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Studies on Seven-membered Ring Compounds. XXXIV.[1] Reactions between Tropylium Cation and Dienamines

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Reaction of tropylium fluoroborate (I) with morpholine dienamine derived from 4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (II) resulted in the hitherto unreported attack of the electrophile at the δ-position of the dienamine, and 8-tropyl- (VI) and 4a-tropyl-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (VII) were obtained. Pyrrolidine dienamines of Δ^4-3-oxosteroids (VIII, IX, and X) similarly gave the corresponding 6-tropyl-Δ^4-3-oxosteroids (XI, XII, and XIII) with I. Reaction of 7-ethoxy-1,3,5-cycloheptatriene (XVIII) with dienamines in the presence of acetic acid was also examined and 6-benzylidenetestosterone (XIX) and 6-benzylidenecholest-4-en-3-one (XX) were obtained respectively by the reaction of XVIII with dienamine of testosterone (VIII) and with that of cholest-4-en-3-one (IX).

In the preceding paper of this series, reactions of tropylium fluoroborate (I) with various ketone enamines were examined, and 2-tropyl-substituted ketones were obtained in fairly good yields when the reaction with morpholine enamines of the ketones was carried out in aqueous dioxane. As an extension of these studies, the present work was carried out on the reaction of I with dienamines derived from α,β-unsaturated ketones.

Reactions of dienamines of α,β-unsaturated ketone with electrophiles wherein the carbon is attacked can take place, in principle, at either the β- or δ-carbon. Nevertheless, previous papers have shown that reactions such as alkylation or acylation without exception take place at the β-position of dienamines.[3] As an example of alkylation, the methylation of morpholine dienamine of 4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (II) with methyl iodide was reported to give exclusively 1-methyl-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone, after alkaline treatment of the reaction products.[4] Alkylation of pyrrolidine dienamines of Δ^4-3-oxosteroids also was described as producing 4-alkylated Δ^4-3-oxosteroids.[3] On the contrary, the present reaction between I and dienamines derived from α,β-unsaturated ketones, including II and Δ^4-3-oxosteroids, resulted in a hitherto unreported reaction taking place at the δ-carbon of dienamines, thereby giving, after hydrolysis, γ-tropyl-substituted α,β-unsaturated ketones. Such details will be described in this paper.

The reaction of I with the morpholine dienamine of II[4] proceeded readily in aqueous dioxane at room temperature, as reported previously with simple ketone enamines,[1] and an oily product, whose analytical values agreed with a tropyl-substituted hexahydronaphthalenone, $C_{17}H_{20}O$, was obtained, after alkaline hydrolysis of the reaction mixture. This product showed an ultraviolet (UV) spectral absorption maximum at 241 mμ and the infrared (IR) spectrum showed $\nu_{C=O}$ at 1678 cm^{-1} indicative of the presence of an α,β-unsaturated ketone group. From these data, it might be expected, by analogy to the previously reported β-methylation of the same dienamine with methyl iodide,[4] that the present product would be 1-tropyl-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone(V). However, this structure (V) was incompatible with the nuclear magnetic resonance (NMR) spectrum, in which two broad

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[1] Part XXXIII: T. Watanabe and N. Soma, *Chem. Pharm. Bull.* (Tokyo), **18**, 1595 (1970).

[2] Location: *Hiromachi, Shinagawa-ku, Tokyo, 140, Japan.*

[3] J. Szmuszkovicz, "Advances in Organic Chemistry: Methods and Results," Vol. 4 ed. by R.A. Raphael, E.C. Taylor, and H. Wynberg. Interscience Publishers, Inc., New York, 1963, p. 86.

