**Summary**

It was found that the compounds having the general formula RCH(X)-C≡C-R′ gave thiazole derivatives by reaction with thiourea. The relationship between the structure of thiazoles and substituent groups was clarified as follows: (1) When R=R′=Ph, 2-amino-4-benzyl-5-phenylthiazole (IId) is obtained, (2) When R=alkyl, R′=H, two kinds of thiazoles are obtained; and (3) when R=R′=alkyl, thiazole derivative is not obtained.

Similarly, propargyl bromide and phenylpropargyl bromide, when reacted with ammonium dithiocarbamate, afforded 2-mercapto-4-methylthiazole (XX) and 2-mercapto-4-benzylthiazole (XXIII), respectively. Further, 2-amino-4-methylimidazole (XXV) was obtained from guanidine and propargyl bromide.

(Received March 25, 1961)

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*UDC 547.92.07*

## 61. Hiromu Mori: Studies on Steroidal Compounds. VI. Grignard Reaction of 19-Nor-4-en-3-oxo-steroids.[1]

(*Research Laboratory, Teikoku Hormone Mfg. Co., Ltd.*[*1])

In the Grignard reaction of cholest-4-en-3-one, 1,2-addition product, 3-methylcholest-4-en-3-ol (I) has been produced even in the presence of cuprous chloride, which is known as a reagent promoting 1,4-addition,[2] and not 1,4-addition product.[3] On the other hand, in the case of 4,6-dien-3-oxo steroids (II) and 16-en-20-oxo steroids (V), 1,6- (III and IV) and 1,4-addition products (VI) have been obtained respectively.[4,5] These differences are considered to depend upon stereochemical factors. The difference of the Grignard reaction between 4-en-3-oxo-steroids and 19-nor-4-en-3-oxo-steroids is described.

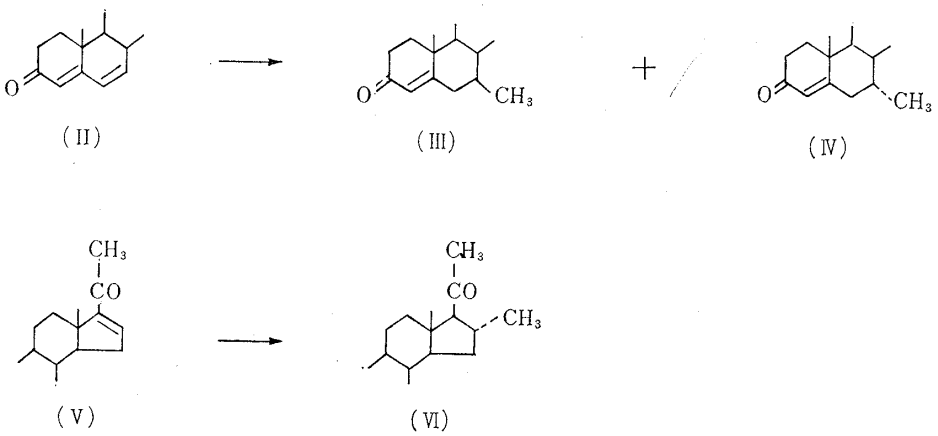


Chart 1.

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*1 1604, Shimosakunobe, Kawasaki-shi, Kanagawa-ken (森 弘).

1) Part V: Yakugaku Zasshi, in press.
2) M. S. Kharasch, O. Reinmuth: "Grignard Reactions," 219 (1954). Prentice-Hall, Inc., New York.
3) O. C. Musgrave: J. Chem. Soc., **1951**, 3121.
4) J. A. Campbell, J. C. Babcock: J. Am. Chem. Soc., **81**, 4069 (1959).
5) R. E. Marker, H. M. Crooks: *Ibid.*, **64**, 1280 (1942).

