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# B-Homoprogesterone

As a continuation of studies on B-ring expanded B-homosteroid, we synthesized some B-homopregnane derivatives.

The starting material 3$\beta$,20$\beta$-diacetoxy-5$\alpha$-pregnan-7-one (II) was cyanohydrated with acetone cyanohydrine to form 7$\alpha$-cyano-5$\alpha$-pregnane-3$\beta$,7$\beta$,20$\beta$-triol 3,20-diacetate (III), which was reduced catalytically to water soluble 7$\beta$-hydroxy-7$\alpha$-aminomethyl acetate (IV). An aqueous acetic acid solution of IV was treated with sodium nitrite under cooling to give 3$\beta$,20$\beta$-diacetoxy-B-homo-5$\alpha$-pregnan-7-one (V, m.p. 201.5°).*1

The location of the keto group of V was deduced at 7 position as referred to the known B-homocholestane derivatives prepared before.[1] This was also confirmed by nuclear magnetic resonance spectral data of its bromo derivatives.

Hydrogen bromide catalyzed bromination of V gave a stable mono bromo ketone (VI, m.p. 206°) in excellent yield with either one or two molar equivalents of bromine in acetic acid solution.

In order to locate the bromine atom in VI, I was submitted to catalytic deuteration[2] with palladium-carbon to give (VII). On alkaline treatment followed by reacetylation with acetic anhydride and pyridine, VII furnished 5$\alpha$-*d*-3$\beta$,20$\beta$-diacetoxy-5$\alpha$-pregnan-7-one (VIII), from which 5$\alpha$-*d*-3$\beta$,20$\beta$-diacetoxy-B-homopregnan-7-one (XI) was prepared by ring expansion reaction as was applied to V.

Bromination of XI gave monobromo 5$\alpha$-*d*-3$\beta$,20$\beta$-diacetoxy-B-homopregnan-7-one (XII).

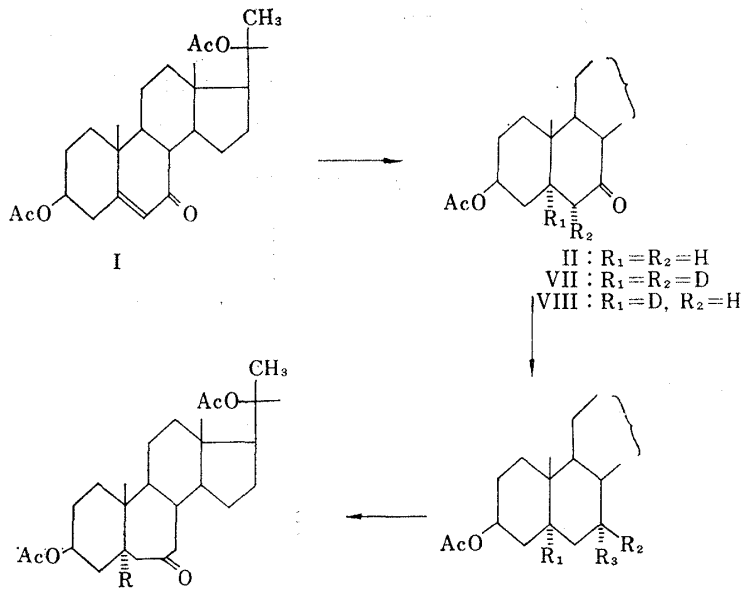


Chart 1.

*1 All melting points were uncorrected.

1) J. Himizu : Yakugaku Zasshi, 83, 620 (1963).
2) F. J. Schmits, W. S. Johnson : Tetrahedron Letters, 1962, 647.

