terminal $-NH_2$ group from the difference Fourier method. It is, however, inconsistent with the infrared spectral data. The considerable double-bond character of the N-N bond and the absorption bands due to the $-NH_2$ deformation vibrations which occur at ca. 1630, 1126, and 951 cm^{-1} as shown in Tables Ⅱ, Ⅲ, Ⅳ, Ⅴ, and Ⅵ suggest that the $-NH_2$ group is almost in the same plane as the amide and the aromatic ring. On the other hand, the $-NH_2$ group of N-Me-INH appears to be non-planar.

For the reason of the less reproducibility between 950 cm^{-1} and 850 cm^{-1} in the spectra of hydrochlorides and N-deuterated hydrochlorides, further investigations are expected.

The authors express their deep gratitude to Prof. T. Kwan, Prof. M. Tsuboi and Prof. Z. Tamura for their encouragement and advice on this work. They are also indebted to Dr. Y. Kyogoku and Mrs. K. Matsuo for their pertinent advice and to Miss M. Ninomiya and Miss F. Suzuki for measurement of IR spectra.

Summary

To give reliable assignments for infrared spectra of metal complexes of isonicotinoylhydrazine and related compounds, the spectra of ligands themselves, their N-deuterated derivatives, their hydrochlorides and their N-deuterated hydrochlorides were investigated. The bands of amide, NH_2 deformation and pyridine ring vibrations were determined carefully, and some effective supports could be given to the assignments described in Part Ⅳ.

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UDC 547.92.07

169. Kikuo Yasuda: Synthesis of 2α-Halo-4-en-3-oxo-steroids.

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

A practical method for preparation of 2α-halo-4-en-3-oxo-steroids required for biological tests was studied.[*2]

Dehalogenation or dehydrobromination of halo-ketones (Ⅰ[1] or Ⅱ[2]) and bromine treatment of 2-ethoxalyl-4-en-3-ones (Ⅲ)[3] to the corresponding 2α-halo-4-en-3-ones (Ⅳ) are well studied. On the other hand bromination of 4-en-3-ones with N-bromosuccinimide

*1 1604, Shimosakunobe, Kawasaki (安田喜久男).

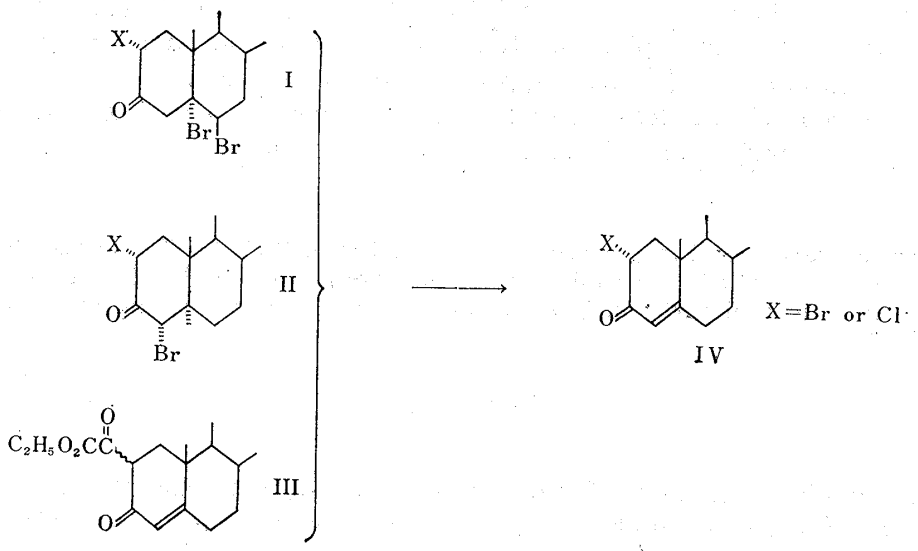
*2 Presented in part at the 18th Annual Meeting of the Pharmaceutical Society of Japan (1963).

1) B.E. Ellis, V. Petrow: J. Chem. Soc., **1956**, 1179.

