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Using a substrate steroidal α-bromo, α-hydroxy and α-acetoxyketones, we studied the mechanism of osazone formation. A synthetic approach for the preparation of cholestano-2'-phenyl[2,3-*d*]triazole is described.

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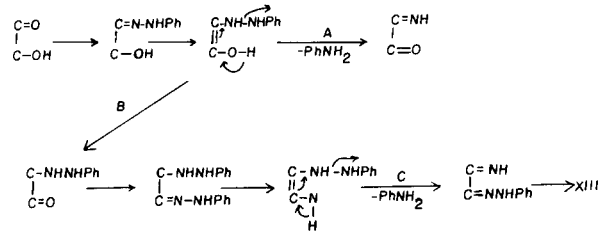
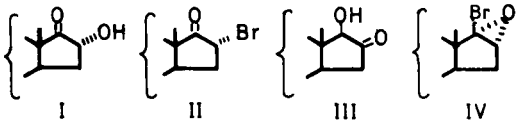
In previous communication [1-3] we have studied the mechanism of osazone formation in steroidal substrate, because of the well defined stereochemistry in such systems.

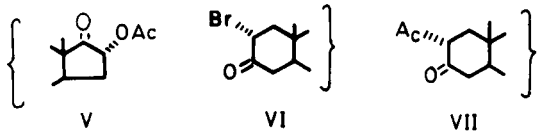
The conversion of 16α-bromoketone II or acetoxyketone V with phenylhydrazine in ethanol gives the phenylhydrazino phenylhydrazone XIII in yields of up to 70%. The latter is readily converted to the yellow osazone XIII on treatment with phenylhydrazine in the presence of acetic acid or in pyridine.

The plausibility of the conversion of XII to XIII *via* enediamine is shown by the following facts:

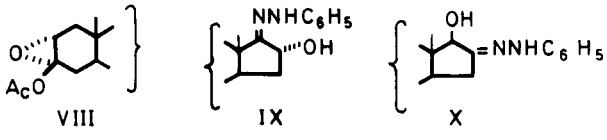




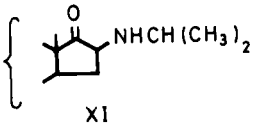
I II III IV



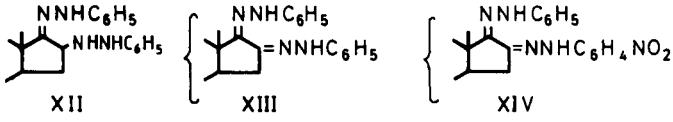
V VI VII



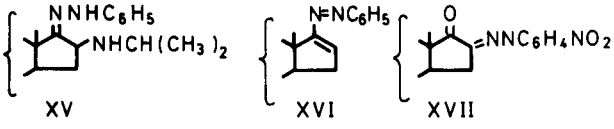
VIII IX X



XI



XII XIII XIV



XV XVI XVII

Treatment of XII with *p*-nitrophenylhydrazine in acetic acid medium the mixed oxazone XIV was isolated. The structure of XIV is apparent from its formation in the reaction of XV with *p*-nitrophenylhydrazine, a sequence which must involve a step analogous to C.

Phenylhydrazone XV was obtained from aminoketone XI. It must note that osazone XIII does not exchange with *p*-nitrophenylhydrazine to give XIV.

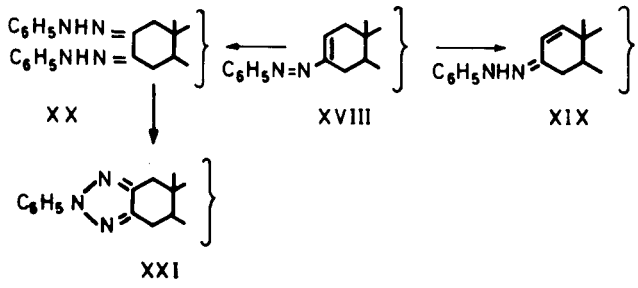
The isolation of XII is converted to XIV demonstrates that path B is possible. Evidence for path A can be obtained by the conversion of hydroxyphenylhydrazone X to ketophenylhydrazone XVII with *p*-nitrophenylhydrazine in the presence of acetic acid at 25°. This probably involves intermediate

Ketone XVII is converted to XIV with phenylhydrazine.

Acetoxy ketone V yields XII on warming with phenylhydrazine in ethanol. The logical pathway is elimination of acetic acid to form azo-compound XVI, to which phenylhydrazine adds in a 1,4-manner. Formation of unsaturated azo-compounds in the reaction of α-halo or acetoxy ketones with hydrazines has been demonstrated [4-5].

Formation of azo-compound in the reaction of α-halo, acetoxyketone or oxidoacetate has been demonstrated in the A ring of cholestan [3].

When acetoxyepoxide VIII, acetoxyketone VII or bromoketone VI exposed to phenylhydrazine-ethanol, yields the yellow 3-phenylazocholest-2-ene XVIII. The transformation of XVIII into XIX can be carried out in the presence of phenylhydrazine hydrobromide but not with either phenylhydrazine or acetic acid alone, indicating the necessity for combined acid-base catalysis [3].