[4] G. Stork and G. Birnbaum, *Tetrahedron Letters*, **1961**, 313.

singlets corresponding to one proton appeared at 4.10 and 4.17 τ with a relative intensity ratio of about 4:1. These two absorptions are, apparently, inconsistent with the structure V, and the each was presumed to arise from the α-proton of a β-substituted α,β-unsaturated ketone. This led to the consideration that the product is not a single substance but a mixture of isomers. By referring to a recent report wherein the dienamine used in this reaction was reported as not a simple diene, but a mixture of the 1,8-diene (IIIa) and 1,4a(8a)-diene (IVa) in a ratio of 3:2,5) the above product was presumed to be a mixture of 8-tropyl- (VI) and 4a-tropyl-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (VII), resulting from the hitherto unreported reaction of the dienamine at the δ-position.

To further investigate this new reaction at the δ-position of a dienamine and to avoid the complication due to an isomeric mixture from the starting dienamine, I was allowed to react with the pyrrolidine dienamine of testosterone (VIII), which has been shown to be a simple 3,5-dienamine.6) This reaction gave white crystals, mp 220°, in a fairly good yield with analytical values agreeing with the expected tropyl-substituted testosterone, $C_{26}H_{34}O_2$.

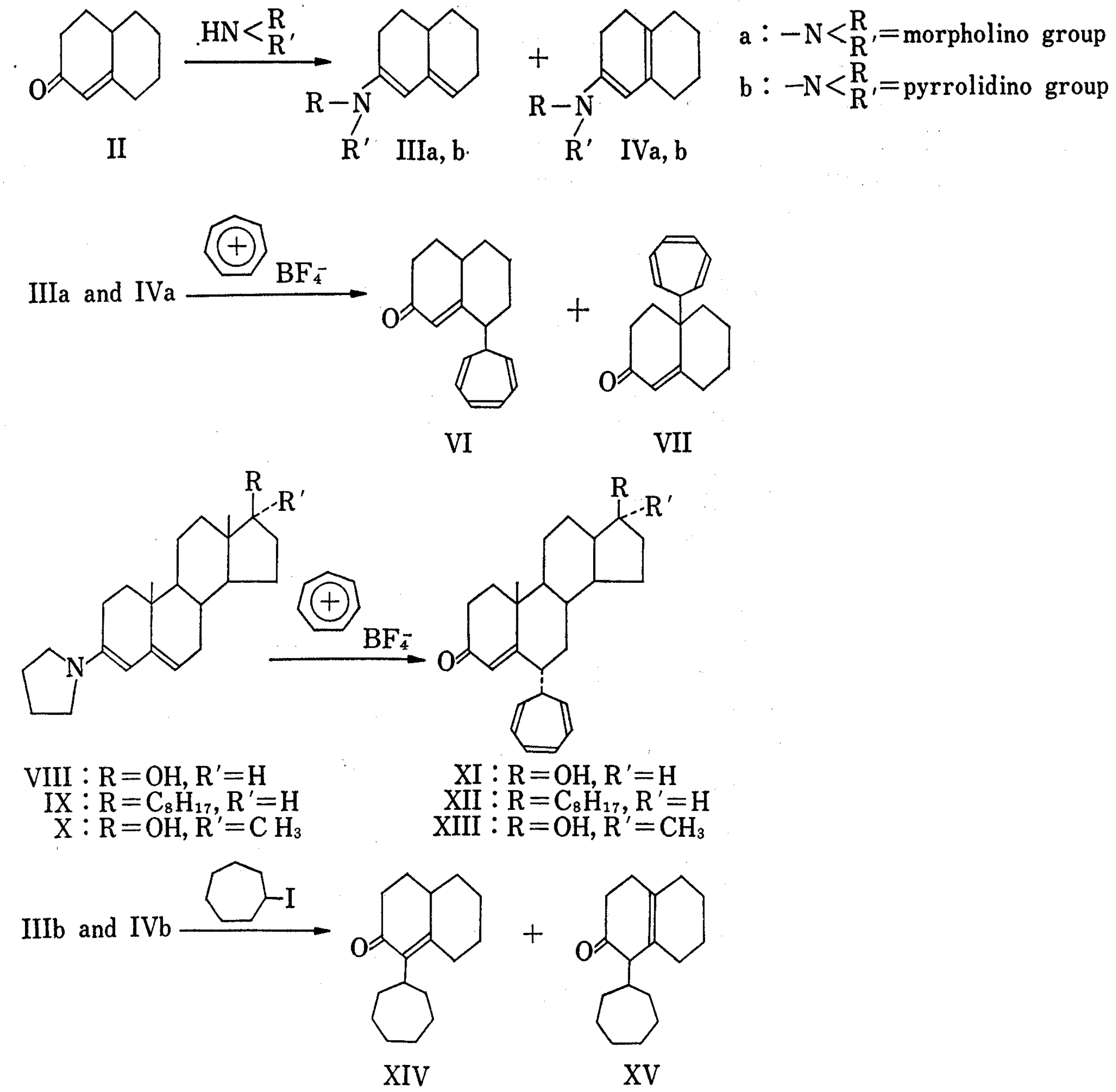

Chart 1

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5) N.F. Firrell and P.W. Hickmott, *J. Chem. Soc.* (*B*), **1969**, 293.

6) J.L. Johnson, M.E. Herr, J.C. Babcock, A.E. Fonken, J.E. Stafford and F.W. Heyl, *J. Am. Chem. Soc.*, **78**, 430 (1956).

The IR spectrum of this product displayed $\nu_{C=O}$ at 1656 cm^{-1} indicating the presence of α,β-unsaturated ketone, and its NMR spectrum showed a broad singlet at 4.18 τ corresponding to one proton, which is assignable to an α-proton of α,β-unsaturated ketone. Therefore, the structure of this product is undoubtedly 6-(tropyl)testosterone (XI). Pyrrolidine dienamines derived from cholest-4-en-3-one and methyltestosterone also gave 6-(tropyl)cholest-4-en-3-one (XII) and 6-(tropyl)methyltestosterone (XIII), respectively, on reaction with I. Compound XII showed an NMR absorption due to α-proton of its α,β-unsaturated ketone at 4.22 τ, and XIII at 4.17 τ. From these results, we concluded that the reaction of dienamines with I takes place exclusively at the δ-position differing from previously reported reactions with nucleophiles.

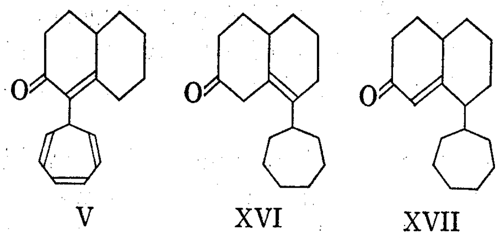
V XVI XVII

Chart 2