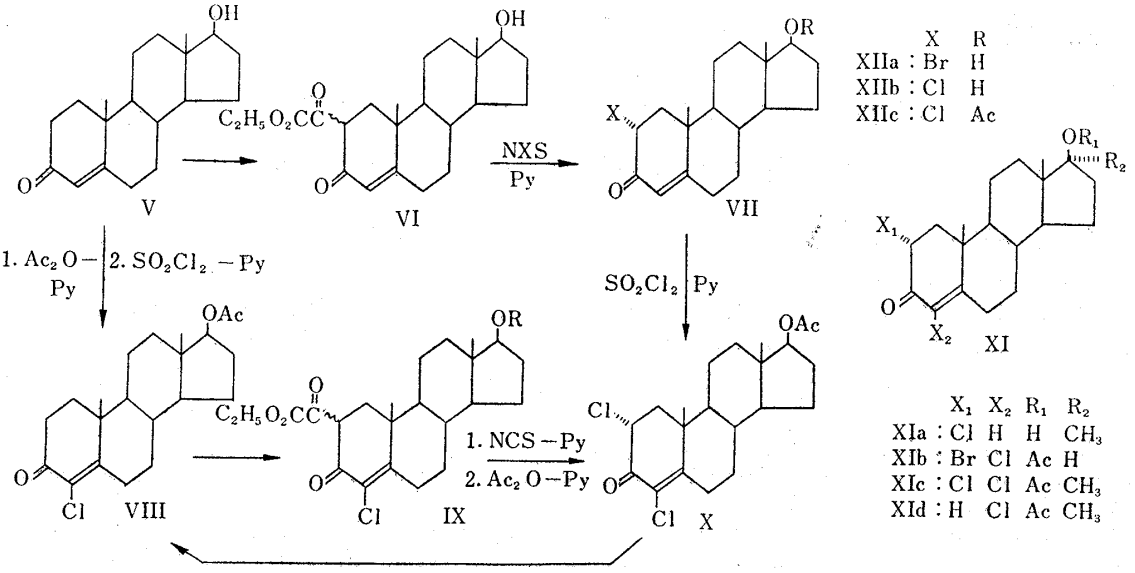
2) *a*) H.H. Inhoffen, G. Zühlsdorff: Ber., **76B**, 233 (1943). *b*) C. Djerassi, C.R. Sholz: J. Am. Chem. Soc., **69**, 2404 (1947). *c*) *Idem*: J. Org. Chem., **13**, 697 (1948). *d*) C. Djerassi: J. Am. Chem. Soc., **71**, 1003 (1949). *e*) J.J. Beerboom, C. Djerassi: J. Org. Chem., **19**, 1196 (1954). *f*) R.M. Evans, J.C. Hamlet, J.S. Hunt, P.G. Jones, A.G. Long, J.F. Oughton, L. Stephenson, T. Walker, B.M. Wilson: J. Chem. Soc., **1956**, 4356.

3) *a*) J.A. Hogg, F.H. Lincoln, A.H. Nathan, A.R. Hanze, W.P. Schneider, P.F. Beal, J. Korman: J. Am. Chem. Soc., **77**, 4438 (1955). *b*) R.E. Shaub, G.R. Allen, Jr., M.J. Weiss: *Ibid.*, **81**, 4962 (1959). *c*) H.M. Kissman, A.M. Small, M.J. Weiss: *Ibid.*, **82**, 2312 (1960). *d*) G.R. Allen, Jr., M.J. Weiss: *Ibid.*, **82**, 2840 (1960). *e*) R. Joly, J. Warnant, B. Goffinet: Fr. Pat., 1,249,939, Mar. 22, 1961 (C.A., **56**, P10235d (1962)).

in carbon tetrachloride[4a,d] gives first 6-bromo-4-en-3-ones and then 2,6-dibromo-4-en-3-ones, and bromination with bromine in ether-acetic acid[4b] causes contamination of a more highly brominated impurity.



Now a modified process *via* 2-ethoxalyl derivatives in view of selective halogenation at C-2 was performed on testosterone (V) as follows; V was converted into 2-ethoxalyltestosterone (VI)[5] almost quantitatively, which was treated with 1.1 molar equivalent of N-bromosuccinimide in pyridine for 1 hour at room temperature to give 2α-bromotestosterone (VIIa) in 45~50% over-all yield and with N-chlorosuccinimide instead to give 2α-chlorotestosterone (VIIb) in 55~60% yield. 4-Chlorotestosterone acetate (VIII) was also converted into 2α,4-dichlorotestosterone acetate (X) *via* the corresponding 2-ethoxalyl derivative (IX).*3 The compound (X) could be reduced to VIII with zinc dust in acetic acid



*3 A mixture of 2-ethoxalyl-4-chlorotestosterone and its acetate owing to partial hydrolysis at C-17 during ethoxalylation.