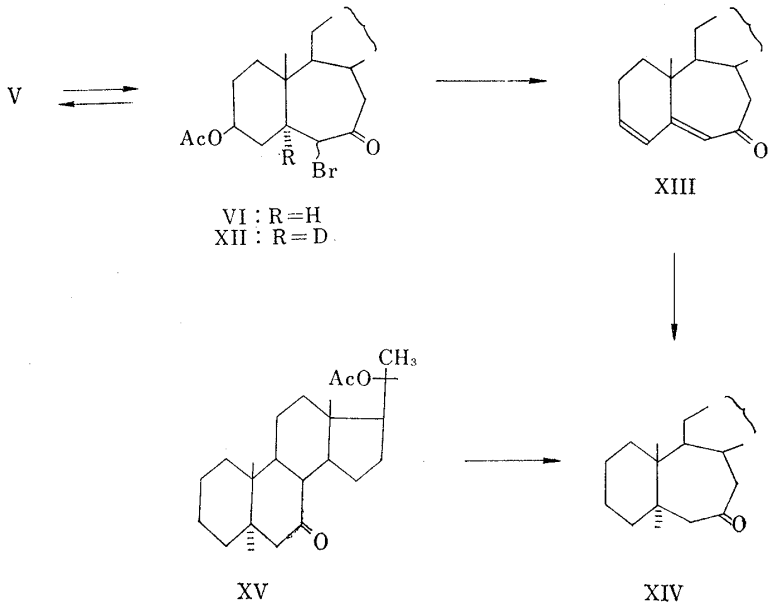


Chart 2.

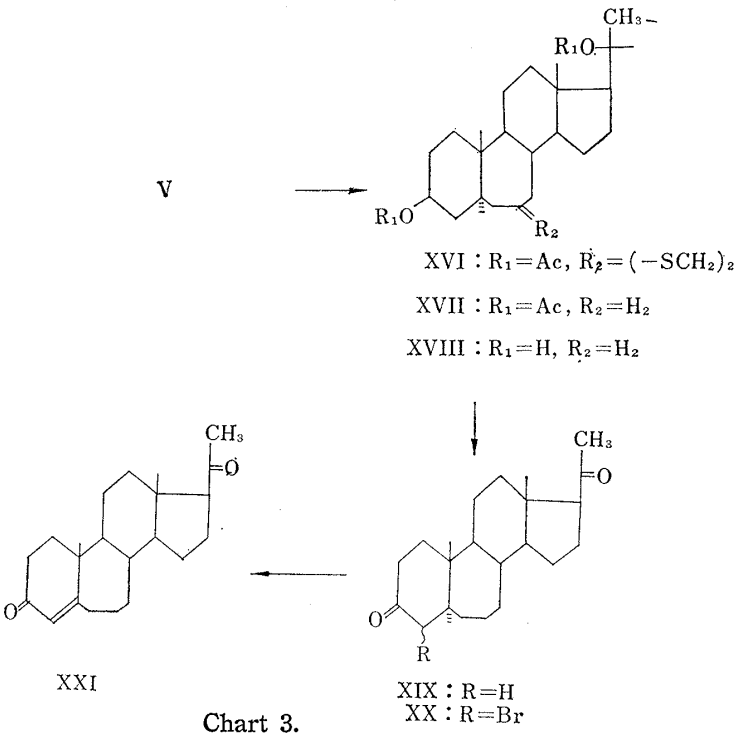


Chart 3.

There exists considerable difference between nuclear magnetic resonance spectra*2 of VI and XII. The most remarkable is the fact that while VI showed a reasonable doublet signal at $\tau$ 6.20, XII exhibited what appeared to be a triplet in the same region. At first sight the latter fact seemed difficult to understand, but it could be construed that the triplet was ostensible and was actually an overlapped signal of a singlet and a doublet due to XII and VI respectively.

*2 NMR spectra were taken on Varian HR-100 recording spectrometer in $CDCl_3$ with $SiMe_4$ as an internal standard.