In order to obtain more information relating to this reaction, the reaction between the pyrrolidine dienamine of II and cycloheptyl iodide, wherein the latter is assumed to be roughly as bulky, was undertaken. Refluxing a mixture of the dienamine and the iodide in anhydrous ethanol for 70 hours gave, after hydrolysis of the reaction mixture, an oily product, whose analytical values agreed with the formula of cycloheptyl-substituted hexahydronaphthalenone, $C_{17}H_{26}O$. The NMR spectrum of this product did not show any absorption in the olefinic proton region but displayed all signals at 6.8—9.2 τ; and the IR spectrum exhibited two carbonyl bands, a strong absorption at 1666 cm^{-1} and a weak one at 1712 cm^{-1}. These spectroscopic data indicated that the reaction proceeded in a different manner than in reaction with I. It did, however, proceed in a fashion similar to that of the reported reaction with methyl iodide which furnished the 1-methylated derivative of II,[4] except that the isomeric saturated ketone was produced as a minor product in this reaction. Accordingly, the structure of the major component of this product was assigned as 1-cycloheptyl-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (XIV). The minor product, the saturated ketone exhibiting $\nu_{C=O}$ at 1712 cm^{-1}, was presumed to be 1-cycloheptyl-3,4,5,6,7,8-hexahydro-2(1*H*)-naphthalenone (XV) from the following considerations. Among all the cycloheptyl-substituted hexahydronaphthalenones expected to be produced by this reaction, two saturated ketones, XV and 8-cycloheptyl-3,4,4a,5,6,7-hexahydro-2(1*H*)-naphthalenone (XVI), are consistent with the above NMR spectral data which indicates the absence of a hydrogen on the double bond. However, the latter structure was rejected by the acid and alkaline behavior of reaction product, which resulted in the decrease of the intensity of the $\nu_{C=O}$ at 1712 cm^{-1} in the IR spectrum while maintaining the absence of olefinic proton absorption in the NMR spectrum. This is understandable by assuming double bond isomerization which transforms XV to XIV, whereas the isomerization of XVI to its stable double bond isomer, 8-tropyl-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (XVII) would give rise to olefinic proton absorption in the NMR spectrum. From these results, the reaction of dienamine of II with cycloheptyl iodide was concluded to take place, as reported in the reaction with methyl iodide, at the β-position, giving XIV and XV. Accordingly, the attack of I at the δ-position of the dienamine seems not to be a simple steric hindrance of I. The reason for the preferential attack of I at the δ-position of the dienamines is not yet completely understood; however, it seems to be important that the cation approaches the dienamines from the axial side overlapping both the β- and δ-carbons. This may enable the reaction to take place at the *a priori* favourable δ-position of the dienamines.