4) *a*) C. Djerassi: J. Am. Chem. Soc., **72**, 4534 (1950). *b*) D.N. Kirk, D.K. Partel, V. Petrow: J. Chem. Soc., **1957**, 1046. *c*) H. Dannenberg, H.-G. Neumann: Ann., **646**, 148 (1961). *d*) C.W. Shoppee, E. Shoppee: "Chemistry of Carbon Compounds", Vol. II Part B, 834 (1953), Elsevier Publishing Co.

5) H.J. Ringold, E. Batres, O. Halpern, P. Necolea: J. Am. Chem. Soc., **81**, 427 (1959).

and, moreover, derived from Ⅶb by treatment with sulfuryl chloride in pyridine, which was already reported by Mori[6] as an elegant method for preparation of 4-chloro-4-en-3-ones from the corresponding 4-en-3-ones. These results were evidential for the structure, X. 2α-Chloro-17α-methyltestosterone (Ⅺa), 2α-bromo-4-chlorotestosterone acetate (Ⅺb), and 17α-methyl-2α,4-dichlorotestosterone acetate (Ⅺc) were also obtained by the similar transformations of 17α-methyltestosterone, 4-chlorotestosterone acetate (Ⅷ) and 4-chloro-17α-methyltestosterone acetate (Ⅺd), respectively.

α-Orientation of a halogen atom at C-2 of each compound described above was readily approved by the significant shift of the infrared absorption band of its 3-ketone in addition to the data of ultraviolet spectrum[1] (Table I).

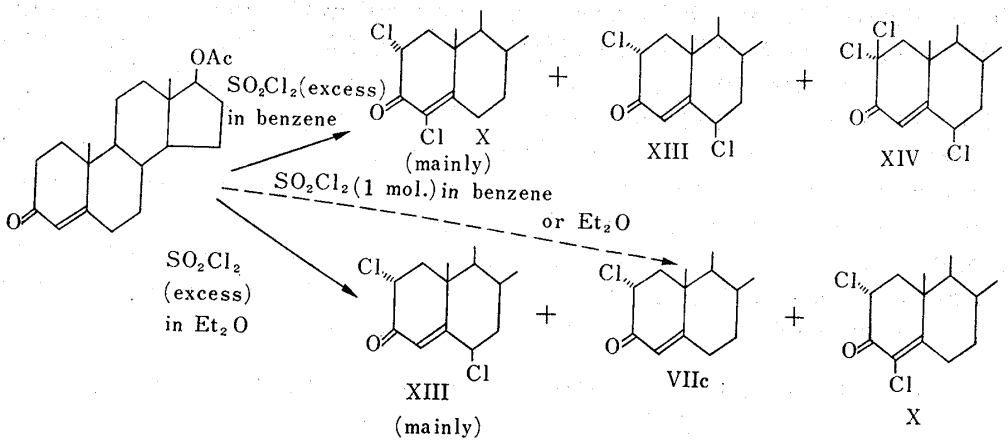
Table I. Ultraviolet and Infrared Absorptions of 2-Halo-4-en-3-ones and their Related Compounds

