REACTIONS OF 1,5-DIKETONES.

XIV.* SYNTHESIS OF COMPOUNDS WITH A 6-OXA-8-AZASTEROID SKELETON

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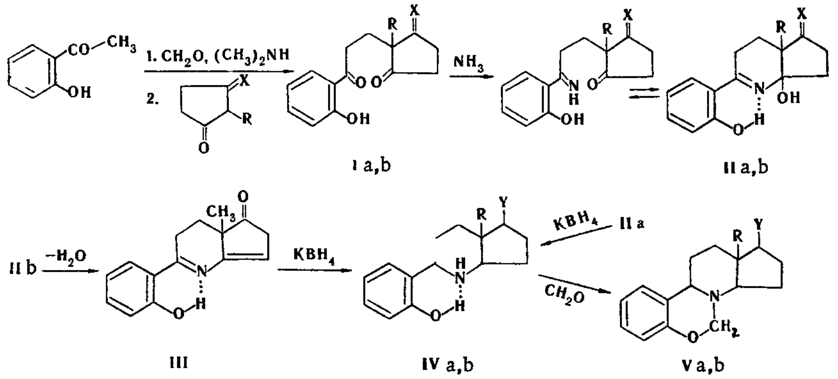
Compounds with a 6-oxa-8-azasteroid skeleton were synthesized from "semicyclic" 1,5-diketones obtained from o-hydroxyacetophenone, formaldehyde, and, respectively, cyclopentanone and 2-methylcyclopentane-1,3-dione.

The synthesis of the simplest compound with a 6-oxa-8-azasteroid skeleton (Va) from semicyclic diketone Ia was briefly reported in [2]. Continuing research in this direction we accomplished the synthesis of a closer analog of natural steroids – 17-β-hydroxy-6-oxa-8-azaestra-1,3,5(10)-triene (Vb).



I, II a $R=H$, $X=H_2$; b $R=CH_3$, $X=O$; IV, V a $R=H$, $Y=H$; IV b $R=CH_3$, $Y=OH$; V b $R=CH_3$, $Y=OH$

The reaction of the hydrochloride of the Mannich base of o-hydroxyacetophenone with 2-methyl-cyclopentane-1,3-dione in the presence of NaOH [3] proved to be the most suitable method for the preparation of triketone Ib. The IR spectrum of Ib contains absorption bands of carbonyl groups of o-hydroxyacetophenone (1660 cm^{-1}) and cyclopentanedione (1730 cm^{-1}, shoulder at 1760 cm^{-1}). Absorption is absent at 3200-3600 cm^{-1}, inasmuch as the OH group is tied up in the form of a chelate. Compound IIb is obtained in almost quantitative yield when dry ammonia is bubbled through a benzene solution of triketone Ib. The IR spectrum of IIb in $CHCl_3$ contains an intense band at 1620 cm^{-1} ($C=N$), and the absorption of a nonassociated OH group appears at 3600 cm^{-1}; this corresponds to the cyclic form of product IIb. Ring–chain tautomerism has been established for IIa [2].

We were unable to convert IIb directly to Vb by borohydride reduction as previously described [2] for the conversion of IIa to IVa, inasmuch as IIb does not undergo dehydration under such mild conditions because of the absence of an angular hydrogen. The dehydration of IIb to give III can be accomplished by acidic

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*See [1] for communication XIII.

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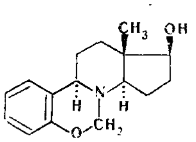
agents (oxalic acid, $SOCl_2$, $KHSO_4$, and p-toluenesulfonic acid); because of the instability of product IIb with respect to the action of acidic reagents, dehydration is accompanied by partial resinification. Better results (a yield of ~60%) are obtained when catalytic amounts of p-toluenesulfonic acid are used or in the case of dehydration by means of $KHSO_4$ in dioxane at 50-70°. The absorption of a free OH group is absent in the IR spectrum of III. The PMR spectrum contains a triplet at 5.8 ppm (1 H), which corresponds to a vinyl proton (when C = 15).