In connection with the above reactions between dienamines and I, the reaction of 7-ethoxy-1,3,5-cycloheptatriene (XVIII) with dienamines was also examined. In the preceding paper,[1] the reaction of simple ketone enamines with XVIII in the presence of acetic acid had been shown to afford the same products, 2-tropyl-substituted ketones, as were obtained

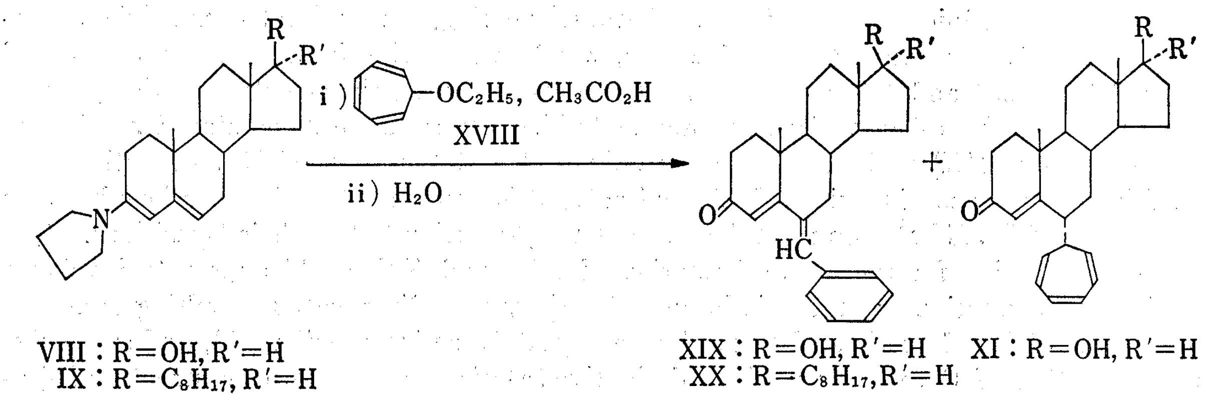

Chart 3

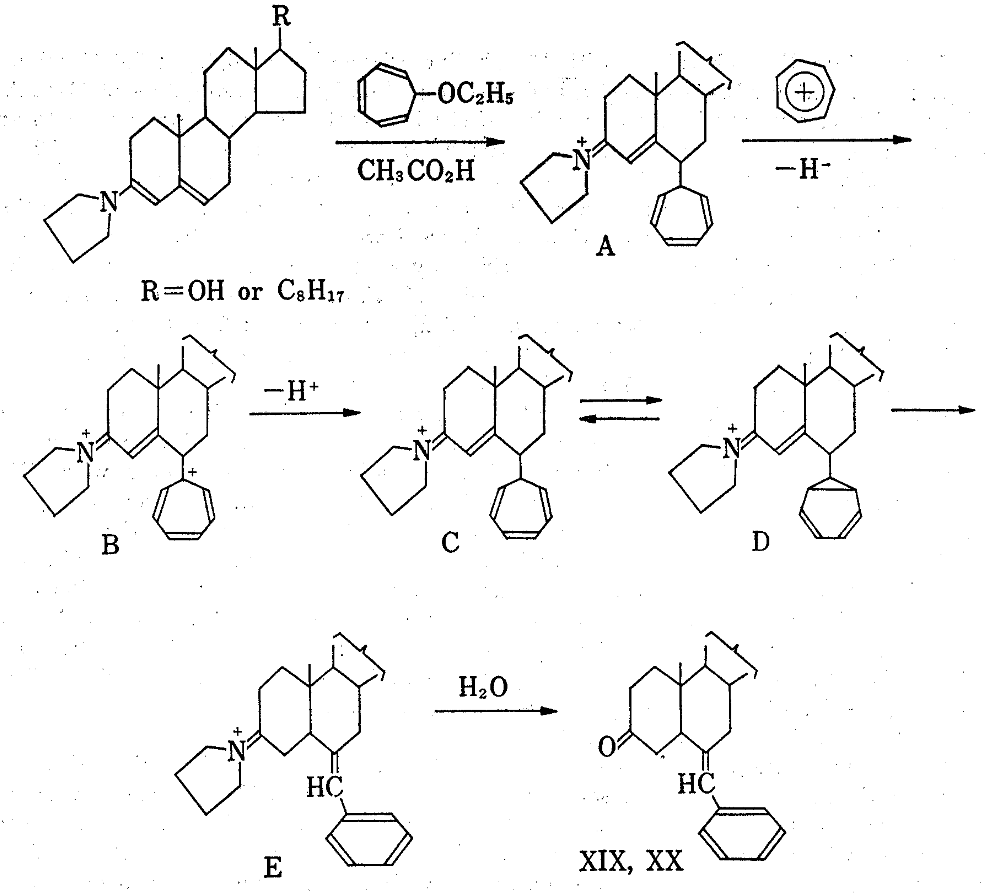

Chart 4

with I. However, in the case of the present reaction of dienamines derived from α,β-unsaturated ketones, a similar result was not obtained. Refluxing a mixture of XVIII and pyrrolidine dienamine of testosterone (VIII) in benzene containing the equimolar amount of acetic acid produced white crystals, mp 170—171°, as the major product, while XI, which was exclusively obtained on the reaction of I with the same dienamine (VIII), was only isolated as a minor product in this reaction. The elemental analytical values and mass spectrum of the above major product showed the constitution of this product was $C_{26}H_{32}O_2$. This formula differs from the composition of XI by two hydrogens, suggesting that dehydrogenation might be involved in the formation of this product. The UV spectrum showed two strong absorptions at 237 and 302 mμ (log ε=4.14 each) indicative of the presence of a δ-phenylsubstituted α,β,γ,δ-unsaturated ketone moiety. The NMR spectrum did not show any absorptions attributable to olefinic protons of a cycloheptatriene ring, but exhibited multiplets poncorresding to five protons at around 2.68 τ, which must arise from phenyl protons, and two singlets at 3.37 and 4.00 τ (1H each). From these results, the structure of this product was presumed to be 6-benzylidenetestosterone (XIX). Pyrrolidine dienamine derived from cholest-4-en-3-one (IX) similarly gave 6-benzylidenecholest-4-en-3-one (XX) on reaction with XVIII in the presence of acetic acid. Accordingly, it is apparent that the reactions between dienamines and XVIII also do not take place at the β-position but at their δ-positions. One possible explanation for the above formation of XIX and XX would appear to involve a hydride ion abstraction from the iminium salt (A) by tropylium cation resulting from the contact of XVIII and acetic acid to produce a heptafulvene intermediate (C), and successive ring contraction of C to a benzylidene derivative (E) *via* the norcaradiene structure (D) as shown in Chart 4.

