Steroidal Triazoles

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Received November 26, 1974

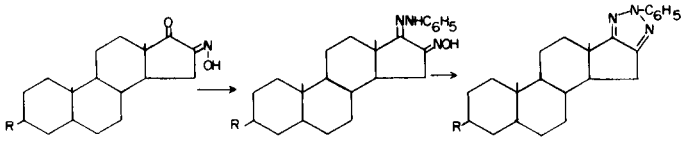
As part of a continuing program, the development of new aza-steroids for biological purposes has been the object of considerable interest in our laboratory (2-5).

In connection with our study of 2-substituted-*v*-triazoles (6), the cyclization of 3β-hydroxy-16-oximino-5α-androstan-17-one phenylhydrazone III and 3β-hydroxy-16-oximino-5-androsten-17-one phenylhydrazone IV was investigated.

The starting oximino ketones were prepared according to published procedures (7,8). The condensation of the 16-oximino-17-ketones I and II with phenylhydrazine gave the corresponding phenylhydrazones III and IV in good yields.

The ir spectra of III and IV showed absorptions at 770, 740 and 680 cm^{-1} attributable to the phenyl ring.

The attachment of the *v*-triazole ring to the steroid skeleton was affected on the basis of a general method of cyclizing phenylhydrazone oximes with acetic anhydride or phosphorus pentachloride in chloroform (9).



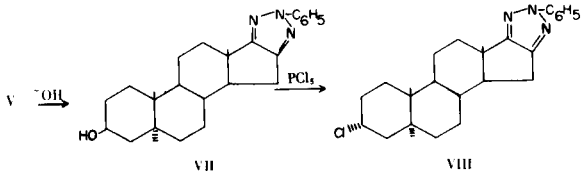
I, R = OH, 5α
II, R = OH, Δ⁵
III, R = OH, 5α
IV, R = OH, Δ⁵
V, R = OCOCH₃, 5α
VI, R = OCOCH₃, Δ⁵

When III was treated with phosphorus pentachloride, the 3α-chloro-5α-androstano-2′-phenyl[16,17]triazole was obtained.

Beside cyclization, Walden inversion takes place and the 3β-hydroxy group of III was transformed to the 3α-chloro VIII (10).

The ir spectrum showed characteristic absorption at 700 cm^{-1} attributable to the 3α-chloro, well established by Barton (11).

3α-Chloro-5α-androstano-2′-phenyl[16,17]triazole was proved by independent synthesis from the reaction of 3β-hydroxy-5α-androstano-2′-phenyl[16,17]triazole with phosphorus pentachloride in chloroform.



VII VIII

The nmr spectra of aromatic protons in triazoles V, VI and VIII, gives signals at τ 1.8 (two protons ortho to the nitrogen, as multiplet) and at τ 2.6 (three protons, as multiplet).

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer 521 in solid phase potassium bromide. Nmr spectra were determined with a Varian Associate A-60 instrument, using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Elemental analyses were performed by the Analytical Laboratory of the Chemistry Department, Demokritos, and National Research Foundation.

3β-Hydroxy-16-oximino-5α-androstan-17-one Phenylhydrazone (III).

To a solution of 1.595 g. of I [(m.p. 218-220°), *v* max 3420, 3200 (OH), 1720 (C=O), 1620 (C=N)] in 100 ml. of ethanol was added 0.8 g. of phenylhydrazine and the solution was heated under reflux for 2 hours. After concentration of the solution the crystalline material was collected by filtration to yield 1.600 g. Recrystallization from ethanol water gave III, m.p. 230-231°; *v* max: 3540, 3250 cm^{-1} (OH), 760, 740, 680 cm^{-1} (phenyl ring).

Anal. Calcd. for $C_{25}H_{35}N_3O_2$: C, 73.34; H, 8.50; N, 10.26. Found: C, 73.32; H, 8.17; N, 10.26.

3β-Hydroxy-16-oximino-5-androsten-17-one Phenylhydrazone (IV).

Following the above procedure, oximino-phenylhydrazone IV was obtained in 70% yield, after recrystallization from ethanol, m.p. 245-246°; *v* max: 3380, 3240 cm^{-1} (OH), 770, 740, 680 cm^{-1} (phenyl ring).

Anal. Calcd. for $C_{25}H_{33}N_3O_2$: C, 73.67; H, 8.16; N, 10.31. Found: C, 74.10; H, 8.17; N, 10.36.