Alcohol IVb is formed by reduction of unsaturated ketone III with potassium borohydride in dioxane. Absorption of OH groups (3620 cm^{-1}) and NH groups (3300 cm^{-1}) is observed in its IR spectrum; its mass spectrum contains an intense peak of ions with m/e 247, and this corresponds to the expected molecular weight. Compound IVb reacts readily with 36% formalin at room temperature to give product Vb. The IR spectrum of the latter does not contain the absorption of an N–H bond at 3300 cm^{-1};at the same time,"Bohlmann absorption" appears at 2780 cm^{-1}, and this indicates the presence of an $O-CH_2-N$ fragment [4]. The m/e value is 259, and this is in agreement with the molecular weight for the proposed formula.

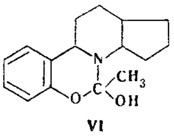
An examination of the PMR and IR spectra makes it possible to propose trans-B/C fusion in products Va, b. In particular a large difference in the chemical shifts of the protons of the $O-CH_2-N$ group (4.6 ppm for the equatorial and 4.0 ppm for the axial group), a considerable geminal constant (J_{gem} = 8 Hz) [4, 5], and the presence of a quartet at 3.2 ppm (1 H) (J_{ea} = 4 Hz, J_{aa} = 10 Hz), which indicates a proton that is axial with respect to the B and C rings when C = 9 [6], are observed. The presence of "Bol'manov absorption" in the IR spectra of Va, b is also in agreement with trans-B/C fusion, inasmuch as a trans-diaxial orientation of the unshared pair of nitrogen electrons and the adjacent C–H bonds is observed in this case.

The PMR spectrum of Vb contains a triplet at 3.67 ppm (1 H) with splittings of 8 Hz, which is a characteristic resonance signal of the 17-α-proton [7]. Consequently, the 17-hydroxy group occupies the β position. The other data also provide evidence in favor of trans C/D fusion. In particular the signal of the 18-CH_3 group in the PMR spectrum of product Vb is shifted only weakly to strong field (singlets at 0.90 and 0.82 ppm, respectively) as the solvent is changed from $CDCl_3$ to C_6D_6, and this is in agreement with the literature data for 8-azaestrone with trans-C/D fusion, whereas the isomer with cis fusion gives a stronger shift (0.24 ppm) [8]. The fact that the β alcohol is formed in the hydride reduction of the keto- "quasisteroid" with trans fusion also indicates trans-C/D fusion to a certain degree [9].

Thus we propose the following configuration for Vb:



We obtained yet another compound (VI) with a 6-oxa-8-azasteroid skeleton from the previously described IVa [2] by acetylation with acetic anhydride. Its molecular ion has an m/e value of 259^+. Structure VI follows from its IR spectrum, in which ester or amide carbonyl absorption is absent, and there is a broad absorption band of a OH group at 3100-3300 cm^{-1} (in mineral oil). The usual triacetate is obtained by acetylation of product IVb. Its IR spectrum contains absorption at 1650 (amide C=O), 1720 (Ar–O–CO–), and 1735 cm^{-1} (Alk–O–CO–).



VI

An attempt to synthesize the complete analog of estrol from o-hydroxy-p-methoxyacetophenone was unsuccessful, inasmuch as we were unable to synthesize the appropriate triketone. A product with m/e 290, which is 12 units more than the value for the expected triketone, was obtained by reaction of the Mannich base of o-hydroxy-p-methoxyacetophenone with 2-methylcyclopentane-1,3-dione. The compound, which does not react with ammonia, is probably the product of condensation of the triketone with formaldehyde.

EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrometer. The mass spectra were recorded with an MKh-1303 spectrometer. The PMR spectra were recorded with a ZKR-60 spectrometer with tetramethylsilane as the internal standard. The course of the reactions and the individuality of the substances were monitored by thin-layer chromatography (TLC) on Silufol.