Experimental

Reaction of Tropylium Fluoroborate (I) with Morpholine Dienamine of 4,4a,5,6,7,8-Hexahydro-2(3*H*)-naphthalenone (II): Formation of 8-Tropyl- (VI) and 4a-Tropyl-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (VII)——A solution of 4.52 g of morpholine dienamine of II[4] in 20 ml of dioxane was added to an aqueous solution (30 ml) of 3.69 g of I, and the mixture was stirred for 1 hr at room temperature. The separated crystals were collected by filtration and added to 40 ml of 10% aqueous NaOH solution covered with ether. After stirring for 2 hr at room temperature, ether solution was separated and the aqueous solution was extracted with ether. The combined ether solution was washed with H_2O and dried over Na_2SO_4. Ether was evaporated, and the oily residue (4.37 g) was purified by an alumina chromatography with benzene–cyclohexane (1:1) as the eluent, giving 2.7 g of colorless oil. *Anal.* Calcd. for $C_{17}H_{20}O$ (a mixture of VI and VII): C, 84.95; H, 8.39. Found: C, 84.74; H, 8.20. UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 241 (4.20). IR (liquid) cm^{-1}: 1678 (C=O). NMR (CCl_4) τ: 3.02 (2H, multiplet), 3.80 (2H, multiplet), 4.10 (0.2H, broad singlet), 4.17 (0.8H, broad singlet), 4.82 (2H, multiplet), 7.5—8.5 (13H, multiplet).

6-(Tropyl)testosterone (XI)——A solution of 6.2 g of pyrrolidine dienamine of testosterone (VIII) in 40 ml of dioxane was added to 30 ml of aqueous solution of 3.1 g of I, and the mixture was stirred for 1 hr at room temperature. After addition of 150 ml of H_2O, the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with dil. HCl, dried over Na_2SO_4, and evaporated. The remaining oily product was poured into 10% aqueous NaOH solution covered with ether, and the mixture was stirred for 3 hr at room temperature. The ether solution was separated and the aqueous solution was extracted with ether. The combined ether solution was washed with H_2O and dried over Na_2SO_4. After evaporation of ether, the residue was recrystallized from benzene to afford 5.0 g of white crystals, mp 220°. *Anal.* Calcd. for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05. Found: C, 82.28; H, 8.89. IR (Nujol) cm^{-1}: 3474 (OH), 1656 (C=O). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 242.5 (4.25). NMR ($CDCl_3$) τ: 3.28 (2H, multiplet, $C_{3'}$- and $C_{4'}$-H), 3.75 (2H, multiplet, $C_{2'}$- and $C_{5'}$-H), 4.18 (1H, singlet, C_4-H), 4.80 (2H, multiplet, $C_{1'}$- and $C_{6'}$-H), 6.33 (1H, broad triplet, J=8.0 cps, C_{17}-H), 8.96 (3H, singlet, 19-CH_3), 9.25 (3H, singlet, 18-CH_3).

6-(Tropyl)cholest-4-en-3-one (XII)——A solution of 5.4 g of pyrrolidine dienamine of cholest-4-en-3-one (IX) in 120 ml of dioxane was added to a solution of 2.2 g of I in 50 ml of H_2O. The mixture was stirred for 1 hr at room temperature and filtered. The separated solid material was added into 50 ml of 10% aqueous NaOH solution covered with ether, and the mixture was stirred for 1 hr at room temperature. After separation of ether solution, the aqueous solution was extracted with ether. The combined ether solution was washed with H_2O and dried over Na_2SO_4. After evaporation of ether, the residue was recrystallized from EtOH giving 1.99 g of white crystals, mp 140°. *Anal.* Calcd. for $C_{34}H_{50}O$: C, 86.01; H, 10.62. Found: C, 86.30; H, 10.77. IR (Nujol) cm^{-1}: 1669 (C=O). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 242.5 (4.26). NMR ($CDCl_3$) τ: 3.33 (2H, multiplet, C_3'- and C_4'-H), 3.80 (2H, multiplet, C_2'- and C_5'-H), 4.22 (1H, singlet, C_4-H), 4.80 (2H, multiplet, $C_{1'}$- and $C_{6'}$-H), 9.00 (3H, singlet, 19-CH_3), 9.10 (3H, singlet, 21-CH_3), 9.14 (6H, doublet, J=5.0 cps, 26- and 27-CH_3), 9.37 (3H, singlet, 18-CH_3).