The Grignard reaction of 17$\beta$-hydroxy-17$\alpha$-methylestr-4-en-3-one (VIIa) gave a white powder having no characteristic absorption in its ultraviolet spectrum. As it was difficult to be purified by recrystallization, Girard separation was made. 3,17$\alpha$-Dimethylestra-3,5-dien-17$\beta$-ol (Xa) and a small amount of oily product were obtained from non-keto and keto fractions, respectively. It is reasonable that (Xa) was produced by the dehydration of (IXa) (1,2-addition product of (VIIa)) during Girard separation, for it has been well known that the dehydration of (I) takes place easily on account of acid to give 3-methylcholesta-3,5-diene.[3,6] The structural assignment of (Xa) was based on its ultraviolet spectrum, which had strong absorption at 233~235 and 239 m$\mu$.

The above-mentioned oily product obtained from the keto fraction exhibited no characteristic ultraviolet absorption and saturated carbonyl band in infrared absorption spectrum, which showed probably that it was a 1,4-addition product. In order to ascertain whether 1,4-addition occurs or not in this case, the Grignard reaction of (VIIa) was made in the presence of cuprous chloride. The 1,4-addition product, 5$\beta$,17$\alpha$-dimethyl-17$\beta$-hydroxyestran-3-one (VIIIa), was formed from the keto fraction and (Xa) was also isolated from the non-keto fraction.

(VIIIb) and (Xb) were obtained by the similar reaction of 17$\beta$-hydroxyestr-4-en-3-one. The oxidation of (VIIIb) with chromium trioxide in acetic acid led to 3,17-dioxo compound (XI).