Substance[a]	UV (MeOH or EtOH*) λ_{max} mμ ($\varepsilon \times 10^{-4}$)	IR (KBr) ν_{max} cm^{-1}		IR (CCl_4 or CS_2*) ν_{max} cm^{-1}	
		3 C=O	Δ^4	3 C=O	Δ^4
T	241 (1.54)[b]	1658	1613	1679	1620
2α-Br-T	244 (1.41)[c]	1695	1620	1700	1625
2α-Cl-T	243 (1.45)	1692	1622	1705	1627
17α-Me-T	241* (1.58)[d]	1663	1610	1681	1621
2α-Cl-17α-Me-T	243～244 (1.39)[c]	1699	1620	1704	1627
4-Cl-17α-Me-TA	254 (1.40)[e]	1691	1589	1695	1589
2α,4-diCl-17α-Me-TA	261 (1.13)	1712	1592	1728	1592
TA	241 (1.58)[d]	1670	1617	1680	1620
2α-Br-TA	244 (1.52)[c]	1690	1625	1700	1628
2α-Cl-TA	243 (1.46)[f 1)]	1692	1624	1703	1625
6α-Cl-TA	236 (1.44)[f 2)]	1683	1621	1688*	1619*
6β-Cl-TA	240 (1.56)[f 3)]	1681	1613	1684*	
2α,6α-diCl-TA	238～239 (1.06)	1703	1630	1702*	1620*
2α,6β-diCl-TA	242 (1.13)	1691	1614	1704*	
2,2,6β--tri-Cl-TA	249 (1.26)	1693	1614	1706*	
4-Cl-TA	255 (1.48)[g]	1685	1586	1696*	
2α-Br-4-Cl-TA	261 (1.25)	1705 1670[h]	1596	1710* 1680*,[h]	
2α,4-diCl-TA	260 (1.12)	1707	1594	1714*	

a) T: testosterone, TA: testosterone acetate
b) L. Dorfman: Chem. Revs., **53**, 113 (1953).
c) cf. Table Ⅱ.
d) Japan Pat. Ⅶ. Part 1 (1961).
e) B. Camerino, R. Modelli, B. Patelli: Farmaco (Pavia) Ed. sci., **13**, 52 (1958) (C.A., **52**, 13769 i (1962)).
f) 1) cf. p. 1221. 2) cf. p. 1223. 3) cf. p. 1222.
g) H. Mori: This Bulletin, **10**, 429 (1962).
h) In this case, $\nu_{3c=o}$ split in two.

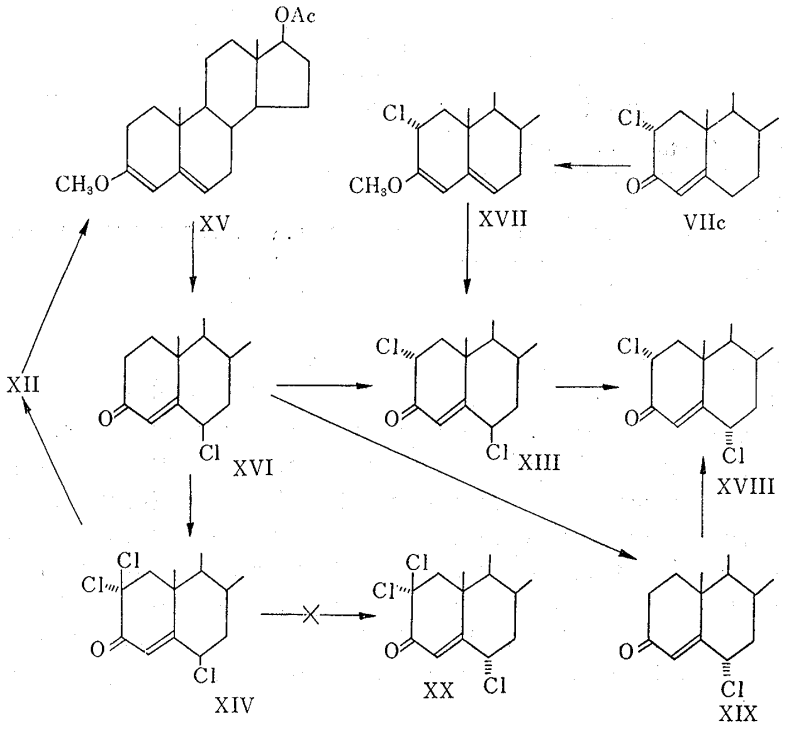
A direct route from 4-en-3-ones to the corresponding 2-chlorides is described in a Danish patent[7]: treatment of 4-en-3-ones with 1 molar equivalent of sulfuryl chloride in benzene under reflux gave the corresponding 2-chloro-4-en-3-ones. Nevertheless the product (m.p. 169～177°) obtained from testosterone acetate (Ⅻ) by this procedure in our laboratory seemed to correspond approximately with that (m.p. 173～175°) which was described as 2-chlorotestosterone acetate in the patent, its constitution could not be designated but assumed as a mixture of 2α-chlorotestosterone acetate (Ⅶc) and 2α,4-dichlorotestosterone acetate (X) on account of the observations described below; Ⅻ was treated with 1 molar equivalent of sulfuryl chloride in dry benzene or dry ether at room temperature to give a small amount of Ⅶc irrespective of the presence or absence of