The following treatment of the filtrate obtained on the above filtration of the reaction mixture gave the further crop of the product. The filtrate was concentrated to remove dioxane and, after addition of 100 ml of H_2O, was extracted with $CHCl_3$. The $CHCl_3$ was evaporated and the oily residue was poured into 50 ml of 10% aqueous NaOH solution. After stirring for 3 hr, the mixture was extracted with ether. The ether extract, dried over Na_2SO_4, was evaporated and the residue was recrystallized from EtOH to furnish 1.79 g of white crystals, mp 140°, which was identified with the above product by mixed mp determination and comparison of IR spectra. Total yield, 3.78 g.

6-(Tropyl)methyltestosterone (XIII)——A solution of 4.8 g of pyrrolidine dienamine of methyltestosterone (X) in 50 ml of dioxane was added to 50 ml of aqueous solution of 2.57 g of I. The mixture was stirred for 1 hr at room temperature, concentrated *in vacuo*, 100 ml of H_2O was added, and the mixture was extracted with $CHCl_3$. By the same procedure as for the preparation of XI, treatment of the $CHCl_3$ extract and alkaline hydrolysis were carried out. The resulting crude oily product (4.02 g) was chromatographed over 150 g of Al_2O_3 with benzene–chloroform (1:1) as the solvent. After evaporation of the eluate, the obtained solid material was recrystallized from EtOH to afford 2.83 g of white crystals, mp 202°. *Anal.* Calcd. for $C_{27}H_{36}O_2$: C, 82.65; H, 9.24. Found: C, 82.35; H, 9.20. IR (Nujol) cm^{-1}: 3546 (OH), 1663 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 242.5 (4.25). NMR ($CDCl_3$) τ: 3.30 (2H, multiplet, $C_{3'}$– and $C_{4'}$–H), 3.80 (2H, multiplet, $C_{2'}$– and $C_{5'}$–H), 4.17 (1H, singlet, C_4–H), 4.80 (2H, multiplet, $C_{1'}$– and $C_{6'}$–H), 8.79 (3H, singlet, C_{17}–CH_3), 8.98 (3H, singlet, 19–CH_3), 9.15 (3H, singlet, 18–CH_3).

Reaction of Pyrrolidine Dienamine of 4,4a,5,6,7,8-Hexahydro-2(3*H*)-naphthalenone (II) with Cycloheptyl Iodide: Formation of 1-Cycloheptyl-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (XIV) and 1-Cycloheptyl-3,4,5,6,7,8-hexahydro-2(1*H*)-naphthalenone (XV)——A mixture of 11.0 g of pyrrolidine dienamine of II and 1.10 g of cycloheptyl iodide in 100 ml of anhydrous EtOH was refluxed for 70 hr. The EtOH was evaporated and the residue was heated in a mixture of 4.5 g of NaOAc, 9 ml of AcOH, and 6 ml of H_2O for 4 hr under reflux. The mixture was cooled and extracted with benzene. After the benzene had been evaporated, the residual oily product (6.8 g) was chromatographed on silica gel with benzene as the eluent, giving 1.95 g of colorless oil, which was distilled under reduced pressure to afford 1.0 g of colorless oil, bp 140—150° (bath temp.) (0.08 mmHg). *Anal.* Calcd. for $C_{17}H_{26}O$ (a mixture of XIV and XV): C, 82.87; H, 10.64. Found: C, 83.04; H, 10.64. IR (liquid) cm^{-1}: 1712 (C=O), 1666 (C=O). NMR (CCl_4) τ: 6.8—9.2 (multiplet). After this oily product (40 mg) was stirred in 40 ml of 3% KOH solution in 95% EtOH for 20 hr at room temperature, the intensity of $\nu_{C=O}$ at 1712 cm^{-1} in the IR spectrum decreased to about 2/3rd of its original intensity, but no NMR signals appeared in the region below 6.0 τ. A similar treatment with 5% HCl solution in EtOH–H_2O (7:1) also gave the same results as above.