1-(o-Hydroxyphenyl)-3-(1'-methyl-2',5'-dioxocyclopentyl)-1-propanone (Ib). A total of 20 ml of 9 N NaOH and 5.6 g (50 mmole) of 2-methylcyclopentane-1,3-dione were added to a refluxing solution of 14.7 g (65 mmole) of the hydrochloride of the Mannich base of o-hydroxyacetophenone in 120 ml of ethanol, after which the mixture was refluxed for 30 min, cooled with ice, and neutralized to pH 7 with concentrated HCl. The ethanol was removed by distillation at reduced pressure, 120 ml of water was added to the residue, and the aqueous mixture was acidified to pH 1 with concentrated HCl and extracted with benzene. The extract was washed with saturated $NaHCO_3$ solution and water, the benzene was removed by distillation at reduced pressure, and the residue was crystallized by trituration with alcohol to give 7 g (54%) of a product with mp 89-90° (from ethanol). Found: C 69.4; H 6.5%. $C_{15}H_{16}O_4$. Calculated: C 69.2; H 6.2%.

8-Hydroxy-5-oxo-9-methyl-2-(o-hydroxyphenyl)-3,4,5,6,8,9-hexahydropyridine (IIb). Dry NH_3 was bubbled through a solution of 4.7 g of Ib in 40 ml of benzene for 1 h, after which the mixture was heated to remove the excess NH_3 and filtered to give 4.5 g (96%) of yellow crystals of IIb with mp 152-153°. Found: C 69.8; H 6.7; N 5.0%. $C_{15}H_{17}NO_3$. Calculated: C 69.5; H 6.6; N 5.4%.

5-Oxo-9-methyl-2-(o-hydroxyphenyl)-3,4,5,6-tetrahydropyridine (III). A solution of 2.6 g of IIb and 70 mg of p-toluenesulfonic acid in 80 ml of toluene was refluxed with a Dean–Stark trap for 3 h, after which the toluene was removed by distillation at reduced pressure, and the residue was crystallized from petroleum ether to give 1.4 g (58%) of III with mp 118-119°. Found: C 74.7; H 6.4; N 5.8%. $C_{15}H_{15}NO_2$. Calculated: C 74.7; H 6.2; N 5.8%.

5-Hydroxy-9-methyl-2-(o-hydroxyphenyl)perhydropyridine (IVb). A solution of 0.97 g (4 mmole) of III in 9 ml of dioxane was added dropwise with stirring to a solution of 0.38 g (7.5 mmole) of KBH_4 in a mixture of 4 ml of water and 4 ml of dioxane, after which the mixture was allowed to stand overnight. A total of 20 ml of 10% HCl was added, the mixture was extracted with ether, and the aqueous layer was made alkaline with 10% Na_2CO_3 solution. The reaction product was extracted with ether, the ether was removed from the extract by evaporation, and the residue was crystallized to give 0.75 g (76%) of IVb with mp 159-160° (from benzene–petroleum ether). Found: C 72.9; H 8.6; N 5.2%. $C_{15}H_{21}NO_2$. Calculated: C 72.9; H 8.4; N 5.7%.

17-β-Hydroxy-6-oxa-8-azaestra-1,3,5(10)triene (Vb). A 0.6-g (24 mmole) sample of IVb was dissolved in 7 ml of ethanol, 1 ml of 36% formalin solution was added, and the mixture was allowed to stand overnight. The solvent was removed by distillation, and the residue was treated with 10 ml of 10% NaOH and extracted with ether. The ether was evaporated to give 0.45 g (67%) of Vb with mp 77-84° (dec., from petroleum ether). Found: C 73.5; H 8.1%. $C_{16}H_{21}NO_2$. Calculated: C 74.0; H 8.2%.

7-Hydroxy-7-methyl-6-oxa-8-aza-6,7,8,9,11,12,13,14,16,17-decahydrocyclopenta[a]phenanthrene (VI). A 0.3-g sample of IVa was dissolved in 2 ml of acetic anhydride, during which the mixture heated up spontaneously. After 2 min, VI began to precipitate. The mixture was filtered after 1 h, and the solid was washed with ether to give 0.34 g (95%) of a product with mp 209-211°. Found: C 73.2; H 8.4; N 5.3%. $C_{16}H_{21}NO_2$. Calculated: C 74.1; H 8.1; N 5.4%.

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