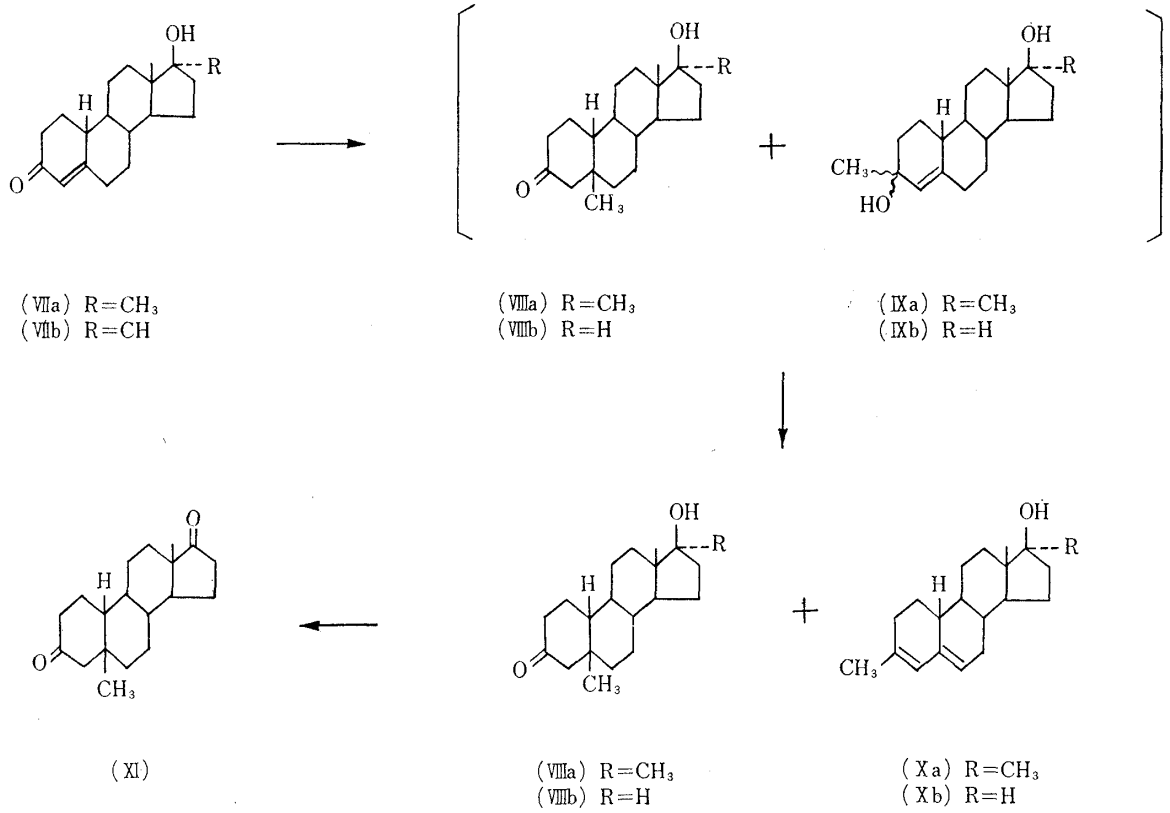


Chart 2.

The compounds derived from the keto fraction was assigned as 5$\beta$-methyl-3-oxo compounds by the following evidences. (VIIIa) and (VIIIb) exhibited saturated carbonyl band at 1710~1713 cm$^{-1}$ in the infrared absorption spectra. Nuclear magnetic resonance spectrum of (VIIIb) showed the presence of an additional angular methyl group besides C-18

6) N.F. Kucherova, M.I. Ushakov : Zhur. Obshcheĭ Khim., **23**, 315 (1953) (C.A., **48**, 2744 h (1954)).

methyl group.[7] It is difficult to explain the result without the introduction of methyl group at C-5 by 1,4-addition of Grignard reagent. Rotatory dispersion curves of (Ⅷa) and (Ⅷb) (Fig. 1), were similar to that for A/B cis 3-oxo-steroids.[8] It is already clear that

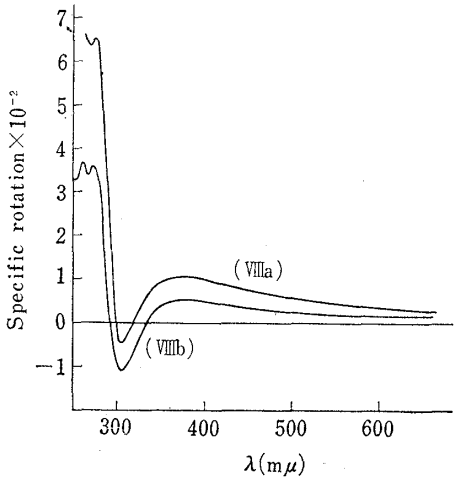


Fig. 1. Rotatory Dispersion Curves of (Ⅷa) and (Ⅷb) (methanol)

the substitution of C-5 hydrogen atom with methyl group does not alter its rotatory dispersion curve. Therefore, $\beta$-configuration for C-5 methyl group introduced was established.

The Grignard reaction of 4-en-3-oxo steroid was next taken up. The Grignard reaction of testosterone acetate was attempted in the presence of cuprous chloride, but 1,4-addition product was not produced and only 3-methylandrosta-3,5-dien-17$\beta$-ol (Ⅻ) was obtained. (Ⅻ) was recently prepared and identified by Pelc.[9]

The steric consequence of 1,4-addition of the Grignard reagent to 19-nor-4-en-3-oxo-steroid can be considered to depend upon the geometry of the transition state involved. A and B show the likely transition states*2 attacked by the Grignard reagent from $\beta$- and $\alpha$-side.

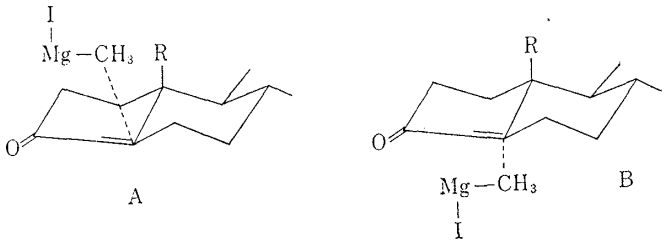


Chart 3.

