Steroidal Quinoxalines

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Received May 21, 1973

The treatment of 3β-hydroxy-16α-bromo-5α-androstan-17-one, 3β-acetoxy-16α-bromo-5-androsten-17-one and 21-bromo-5-pregnen-3β-ol-20-one with 4,5-dimethyl-*o*-phenylenediamine gave substituted quinoxalines.

Hydrolysis of 3β-acetoxy-5-androsteno[16,17-*b*]-6′,7′-dimethylquinoxaline produced the corresponding 3β-hydroxy compound. 3-Oxo-4-androsteno[16,17-*b*]-6′,7′-dimethylquinoxaline was obtained by Oppenauer oxidation of the corresponding alcohol.

A condensation of *o*-phenylenediamine with 2-bromocyclopentanone gives 2,3-dihydro-1*H*-cyclopenta[*b*]quinoxaline (1-2). The closely related cyclizations such as that of cyclopentanone with *o*-phenylazoaniline (3), benzofuran oxide with an enamine of cyclopentanone (4) and direct condensation of *o*-phenylenediamine with 1,2-cyclopentanedione have also been reported (5).

While in search for a method of steroidal quinoxaline formation for pharmacological purposes, we felt that a reaction of dimethyl-*o*-phenylenediamine with 16α-bromo-17-ketones might be feasible.

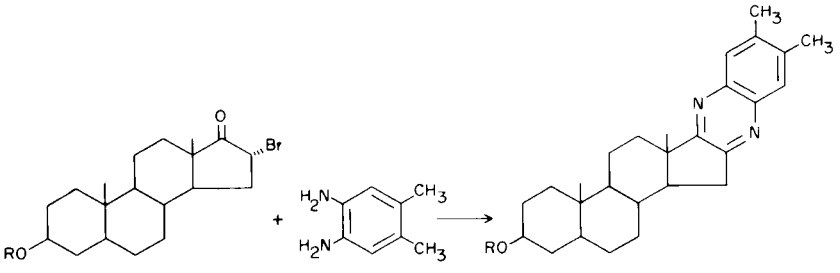
We found that 3β-hydroxy-16α-bromo-5α-androstan-17-one (I) and 3β-acetoxy-16α-bromo-5-androsten-17-one (Ia) react with 4,5-dimethyl-*o*-phenylenediamine (II) in xylene to give the fused quinoxalines III in good yield.

The aromatic proton signals of compound III appears in the nmr spectrum at τ 2.13 and 2.20 and that of the methyl groups of the quinoxaline ring at τ 7.50 (singlet). Compound IIIa can be obtained by acetylation of III.

Oppenauer oxidation of the quinoxaline IIIb gave 3-oxo-4-androsteno[16,17-*b*]-6′,7′-dimethylquinoxaline (IV) in 60% yield.

The structure of IV was confirmed by its analytical and spectral data 1650 (C=O), 1615 (C=C) cm^{-1}. The singlet for the vinyl proton in the nmr spectrum of IV appears at τ 4.15.

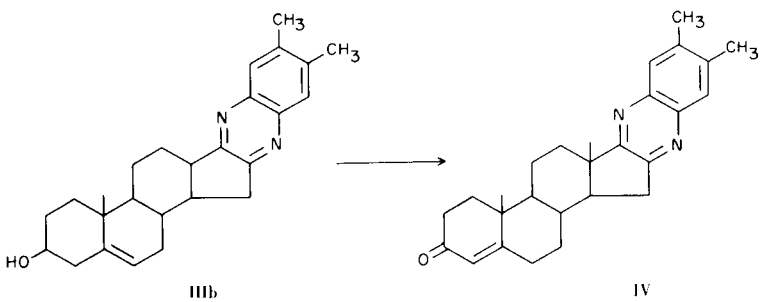
Extension of this reaction to 21-bromo-3β-hydroxy-5-pregnen-20-one with 4,5-dimethyl-*o*-phenylenediamine, yielded 3β-hydroxy-5-pregnen[20,21-*b*]-6′,7′-dimethylquinoxaline (VI). The nmr spectrum of compound VI



I, R = H
Ia, R = $COCH_3$, Δ^5

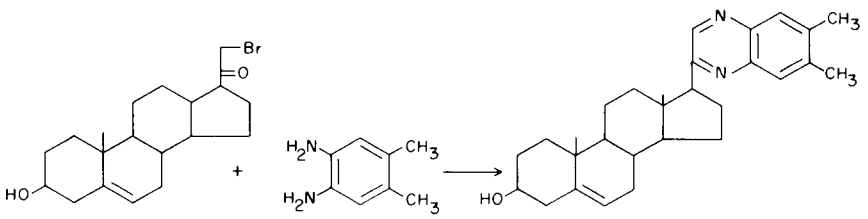
II

III, R = H
IIIa, R = $COCH_3$
IIIb, R = H, Δ^5
IIIc, R = $COCH_3$, Δ^5



IIIb

IV



V VI

gives signals at τ 2.10 and 3.40, which correspond to the two aromatic and to the C_{21}-H protons, respectively. The singlets at τ 7.50 must be due to the two methyl groups of quinoxaline ring.

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 Associates 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 Division, Democritos.

Procedure for the Preparation of Substituted Quinoxalines.

