solid residue was obtained after the evaporation of ether. Silica gel column chromatography of the solid furnished the unchanged diosgenin acetate on elution with CCl4. Further elution of the column with CCl4-CH2Cl2 (1:1) gave a white solid. Crystallization of the solid from pentane yielded the desired product 3 (1.36 g, 22%), m.p. 196–197 °C (lit. [14] m.p. 196 °C).

**3ß-Acetoxy diosgenin-5(6)-en-7-one oxime (4)**

Oxime (4) (0.5 g, 1.03 mmol) in dry dioxane (30 ml) was warmed to 60 °C and thionyl chloride (5 ml) was added with stirring during 10 min. The reaction mixture was kept at 60 °C for additional 1 h. Then it was cautiously neutralized with saturated solution of sodium bicarbonate, extracted with a large volume of ether and the ether layer was dried (MgSO4). A dark brown oil was obtained after the evaporation of solvent. The oil was subjected to preparative TLC on a neutral alumina plate (20 × 100 cm) using benzene-ethyl acetate (4:1) as developing solvent, which furnished the desired product (225 mg, 45%). It was further purified by crystallization from ethanol, m.p. 201–202 °C.

**Analysis for C_{29}H_{42}O_5**

Calcd C 74.00 H 9.00,
Found C 74.30 H 8.96.

**3ß-Acetoxy diosgenin-5(6)-en-7-one oxime (4)**

7-Ketodiosgenin acetate (1 g, 2.12 mmol), hydroxyamine hydrochloride (2 g, 28.76 mmol) and sodium acetate trihydrate (2.6 g, 19.11 mmol) in 90% methanol (50 ml) were refluxed on a water-bath for 2.5 h. Water (15 ml) was added and again refluxed for 10 min. From the reaction mixture a white compound was deposited on cooling. It was filtered and washed with water. Further purification was effected by chromatography on neutral alumina column. Elution with benzene-ethyl acetate (4:1) gave the desired product (0.78 g, 76%) which crystallized from acetone in colorless crystals, m.p. 228–230 °C.

**Analysis for C_{29}H_{43}O_5N**

Calcd C 71.75 H 8.86 N 2.88, 
Found C 71.80 H 8.75 N 3.10.

**3ß-Acetoxy-7a-aza-B-homo-22a-spirost-5(6)-en-7-one (5)**

Analysis for C_{29}H_{45}O_5N

Calcd C 71.75 H 8.86 N 2.88, 
Found C 71.80 H 8.75 N 3.10.