6) H. Mori: This Bulletin, **10**, 429 (1962).
7) Danish pat., 83,631, Oct. 14, 1957 (C.A., **53**, P11452i (1963)).



benzoyl chloride,[8] and with excess of sulfuryl chloride in dry benzene to give mainly X accompanied with a small amount of 2α,6β-dichlorotestosterone acetate (XIII) and 2,2,6β-trichlorotestosterone acetate (XIV), and with excess of sulfuryl chloride in dry ether to give mainly XIII accompanied with only a small amount of VIIc and X.

Further study on chlorination with sulfuryl chloride was carried out for confirmation of the above-mentioned observations. Testosterone acetate 3-enol methyl ether (XV) was treated with N-chlorosuccinimide and successively the resulting unpurified 6β-chlorotestosterone acetate (XVI) was converted into 2,2,6β-trichlorotestosteron acetate (XIV) with excess of sulfuryl chloride in dry ether. On the other hand, crystalline XVI which was purified by recrystallization gave 2α,6β-dichlorotestosterone acetate (XIII) with the same treatment as above. XIII was also derived from 2α-chlorotestosterone acetate (VIIc) *via* the corresponding 3-enol methyl ether (XVII). XIII was isomerized to 2α,6α-dichlorotestosterone acetate (XVIII) with hydrogen chloride in acetic acid, which was also obtained from 6α-chlorotestosterone acetate (XIX) by treatment with sulfuryl chloride in dry ether.



8) C. Djerassi, C. R. Sholz : J. Am. Chem. Soc., **69**, 2404 (1947).

Validity of each chloride except 2,2,6β-trichlorotestosterone acetate (XIV) was concluded inevitably from the reaction sequence described above, and from its infrared and ultraviolet spectra (Table I). The structural assignment of XIV was achieved on the basis of the fact that XIV could be reduced to testosterone acetate (XII) with zinc dust in acetic acid indicating no 4-substitution (cf. p. 1218), infrared spectrum of XIV was close not to 2α,6α-dichlorotestosterone acetate (XVIII) but 2α,6β-dichlorotestosterone acetate (XIII) and the nuclear magnetic resonance[9,10] supported 6β-substitution. XIV could not be isomerized to the corresponding 2,2,6α-trichloride (XX) by treatment with hydrogen chloride in acetic acid even for 3 days.

Experimental*4

General Procedures

1) Ethoxalylation*5——A 4-en-3-one (1 part) was added to a mixture of dry benzene (1 part), diethyl oxalate (2 moles) and 50% NaH-suspension in oil*6 (1/2 part) with vigorous stirring in an ice-water bath. After stirring for additional 4 hr. at 10~20°, Et_2O (ca. 20 parts) was added to the reaction mixture. The precipitate was collected after 1 hr., washed with Et_2O, dried in vacuum and dissolved in H_2O. The solution was acidified with a mineral acid to give the corresponding 2-ethoxalyl derivative which was collected by filtration, washed with H_2O, dried at room temperature and subjected to a next step.

2) Halogenation of 2-Ethoxalyl Derivatives——To a solution of a 2-ethoxalyl-4-en-3-one (1 part) in pyridine (5 parts) was added NCS (or NBS) (1.2 moles) with stirring in an ice-water bath. In a few min. NCS was dissolved. The reaction mixture was stored for additional 1 hr. at room temperature, and then poured into ice-floating dil. H_2SO_4. The whole was extracted with Et_2O and the extract was washed with H_2O, 10% $Na_2S_2O_3$, 4% NaOH and H_2O, dried with Na_2SO_4, and condensed to dryness with caution of over-heating. The residue was recrystallized from a suitable solvent.