Procedure for the Preparation of Triazoles.

To a solution of oximino-phenylhydrazone (2 g.) in 30 ml. of

glacial acetic acid was added 20 ml. of acetic anhydride. The mixture was heated under reflux for 12 hours. After this time the solution was poured into ice-water and extracted several times with 200 ml. of chloroform. The organic layer was washed with water, dried over magnesium sulfate and the solvent removed under reduced pressure to yield a residue which was crystallized from methanol-chloroform.

The triazoles obtained showed medium-intensity doublet, at 1330 cm^{-1} useful for the characterization of the ν-triazole nucleus (12).

3β-Acetoxy-5α-androstano-2′-phenyl[16,17]triazole (V).

This compound, m.p. 208-209°, was obtained in 50% yield; ν max: 1720, 1240 cm^{-1} (CH_3CO), 1330 cm^{-1} (triazole ring), 755, 685, 665, 625 cm^{-1} (phenyl ring); nmr: at τ 9.1 (18-CH_3), 8.9 (19-CH_3), 7.95 (CH_3CO), 5.25 (C_3-H), 2.6 (three aromatic protons, multiplet), 1.9 (two aromatic protons, multiplet).

Anal. Calcd. for $C_{27}H_{35}N_3O_2$: C, 74.82; H, 8.08; N, 9.70. Found: C, 75.15; H, 8.26; N, 9.66.

3β-Acetoxy-5-androsteno-2′-phenyl[16,17]triazole (VI).

This compound, m.p. 178-179°, was obtained in 42% yield; ν max: 1720, 1240 cm^{-1} (CH_3CO), 1320 cm^{-1} (triazole ring), 765, 690, 665, 635 cm^{-1} (phenyl ring); nmr: at τ 8.87 (18-CH_3, 19-CH_3, singlet), 7.92 (CH_3CO), 5.3 (C_3-H), 4.5 (C_6-H), 2.6 (three aromatic protons, multiplet), 1.8 (two aromatic protons, multiplet).

Anal. Calcd. for $C_{27}H_{33}N_3O_2$: C, 75.17; H, 7.65; N, 9.77. Found: C, 75.04; H, 7.59; N, 9.67.

3α-Chloro-5α-androstano-2′-phenyl[16,17]triazole (VIII).

To a solution of III (1 g.) in 50 ml. of chloroform was added 3 g. of phosphorus pentachloride. The mixture was heated under reflux for 75 minutes. Then the solution was poured into ice-water and the organic layer after separation was washed several times with water, dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The remaining residue was dissolved in chloroform and chromatographed on a silica gel column.

Elution with chloroform gave compound VIII (400 mg.), m.p. 217-218° ($CH_3COOC_2H_5$); ν max: 1330 cm^{-1} (triazole ring), 750, 680 cm^{-1} (phenyl ring) and at 700 cm^{-1} (3α-Cl); nmr: at τ 9.13 (18-CH_3), 8.9 (19-CH_3), 5.42 (C_3-H), 2.55 (three aromatic protons), 1.9 (two aromatic protons).

Anal. Calcd. for $C_{25}H_{32}N_3Cl$: C, 73.26; H, 7.81; N, 10.26. Found: C, 73.70; H, 7.94; N, 10.27.

Hydrolysis of 3β-Acetoxy-5α-androstan-2′-phenyl[16,17]triazole.

Compound V (0.8 g.) was dissolved in 100 ml. of methanol and to this solution was added 1 g. of potassium hydroxide. The mixture was agitated at room temperature for 3½ hours. Then the solution was poured into water and the precipitate collected by filtration (500 mg.). Crystallization twice from chloroform-methanol gave m.p. 206-207°.

Anal. Calcd. for $C_{25}H_{33}N_3O$: C, 76.72; H, 8.44; N, 10.74. Found: C, 77.10; H, 8.58; N, 10.86.

3α-Chloro-5α-androstan-2′-phenyl[16,17]triazole (VIII) from 3α-Hydroxy-5α-androstan-2′-phenyl[16,17]triazole (VII).

To 300 mg. of VII in 20 ml. of chloroform was added 500 mg. of phosphorus pentachloride and the mixture was heated under reflux for 2 hours. After this time 40 ml. of chloroform was added and the solution was washed several times with water and evaporated. The residue was crystallized from ethyl acetate (200 mg.), identical by a mixture melting point experiment and infrared spectra with an authentic sample.

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