Reaction of 7-Ethoxy-1,3,5-cycloheptatriene (XVIII) with Pyrrolidine Dienamine of Testosterone (VIII)——To a solution of 3.67 g of XVIII in 150 ml of benzene containing 1.62 g of AcOH, 9.2 g of pyrrolidine dienamine of VIII was added, and the mixture was refluxed for 8 hr. The cooled reaction mixture was extracted with 5% HCl. The aqueous solution, after being neutralized with aqueous $NaHCO_3$, was stirred at room temperature for 30 min, and extracted with $CHCl_3$. The $CHCl_3$ was evaporated and the oily residue (4.5 g) was chromatographed on Al_2O_3 with benzene–cyclohexane (8:2) as the eluent. The resulting crude crystalline product was recrystallized from benzene, giving 0.4 g of white crystals, mp 220°, which was identical with 6-(tropyl)testosterone (XI) obtained by the reaction of I with pyrrolidine dienamine of VIII. The filtrate from the above recrystallization was evaporated and the residue was recrystallized from EtOH, giving 0.8 g of white crystals, 6-benzylidenetestosterone (XIX), mp 170—171°. *Anal.* Calcd. for $C_{26}H_{32}O_2$: C, 82.93; H, 8.57. Found: C, 83.13; H, 8.70. UV λ_{max}^{EtOH} mμ (log ε): 237 (4.14), 302 (4.14). NMR ($CDCl_3$) τ: 2.68 (5H, multiplet, aromatic protons), 3.37 (1H, broad singlet, Ph–C$\underline{H}$=), 4.00 (1H, singlet, C_4-H), 6.32 (1H, broad triplet, $J=8.0$ cps, C_{17}-H), 8.13 (1H, singlet, O$\underline{H}$), 8.85 (3H, singlet, 19-CH_3), 9.25 (3H, singlet, 18-CH_3). Mass Spectrum: *m/e* 376 (M^+, $C_{26}H_{32}O_2$, Calcd. 376).

Reaction of 7-Ethoxy-1,3,5-cycloheptatriene (XVIII) with Pyrrolidine Dienamine of Cholest-4-en-3-one (IX)——To a solution of 0.53 g of XVIII in 50 ml of benzene containing 0.23 g of AcOH, 1.7 g of pyrrolidine dienamine of IX was added, and the mixture was refluxed for 8 hr. The reaction mixture was treated as described for the reaction of XVIII with the dienamine of VIII except that in the chromatography cyclohexane–benzene (3:2) was used as the eluent. Recrystallization of the resulting crystals from EtOH gave 6-benzylidenecholest-4-en-3-one (XX), mp 129°. Yield, 0.46 g. *Anal.* Calcd. for $C_{30}H_{48}O$: C, 86.38; H, 10.24. Found: C, 86.19; H, 10.25. UV λ_{max}^{EtOH} mμ (log ε): 238 (4.27), 302 (4.24). IR (Nujol) cm^{-1}: 1658 (C=O). Mass Spectrum: *m/e* 472 (M^+, $C_{34}H_{48}O$, Calcd.: 472). NMR ($CDCl_3$) τ: 2.72 (5H, singlet, aromatic protons), 3.38 (1H, broad singlet, Ph–C$\underline{H}$=), 4.02 (1H, singlet, C_4-H), 8.87 (3H, singlet, 19-CH_3), 9.08 (3H, singlet, 21-CH_3), 9.13 (6H, doublet, $J=6.0$ cps, 26- and 27-CH_3), 9.32 (3H, singlet, 18-CH_3).

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