3) Chlorination with SO_2Cl_2——To a solution of a 4-en-3-one (1 part) in dry benzene or dry Et_2O (15 parts) was added SO_2Cl_2 (1 or 4 moles) dropwise with stirring in an ice-water bath. After stirring for additional 5 min. the reaction mixture was allowed to stand for 1/2 hr. at 10~20°, and then poured into ice-water (containing 2 or 8 moles of pyridine). The product was extracted with Et_2O and the ethereal extract was washed with H_2O, 4% NaOH, H_2O, 10% HCl and H_2O, dried with Na_2SO_4, and condensed to dryness with caution of over-heating. The residue was recrystallized from a suitable solvent.

4) Acetylation——To a solution of a carbinol (1 part) in pyridine (5 parts) was added Ac_2O (3 parts). The mixture was set aside overnight at room temperature and then poured into H_2O. The precipitate was collected, washed with H_2O, dried in vacuum and recrystallized from a suitable solvent.

2α-Chlorotestosterone (VIIb)——2-Ethoxalyltestosterone (VI)[5] (12 g.) (obtained from 10 g. of testosterone (V) by procedure (1)) was treated by procedure (2) with NCS. Recrystallization of the resulting residue from Et_2O-EtOH gave VIIb (8 g.) as colorless needles, m.p. 158~159°, $[\alpha]_D^{21}$ +131° (c=1.00). *Anal.* Calcd. for $C_{19}H_{27}O_2Cl$: C, 70.68; H, 8.17. Found: C, 70.43; H, 8.38.

2α-Chlorotestosterone Acetate (VIIc)——The foregoing crude residue (obtained from 10 g. of V) was treated by procedure (4). Recrystallization from Me_2CO gave VIIc (7.1 g.), m.p. 201~203°. One more recrystallization afforded an analytical sample as colorless needles, m.p. 203~205°, $[\alpha]_D^{21}$ +98° (c=1.61) (in the lit.,[1] m.p. 199~200°, $[\alpha]_D^{23}$ +90° (c=1.22, $CHCl_3$), UV: $\lambda_{max}^{iso\text{-}PrOH}$ 242 mμ (log ε 4.14)). *Anal.* Calcd. for $C_{21}H_{29}O_3CI$: C, 69.12; H, 8.01. Found: C, 68.98; H, 7.89.

2α,4-Dichlorotestosterone Acetate (VIII)——Procedure (1) was applied to 10 g. of VII. The resulting 2-ethoxalyl derivative (IX)*3 (8 g.) was treated by procedure (2) and successively the product was acetylated by procedure (4). The resulting precipitate was recrystallized from Me_2CO to X (5.5 g.), m.p. 238~242° (decomp.). Several recrystallizations from the same solvent gave an analytical sample as colorless needles, m.p. 245~247° (decomp.), $[\alpha]_D^{21}$ +97° (c=1.00). *Anal.* Calcd. for $C_{21}H_{28}O_3Cl_2$: C, 63.15; H, 7.07. Found: C, 62.95; H, 7.10.

b) From 2α-Chlorotestosterone Acetate (VIIc)——To a solution of VIIc (1 g.) in pyridine (10 ml.) was added SO_2Cl_2 (0.5 ml.) dropwise with stirring in an ice-water bath. Then the mixtre was kept stirring

*4 Melting points are uncorrected. Rotations were measured in $CHCl_3$ and UV spectra in MeOH unless stated otherwise. UV and IR spectral data which were not shown in experimantal were listed in Table I and II.

*5 This procedure, which was essentially same with the method of Hogg *et al.*,[3a] was devised for a substance with a small solubility, such as 4-chlorotestosterone acetate.

*6 Metal Hydride Inc., made in U. S. A.

9) Y. Kondo, T. Takemoto, K. Yasuda: This Bulletin, 12, 976 (1964).
10) S. K. Malhotra, H. J. Ringold: J. Am. Chem. Soc., 85, 1538 (1963); T. A. Wittstruck, S. K. Malhotra, H. J. Ringold: *Ibid.*, 85, 1699 (1963).

for 1 hr. at room temperature and poured into H_2O. The precipitate was collected, washed with H_2O, dried and recrystallized from Me_2CO to give slightly orange needles (800 mg.), m.p. 228~230° (decomp.). One more recrystallization afforded colorless needles, m.p. 238~240° (decomp.), which were identical with X obtained from Ⅷ.