A comparison of calculated conformational interactions present in A and B indicates that A is destabilized relative to B, an energy difference as great as three 1:3 hydrogen-methyl minus one 1:2 R-methyl interactions. In the case of 19-nor series (R=H), A is the more stable by an energy difference at least as great as two 1:3 hydrogen-methyl interaction (even if 1:3 hydrogen-methyl interaction were equal to 1:2 hydrogen-methyl interaction). Accordingly the product predicted from stereochemical viewpoint is 5$\beta$-methyl product and this agrees with the experimental result.

*2 When Werner complex is considered as a transition state, it is necessary to consider the distortion of ring A and it becomes difficult to calculate conformational interactions.

7) J.N. Shooley, M.T. Rogers : J. Am. Chem. Soc., **80**, 5121 (1958).
8) C. Djerassi : "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, 49 (1960).
9) B. Pelc : Collection Czechoslov. Chem. Communs., **25**, 1624 (1960).

There is an additional problem concerning the direction of the reaction, whether 1,2- or 1,4-addition will take place. However, this problem is not solved by the calculation of non-bonded interactions of the transition states of 1,2- and 1,4-addition. Nevertheless, it is possible to explain the reason why 1,4-addition occurs in 19-nor-4-en-3-oxo-steroids but not in 4-en-3-oxo-steroids. Neither A nor B in 4-en-3-oxo-steroid (R=$CH_3$) is destabilized relative to B in 19-nor-4-en-3-oxo-steroid (R=H) and 1,4-addition to 4-en-3-oxo-steroid might become more difficult than in 19-nor-4-en-3-oxo-steroid. Probably 1,2-addition would occur exclusively on account of steric hindrance described above.

## Experimental*3

**Grignard Reaction of 17β-Hydroxy-17α-methylestr-4-en-3-one (VIIa)**——a) In the absence of $Cu_2Cl_2$: To the Grignard reagent prepared from Mg (1.1 g.), MeI (2.9 cc.), and $Et_2O$ (50 cc.), a solution of 17β-hydroxy-17α-methylestr-4-en-3-one (VIIa) (2.0 g.) in tetrahydrofuran (30 cc.) was added dropwise with stirring at −10° to −15° and stirring was continued for 1 hr. at room temperature. 10% $NH_4Cl$ was added to decompose excess Grignard reagent and the product was extracted with $Et_2O$. After washing with 10% $NH_4Cl$ and water, and drying over $Na_2SO_4$, $Et_2O$ was evaporated. The solution of the residue in EtOH (100 cc.) and AcOH (10 cc.) was refluxed with the Girard T-reagent (2.0 g.) for 1 hr. After cool, the solution was poured into water containing $Na_2CO_3$ (9.0 g.) and 5% $Na_2CO_3$ was added until pH became 7.0. The resulting mixture was extracted with $Et_2O$. $Et_2O$ layer (non-keto fraction) was washed with 5% $Na_2CO_3$ and water, dried over $Na_2SO_4$, and the solvent was evaporated. The residue was recrystallized from MeOH to 3,17α-dimethylestra-4,6-dien-17β-ol (Xa), m.p. 102～106°. Yield, 1.5 g. Further recrystallization from MeOH gave white plates, m.p. 105～108°, $[\alpha]_D^{23}$ −205° (c=1.00, $CHCl_3$). UV $\lambda_{max}^{MeOH}$ mμ (log ε): 233～235 (4.28), 239 (4.29). IR: $\nu_{max}^{KBr}$ 3480 $cm^{-1}$: (OH). *Anal.* Calcd. for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.47; H, 10.50.