The reason why this triplet band was actually a duplicated signal of a singlet and doublet ones, is attributed to the contamination of Ⅵ in Ⅻ, which presumably occurred either during the catalytic hydrogenation of the cyano hydrine,[3] or through the acid catalyzed bromination of[4] Ⅺ, or even in the stage of first deuteration.*[3]

Now, the synthesis of B-homoprogesterone *via* the intermediate Ⅵ was performed. Attempted dehydrobromination of Ⅵ in boiling pyridine recovered unchanged Ⅵ, and treatment with refluxing s-collidine gave the reduced product (Ⅴ) in good yield.

Further study in dimethylformamide with lithium chloride and lithium carbonate, resulted in the dehydrobromination accompanied by deacetoxylation to give 20$\beta$-acetoxy-B-homopregna-3,5-dien-7-one (XIII, m.p. 163°), which exhibited in UV $\lambda_{max}^{EtOH}$ m$\mu$ ($\varepsilon$) : 279 (24500). Upon catalytic hydrogenation XIII consumed readily two molar equivalents of hydrogen to give 20$\beta$-acetoxy-B-homo-5$\alpha$-pregnan-7-one (XIV, m.p. 191°). The structure of XIV was supported by an independent synthesis of XIV from 20$\beta$-acetoxypregnan-7-one (XV), by Tiffeneau ring expansion method.

The failure of the dehydrobromination of Ⅵ to 3$\beta$,20$\beta$-diacetoxy-B-homopregn-5-en-7-one made us to take another route to synthesize B-homopregesterone.

Treating Ⅴ with ethylenedithiol with catalytic amount of boron trifluoride etherate in acetic acid, the ethylenedithioketal (XVI, m.p. 201°) was obtained, which exhibited on the nuclear magnetic resonance spectrum*[4] the signal of $-S-CH_2-$ at 6.80. The latter was desulfurized to 3$\beta$,20$\beta$-diacetoxy-B-homo-5$\alpha$-pregnane (XVII, m.p. 107°) with Raney nickel in ethanol. Hydrolysis of XVII afforded the diol (XVIII, m.p. 187°), which was oxidized to B-homo-5$\alpha$-pregnane-3,20-dione (XIX, m.p. 161.5°) with chromium trioxide in acetic acid.

Acidic bromination of XIX with one molar equivalent of bromine in acetic acid gave mono bromo-ketone (XX, m.p. 137°) in satisfactory yield, whose bromine atom was proved to be located at position 4 by nuclear magnetic resonance spectral data.

It is remarkable that bromination of B-homo-5$\alpha$-steroidal 3-ketone occurred exclusively at 4 position, though 2$\alpha$-bromination appeared probable based on the many observed facts of bromination of steroidal 5$\alpha$-3-ketones and *trans*-2-decalone derivatives.[5]

This may well be explained by the conformational difference of the B-homosteroid from the normal one, and the flexibility of B-seven membered ring, which influenced the course of the bromination.

B-Homoprogesterone (XXI, m.p. 140°) was obtained by heating XX with lithium chloride in dimethylformamide. XXI showed on nuclear magnetic resonance spectrum*[4] a singlet signal of $\tau$ 4.32, UV $\lambda_{max}^{EtOH}$ m$\mu$ ($\varepsilon$) : 246 (10900), and a strong negative Cotton curve on optical rotatory dispersion.

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*3 This point is under investigation by mass spectrometry.
*4 NMR spectra were taken on JEO C-60 recording spectrometer $CDCl_3$ with $SiMe_4$ as an internal standard.
* All analytical data of these compounds showed good agreement with the calculated amount.

3) D. K. Fukushima, T. F. Gallagehr, J. Biol. Chem., **198**, 861 (1952).
4) W. D. Emons, M. F. Hawthone : J. Am. Chem. Soc., **78**, 5593 (1956).
5) M. Yanagita, K. Yamakawa : J. Org. Chem., **21**, 500 (1956); C. Djerassi, J. E. Gurst : J. Am. Chem. Soc., **86**, 1755 (1964).