Halogenations of the other 2-ethoxalyl derivatives were performed by similar treatment and listed in Table Ⅲ.

Table Ⅱ. Halogenaton of 2-Ethoxalyl-4-en-3-ones by Procedure (2) and (4)

Starting[a] material	Product	Yield (Recryst. solvent)	Physic. const. of anal. sample[e]	Analysis	
T	2α-Br-T	46% (Et_2O-EtOH)	m.p. 127~128°[b] (decomp.) $[\alpha]_D^{21}$ +121° (c=1.41)	Calcd. for $C_{19}H_{27}O_2Br$	C 62.13, H 7.42
				Found	C 62.02, H 7.41
T	2α-Br-TA	41% (Me_2CO)	m.p. 169~170°[c] (decomp.) $[\alpha]_D^{21}$ +100° (c=1.31)	Calcd. for $C_{21}H_{29}O_3Br$	C 61.61, H 7.14
				Found	C 61.69, H 7.22
4-Cl-TA	2α-Br-4-Cl-TA	39% (MeOH)	m.p. 209° (decomp.) $[\alpha]_D^{21}$ +98° (c=1.03)	Calcd. for $C_{21}H_{28}O_3BrCl$	C 56.82, H 6.36
				Found	C 56.29, H 6.37
17α-MeT	2α-Cl-17α-MT	54% (Et_2O-MeOH)	m.p. 154~156°[d] $[\alpha]_D^{21}$ +94° (c=1.61)	Calcd. for $C_{20}H_{29}O_2Cl$	C 71.30, H 8.05
				Found	C 71.32, H 8.29
4-Cl-17α-MeTA	2α,4-diCl-17α-MeTA	58% (Me_2CO)	m.p. 218~219° $[\alpha]_D^{21}$ +88° (c=0.72)	Calcd. for $C_{22}H_{30}O_3Cl_2$	C 62.57, H 7.15
				Found	C 62.81, H 7.28

a) T: testosterone, TA: testosterone acetate.
b) In the lit., m.p. 120° then 160°, $[\alpha]_D$ +121±2° (1% $CHCl_3$), UV: λ_{max} 244 mμ (ε 13,400) (R. Joly, J. Warnant, B. Goffinet: Fr. pat., 1,249,939, Mar. 22, 1961 (C. A., **56**, P 10235d (1963)).
c) In the lit., m.p. 167~169° (decomp.) (H.H. Inhoffen, G. Zührsdorf: Ber., **76B**, 233 (1943)).
d) In the lit., m.p. 154~155° (sinters 100~110°), $[\alpha]_D^{23}$ +79° (c=1.08, $CHCl_3$), UV: $\lambda_{max}^{iso\text{-}PrOH}$ 243 mμ (log ε 4.10) (Rf. 1).
e) UV and IR spectral data are shown in Table I.

2α,6β-Dichlorotestosterone Acetate (XIII). a) From 6β-Chlorotestosterone Acetate (XVI)——To a mixture of 3-methoxyandrosta-3,5-dien-17β-ol acetate (XV)[11] (3 g.) in Me_2CO (30 ml.) and 5% NaOAc (5 ml.) was added 75% NCS (2 g.). After a night the reaction mixture was poured into H_2O. The precipitate was collected, washed with H_2O and then dissolved in Et_2O. The ethereal solution was washed with 4% NaOH and H_2O, dried with Na_2SO_4, and evaporated almost to dryness. To the residue was added a small amount of EtOH. After a few hours were collected XVI (2 g.) as colorless prisms, m.p. 153~156°. One more recrystallization gave an analytical sample, m.p. 158.5~159.5°, $[\alpha]_D^{21}$ 0° (c=1.00) (in the lit.,[12] m.p. 156~157°, $[\alpha]_D$ +3° ($CHCl_3$), UV: $\lambda_{max}^{95\%\ EtOH}$ 240 mμ (log ε 4.16), IR ν_{max}^{KBr} cm^{-1}: 1680, 1616 (conjugated ketone)). *Anal.* Calcd. for $C_{21}H_{29}O_3Cl$: C, 69.12; H, 8.01. Found: C, 69.38; H, 8.01.