The aqueous layer (keto fraction) was acidified with 10% HCl and stored at room temperature overnight. The resulting product was extracted with $Et_2O$. After washing with 5% $Na_2CO_3$ and water, and drying over $Na_2SO_4$, $Et_2O$ was evaporated. The residue was a small amount of oily product which did not crystallize and showed no characteristic ultraviolet absorption.

b) In the presence of $Cu_2Cl_2$: (VIIa) (2.0 g.) was treated with MeMgI in the presence of $Cu_2Cl_2$ (400 mg.) and Girard separation was made in the same manner as above. From the non-keto fraction, (Xa), m.p. 98～100°, was obtained. Yield, 240 mg.

The product obtained from the keto-fraction was recrystallized from MeOH to 5β,17α-dimethyl-17β-hydroxyestran-3-one (VIIIa), m.p. 152～155°. Yield, 1.04 g. Further recrystallization from MeOH gave white plates, m.p. 153～155°, $[\alpha]_D^{23}$ +9° (c=1.03, $CHCl_3$). IR $\nu_{max}^{CS_2}$ $cm^{-1}$: 3630 (-OH), 1713 (3-oxo), RD (c=0.11, MeOH); $[\alpha]_{700}$ +8°, $[\alpha]_{589}$ +22°, $[\alpha]_{305}$ −128° (trough), $[\alpha]_{267.5}$ +365°, $[\alpha]_{265}$ +340°, $[\alpha]_{260}$ +374° (peak), $[\alpha]_{250}$ +319°. *Anal.* Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.78; H, 10.68.

**Grignard Reaction of 17β-Hydroxyestr-4-en-3-one (VIIb)**——a) In the absence of $Cu_2Cl_2$: Grignard reaction of 17β-hydroxyestr-4-en-3-one (VIIb) (2.0 g.) in the absence of $Cu_2Cl_2$ and Girard separation of its product were carried out as described above. From the non-keto fraction, 3-methylestra-3,5-dien-17β-ol (Xb), m.p. 94～104°, was obtained. Yield, 1.24 g. Further recrystallization from MeOH gave white plates, m.p. 102～106°, $[\alpha]_D^{26}$ −195° (c=1.17, $CHCl_3$). UV $\lambda_{max}^{MeOH}$ mμ (log ε): 233～235 (4.25), 239 (4.26). *Anal.* Calcd. for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.59; H, 10.49.

b) In the presence of $Cu_2Cl_2$: The Grignard reaction of (VIIb) (2.0 g.) in the presence of $Cu_2Cl_2$ (400 mg.) and Girard separation of its product were carried out as described above. From the keto fraction, 17β-hydroxy-5β-methyl-estran-3-one (VIIIb), m.p. 157.5～159.5°, was obtained. Yield, 1.27 g. Further recrystallization from $Me_2CO$-hexane mixture gave white prisms, m.p. 157.5～159.5°, $[\alpha]_D^{23}$ +36° (c=1.03, $CHCl_3$). IR $\lambda_{max}^{CS_2}$ $cm^{-1}$: 3630, 3500 (-OH), 1710 (3-oxo). RD (c=0.10, MeOH); $[\alpha]_{700}$ +24°, $[\alpha]_{589}$ +39°, $[\alpha]_{305}$ −65° (trough), $[\alpha]_{265}$ +640°, $[\alpha]_{262.5}$ +625°, $[\alpha]_{260}$ +635°. *Anal.* Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.74; H, 10.83.

**5β-Methylestrane-3,17-dione (XI)**——To a solution of 17β-hydroxy-5β-methylestran-3-one (VIIIb) (200 mg.) in AcOH (7 cc.), a solution of $CrO_3$ (60 mg.) in water (1.0 cc.) was added and the mixture was stored at room temperature for 1 hr. The solution was poured into water, and the precipitate was collected, washed with 5% $Na_2CO_3$ and water, and dried. The white powder was recrystallized from MeOH to 5β-methyl-estrane-3,17-dione (XI), m.p. 151～154°. Yield, 110 mg. Further recrystallization from MeOH gave white needles, m.p. 152～154°, $[\alpha]_D^{26}$ +107° (c=0.97, $CHCl_3$). IR $\nu_{max}^{CS_2}$ $cm^{-1}$: 1742 (17-oxo), 1711 (3-oxo). *Anal.* Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.11; H, 9.86.