XXI

In connection with our study of steroidal 2-substituted *v*-triazoles [6], we attempted to isolate 2-oximino-3-cholestamone as a substrate for the synthesis of 2-substituted *v*-triazoles, we were unsuccessful. Nevertheless, we succeeded in the synthesis of cholestano-2′-phenyl[2,3-*d*]triazole starting from cholestanone-2,3-dione bisphenylhydrazone (XX) and cupric bromide.

EXPERIMENTAL

Melting points were determined on a Galenkamp melting point apparatus and are uncorrected. The ir spectra were recorded with a Perkin Elmer 521 in solid phase potassium bromide. Ultraviolet spectra are measured in chloroform solution on a Cary Model 14 instrument. The nmr spectra were determined with a Varian Associates A-60 instrument, using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Elemental analysis was performed by the Analytical Laboratory of the Chemistry Department of NRC "Democritos".

3β-Acetoxy-5α-androstan-17-one-16β-phenylhydrazine-17-phenylhydrazone (XIIa).

To a solution of 410 mg of 3β-acetoxy-16α-bromo-5α-androstan-17-one [7] in 15 ml of absolute ethanol, 325 mg of phenylhydrazine was added and the mixture was heated under reflux for 2 hours. The solution was cooled and the precipitate collected by filtration to yield white product 330 mg of the phenylhydrazine-phenylhydrazone XII, mp 213-215° (acetone); ν max 3300, 1600 cm^{-1}; λ max 280 mμ (ϵ 16840); nmr: τ 5.05 triplet, H at C-16.

Anal. Calcd. for $C_{33}H_{44}N_4O_2$: C, 74.96; H, 8.39; N, 10.60. Found: C, 75.04; H, 8.54; N, 10.74.

Under the same reaction conditions, the following compounds were obtained:

3β-Hydroxy-5α-androstan-17-one-16β-phenylhydrazine-17-phenylhydrazone (XIIb).

This compound was prepared from 3β-hydroxy-16α-bromo-5α-androstan-17-one [7] in 84% yield, mp 223-224° (acetone).

Anal. Calcd. for $C_{31}H_{42}N_4O$: C, 76.54; H, 8.64; N, 11.52. Found: C, 76.83; H, 8.69; N, 11.10.

3β-Acetoxy-5-androsten-17-one-16β-phenylhydrazine-17-phenylhydrazone (XIIc).

This compound was prepared from 3β-acetoxy-16α-bromo-5-androsten-17-one [8] in 75% yield, mp 219-222° (ethanol).

Anal. Calcd. for $C_{33}H_{42}N_4O_2$: C, 75.28; H, 7.98; N, 10.03. Found: C, 75.49; H, 7.80; N, 10.00.

The above compound was prepared from 2β,16α-diacetoxy-5-androsten-17-one [9] in 70% yield and it was identical to XIIc by melting point and ir.

3β-Acetoxy-5α-androstano-16,17-one-dione Bisphenylhydrazone (XIIIa) With Acetic Acid.

A solution of 3β-acetoxy-16α-bromo-5α-androstan-17-one, 460 mg in 20 ml of glacial acetic acid containing 500 mg of phenylhydrazine was allowed to stand at room temperature for 14 hours. After this time the solution was poured into water and the precipitate collected by filtration washed with water and dried to give 430 mg of yellow compound.

Recrystallization from methanol-acetone gave osazone XIII, mp 292-294°.

Anal. Calcd. for $C_{33}H_{44}N_4O_2$: C, 75.00; H, 8.33; N, 10.60. Found: C, 74.93; H, 8.21; N, 10.76.

Using as starting material 3β-acetoxy-17β-bromo-16α,17α-oxido-5α-androstan (IV) [10], osazone XIII was obtained in 85% yield identical by melting point and ir spectrum to the compound prepared from bromoketone.

3β-Acetoxy-5α-androstano-16,-17-dione Bisphenylhydrazone (XIIIa) With Pyridine.

To a solution of 100 mg of 3β-acetoxy-16α-bromo-5α-androstan-17-one in 5 ml of pyridine, 100 mg of phenylhydrazine was added and the mixture was heated in an oil bath for 2 hours. The solution was poured into ice-water and extracted with chloroform. After evaporation of the solvent the residue was crystallized from acetone-methanol giving yellow needles (65 mg) mp 291-293°.

The infrared spectrum was identical to the osazone prepared from the bromoketone.

Under the same reaction condition, 3β-hydroxy-5α-androstano-16,17-dione bisphenylhydrazone obtained in 90%, mp 229-230° (acetone-methanol).

Anal. Calcd. for $C_{31}H_{40}N_4O$: C, 76.86; H, 8.26; N, 11.57. Found: C, 76.53; H, 8.30; N, 11.30.

3β-Hydroxy-5-androsteno-16,17-dione-17-phenylhydrazine-16-phenylhydrazone (XIV).