To a solution of 3 mmoles of I (6), Ia (7) or V (8) in 25 ml. of anhydrous xylene was added 6 mmoles of 4,5-dimethyl-*o*-phenylenediamine. The mixture was heated under reflux for 45 to 60 hours. The cooled mixture was filtered. The solvent was evaporated under reduced pressure and the residue was obtained in crystalline form by addition of chloroform-methanol in 65-70% yield. The following compounds were obtained.

3β-Hydroxy-5α-androstano[16,17-*b*]-6′,7′-dimethylquinoxaline (III).

This compound had m.p. 228-230°; ν max 3220 (OH), 1030, 870 cm^{-1} (quinoxaline); nmr at τ 8.9 (18-CH_3), 8.08 (19-CH_3), 7.5 ($2CH_3$, singlet, quinoxaline), 2.1 and 2.17 (2 aromatic protons).

Anal. Calcd. for $C_{27}H_{36}N_2O$: C, 80.20; H, 8.91; N, 6.93. Found: C, 80.60; H, 9.30; N, 6.92.

3β-Acetoxy-5α-androstano[16,17-*b*]-6′,7′-dimethylquinoxaline (IIIa).

This compound was obtained in 85% yield by acetylation of III with pyridine-acetic anhydride at room temperature, m.p. 216-218° (chloroform-methanol); ν max 1720, 1240 (CH_3CO), 1020, 870 cm^{-1} (quinoxaline); nmr at τ 9.1 (18-CH_3), 8.93 (19-CH_3), 7.94 (CH_3CO), 7.52 ($2CH_3$, singlet), 5.2 (C_3-H), 2.15 and 2.2 (two aromatic protons).

Anal. Calcd. for $C_{29}H_{38}N_2O_2$: C, 78.02; H, 8.52; N, 6.28. Found: C, 78.10; H, 8.90; N, 6.30.

3β-Acetoxy-5-androsteno[16,17-*b*]-6′,7′-dimethylquinoxaline (IIIc).

This compound had m.p. 205-206°; mass spectrum M^+ 444; ν max 1720, 1230 (CH_3CO), 1020, 870 cm^{-1} (quinoxaline); nmr at τ 8.85 ($2CH_3$ of steroid, singlet), 7.9 (CH_3CO), 7.48 ($2CH_3$, singlet), 5.33 (C_3-H), 4.5 (C_6-H), 2.14 and 2.2 (two aromatic protons).

Anal. Calcd. for $C_{29}H_{36}N_2O_2$: C, 78.39; H, 8.10; N, 6.30. Found: C, 78.80; H, 8.11; N, 6.29.

3β-Hydroxy-5-androsteno[16,17-*b*]-6′,7′-dimethylquinoxaline (IIIb).

To a solution of 100 ml. of methanol containing 4 g. of potassium hydroxide, 4 g. of IIIc were added and the mixture was refluxed for 30 minutes. The solution was poured into ice-water. The resulting precipitate was collected by filtration to yield compound IIIb in 93% yield, m.p. 160-161° (methanol); ν max 3270 (OH), 1040, 870 cm^{-1} (quinoxaline); nmr at τ 8.85 ($2CH_3$ of steroid, singlet).

Anal. Calcd. for $C_{27}H_{34}N_2O$: C, 80.60; H, 8.45; N, 6.96. Found: C, 80.20; H, 8.35; N, 6.80.

3β-Hydroxy-5-pregneno[20,21-*b*]-6′,7′-dimethylquinoxaline (VI).

This compound had m.p. 200-202° (ether); ν max 3400 (OH), 1050, 870 cm^{-1} (quinoxaline); nmr at τ 9.5 (18-CH_3), 9.0 (19-CH_3), 7.5 ($2CH_3$, quinoxaline singlet), 4.57 (C_6-H), 3.4 (C_{21}-H), 2.1 (two aromatic protons).

Anal. Calcd. for $C_{29}H_{38}N_2O$: C, 80.93; H, 8.83; N, 6.51. Found: C, 81.09; H, 8.95; N, 6.45.

3-Oxo-4-androsteno[16,17-*b*]-6′,7′-dimethylquinoxaline (IV).

A solution of 2 g. of the 3β-hydroxy-5-androsteno[16,17-*b*]-6′,7′-dimethylquinoxaline in 22 ml. of cyclohexanone, 90 ml. of dry dioxane and 80 ml. of dry toluene was distilled slowly as a solution of 2.2 g. of aluminium isopropylate in 10 ml. of toluene was added. Distillation was continued for two hours as 50 ml. of toluene was added and 140 ml. of distillate collected. Then the mixture was refluxed for four hours and let stand at room temperature overnight. The mixture was filtered to remove the precipitate containing the aluminum. The filtrate was distilled, extracted with chloroform, and evaporated. The quinoxaline IV was crystallized from chloroform-methanol, m.p. 266-267°, yield 60%; ν max 1650 (C=O), 1615 (C=C), 865, 1050 cm^{-1} (quinoxaline); nmr at τ 8.7 (19-CH_3), 8.83 (18-CH_3), 7.5 ($2CH_3$, singlet), 4.15 (C_4-H), 2.12, 2.17 (2 aromatic protons).

Anal. Calcd. for $C_{27}H_{32}N_2O$: C, 81.0; H, 8.0; N, 7.0. Found: C, 81.39; H, 7.96; N, 6.98.

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