*3 All melting points are uncorrected.

**Grignard Reaction of Testosterone Acetate in the Presence of $Cu_2Cl_2$**——The Grignard reaction of testosterone acetate (3.0 g.) in the presence of $Cu_2Cl_2$ (600 mg.) and Girard separation were made as described above. From the keto fraction no product was obtained. From the non-keto fraction, 3-methylandrosta-3,5-dien-17$\beta$-ol (XII), m.p. 126~132°, was obtained. Yield, 1.6 g. Repeated recrystallization from MeOH gave white needles, m.p. 131~134°, $[\alpha]_D^{26}$ −175° (c=1·02, $CHCl_3$), UV $\lambda_{max}^{MeOH}$ mμ (log $\varepsilon$): 231~232 (4.28), 239 (4.31). reported[9] m.p.134~136°, $[\alpha]_D^{20}$: −175°. UV $\lambda_{max}^{EtOH}$ mμ (log $\varepsilon$): 232 (4.46), 240 (4.49).

The author is very grateful to Dr. M. Chuman, President of Tsurumi Research Laboratory of Chemistry, Dr. S. Niinobe, Director of Research Laboratory of this company, Mr. M. Sawai, and Dr. J. Yamada for their valuable advices and to Dr. E. Yamaguchi, President of this company, and to Dr. F. Ueno, Director of the Manufacturing Section of this company, for their encouragement throughout this work. The author is also indebted to Mr. K. Hirama for for his technical help.

## Summary

The Grignard reaction of 17$\beta$-hydroxy-17$\alpha$-methylestr-4-en-3-one (VIIa) in the presence of cuprous chloride gave 5$\beta$,17$\alpha$-dimethyl-17$\beta$-hydroxyestran-3-one (VIIIa) and 3,17$\alpha$-dimethylestra-3,5-dien-17$\beta$-ol (Xa). Similarly, (VIIIb) and (Xb) were obtained by the Grignard reaction of 17$\beta$-hydroxyestr-4-en-3-one (VIIb). The oxidation of (VIIIb) with chromium trioxide gave 5$\beta$-methyl-estrane-3,17-dione (XI). Discussion was made on the configuration of C-5 methyl group in (VIIIa) and (VIIIb).

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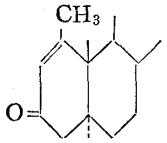
## 62. Hiromu Mori: Studies on Steroidal Compounds. VII.[1] Synthesis of 1$\alpha$-Methyl Steroids.

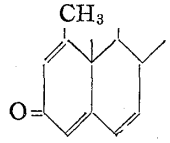
(*Research Laboratory, Teikoku Hormone Mfg. Co., Ltd,*[*1])

Many methylated steroidal hormones have been prepared and some of them show higher hormonal activity than their parent steroidal hormones.[2] 1-Methylated steroids which have been prepared up to date are 1-methyl-1-en-3-oxo (I) and 1-methyl-1,4,6-trien-3-oxo (II) type steroids,[3] other than estrane series. Some observations on 1$\alpha$-methylated steroids[4] will be described.

In the preceding paper,[1] 1,4-addition of Grignard reagent to 19-nor-4-en-3-oxo-ster-



(I)



(II)

*1 1604, Shimosakunobe, Kawasaki, Kanagawa-ken (森　弘).

1) Part VI: This Bulletin, **10**, 382 (1962).
2) A. Zaffaroni: Acta Endocrinol., Suppl. 50, **34**, 139 (1960).
3) R. Wiechert, E. Kaspar: Chem. Ber., **93**, 1710 (1960).
4) In estrane series, many 1-methylated steroids have been prepared.