A. From 3β-Hydroxy-5-androsteno-16β-phenylhydrazine-17-phenylhydrazone.

To a solution of 860 mg of 3β-hydroxy-5-androsteno-16β-phenylhydrazine-17-phenylhydrazone (XII) in 100 ml of acetic acid, 610 mg of *p*-nitrophenylhydrazine was added and the reaction mixture was allowed to stand at room temperature for 18 hours. After this time the solution was poured into water and extracted with chloroform, dried over magnesium sulfate and the solvent removed under reduced pressure. The remaining residue was dissolved in chloroform and chromatographed on silica gel column. Elution with ether gave compound XIV, mp 262-264° (acetone).

Anal. Calcd. for $C_{31}H_{37}N_5O_3$: C, 70.56; H, 7.07; N, 13.28. Found: C, 70.53; H, 6.99; N, 13.00.

B. From 16β-Isopropylamino-17-ketoandrostan-3β-ol acetate (XI).

3β-Acetoxy-16β-isopropylaminoandrostan-3β-ol acetate, mp 144-146°, was obtained in 45% yield by the reaction of 3β-acetoxy-17β-bromo-16α,17α-oxidoandrostane with isopropylamine [10].

To a solution of 389 mg of XI in 10 ml of absolute ethanol, 110 mg of fresh distilled phenylhydrazine was added and the mixture was heated under reflux for 2.5 hours. After this time the solvent was removed and the residue was crystallized from acetone-methanol to give 100 mg of isopropylaminophenylhydrazine XV, mp 197-199°.

Anal. Calcd. for $C_{40}H_{45}N_3O_2$: C, 75.11; H, 9.46; N, 8.76. Found: C, 74.65; H, 8.99; N, 8.30.

Under the same reaction conditions as for the above experiment, XIV was obtained from XV. It was identical by infrared spectrum and melting point to XIV.

3β,17β-Dihydroxy-5α-androstan-17-one Phenylhydrazone (Xa).

To a solution of 135 mg of 3β,17β-dihydroxy-5α-androstan-16-one [9] in 5 ml of benzene, 110 mg of phenylhydrazine was added and the mixture was heated under reflux for 2 hours. Then the solvent was evaporated and the residue was crystallized from methanol to give 80 mg of X mp 188-190°.

Anal. Calcd. for $C_{25}H_{36}N_2O_2$: C, 75.75; H, 9.09; N, 7.57. Found: C, 75.52; H, 8.76; N, 7.19.

3β,17β-Dihydroxy-5-androsten-17-one Phenylhydrazone (Xb).

To a solution of 335 mg of 3β,17β-dihydroxy-5-androsten-17-one [9] in 10 ml of absolute ethanol, 200 mg of phenylhydrazine was added and the mixture was heated under reflux for 3 hours. After this time, part of the solvent was evaporated and the precipitate collected by filtration to give phenylhydrazone 240 mg, mp 183-185° (ethanol); λ max 274 mυ, ε 17300.

Anal. Calcd. for $C_{25}H_{34}N_2O_2$: C, 76.14; H, 8.63; N, 7.10. Found: C, 76.02; H, 8.70; N, 7.00.

3β-Hydroxy-5-androsten-16,17-dione-16-*p*-nitrophenylhydrazone (XVII).

To a solution of 750 mg of 3β,17β-dihydroxy-5-androsten-16-one phenylhydrazone (X) in 35 mg of glacial acetic acid, 600 mg of *p*-nitrophenylhydrazine was added and the mixture was allowed to stand at room temperature for 6 hours. The yellow precipitate was collected and dried (450 mg). After recrystallization from dichloromethane-acetone brought mp >300°; ν max 1710, 1600 cm^{-1}; λ max 370 mμ, (ε 35800).

Anal. Calcd. for $C_{25}H_{31}N_3O_4$: C, 68.31; H, 7.57; N, 9.66. Found: C, 68.51; H, 7.42; N, 9.73.

3β-Hydroxy-5-androsteno-16,17-dione-17-phenylhydrazone-17-*p*-nitrophenylhydrazone (XIV) was obtained from 3β-hydroxy-5-androsten-16,17-dione-16-*p*-nitrophenylhydrazone and phenylhydrazine in acetic acid. This compound was identical by infrared spectrum to the compound prepared before from 3β-hydroxy-5-androsten-16β-phenylhydrazine-17-phenylhydrazone.

Cholestano-2'-phenyl[2,3-*d*]triazole (XXI).

Cholestanone-2,3-dione bisphenylhydrazone (XX) was obtained in 65% yield by the reaction of 2α-bromo-3-cholestanone in acetic acid, mp 207-209° (acetone-methanol); λ max 390, 305, 263 mμ (ε, 17980, 14500, 18560 respectively).

Compound XX (600 mg) was dissolved in 30 ml of methanol and to this solution was added 1 g of cupric bromide. The mixture was heated under reflux for 20 hours and the precipitate was filtered off. The solvent was removed and the residue was dissolved in chloroform and washed several times with water and evaporated. The residue was crystallized from acetone (300 mg), mp 126-128°; ν max 1330 (triazole ring), 1590, 740, 675 cm^{-1} (phenyl ring).

Anal. Calcd. for $C_{33}H_{49}N_3$: C, 81.31; H, 10.06; N, 8.62. Found: C, 80.97; H, 9.98; N, 8.47.

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