XVI (m.p. 153~156°) (1 g.) was subjected to procedure (3) with excess (4 moles) of SO_2Cl_2 in dry Et_2O. The resulting residue was recrystallized from Me_2CO-hexane to 500 mg. of XIII as colorless prisms, m.p. 197° (decomp.). Several recrystallization from the same solvent gave an analytical sample as colorless needles, m.p. 211~211.5° (decomp.), $[\alpha]_D^{21}$ +36° (c=1.15). *Anal.* Calcd. for $C_{21}H_{28}O_3Cl_2$: C, 63.15; H, 7.07. Found: C, 63.14; H, 6.97.

b) From 2α-Chlorotestosterone Acetate (VIIc)——A mixture of Ⅶc (2 g.), methyl orthoformate (2 ml.), *p*-TsOH·H_2O (200 mg.) and dioxane (20 ml.) was stirred for 1 hr. at 40~50° under N_2 atmosphere. The reaction mixture was poured into H_2O (containing pyridine, 2 ml. in 200 ml.). After a while the precipitate was collected, washed with H_2O and dried in vacuum. Recrystallization from Et_2O (containing 1 drop of pyridine) gave 2α-chloro-3-methoxyandrosta-3,5-dien-17β-ol acetate (XVII) (1.5 g.), m.p. 165°

11) A.L. Nussbaum, E. Yuan, D. Dincer, E.P. Oliveto: J. Org. Chem., **26**, 3925 (1961); K. Yasuda: This Bulletin, **11**, 1167 (1963).
12) A.D. Cross, H. Carpio, H.J. Ringold: J. Med. Chem., **6**, 198 (1963).

(decomp.). Two recrystallization from Me_2CO (containing 1 drop of pyridine) afforded an analytical sample as colorless scales, m.p. 176~177° (decomp.), $[\alpha]_D^{21}$ −17° (c=1.14),*7 UV : λ_{max} 245~246 mμ (ε 5,100),*8 IR cm^{-1} : $\nu_{C=C}$ 1628, 1657 (KBr). *Anal.* Calcd. for $C_{22}H_{31}O_3Cl$: C, 69.73; H, 8.24. Found : C, 69.53; H, 8.38.

To a solution of XVII (m.p. 165° (decomp.)) (300 mg.), Me_2CO (80 ml.) and 5% NaOAc (20 ml.) was added 75% NCS (400 mg.). The mixture become homogeneous after stirring for 30 min., then set aside overnight and poured into H_2O. The precipitate was collected, washed with H_2O and then dissolved in Et_2O. The ethereal solution was washed with 4% NaOH and H_2O, dried with Na_2SO_4 and condensed almost to dryness with caution of over-heating. The mother liquor was stored overnight in an ice-box to give 70 mg. of colorless prisms, m.p. 178~181°, which showed the same IR chart with XIII but needed several recrystallization to afford an analytical sample as obtained above.

2α,6β-Dichlorotestosterone Acetate (XVIII). **a) From 6α-Chlorotestosterone Acetate (XIX)**——A solution of 6β-chlorotestosterone acetate (XVI) (2 g.) in AcOH (100 ml.) and conc. HCl (5 ml.) was stored overnight at room temperature and then poured into H_2O. The precipitate was collected, washed with H_2O and dissolved in Et_2O. The ethereal solution was washed with 4% NaOH and H_2O, dried with Na_2SO_4 and evaporated nearly to dryness. Addition of a small amount of MeOH afforded XIX (1.3 g.) as colorless scales, m.p. 152~154°. One more recrystallization gave an analytical sample, m.p. 155~156°, $[\alpha]_D^{21}$ +59° (c=1.37) (in the lit.,[12] m.p. 157~158°, $[\alpha]_D$ +69° ($CHCl_3$), UV : $\lambda_{max}^{95\%\ EtOH}$ 236 mμ (log ε 4.14), IR ν_{max}^{KBr} cm^{-1} : 1682, 1620 (conjugated ketone)). *Anal.* Calcd. for $C_{21}H_{29}O_3Cl$: C, 69.12; H, 8.01. Found : C, 69.11; H, 8.12.

XIX (m.p. 152~154°) (500 mg.) was subjected to procedure (3) with excess (4 moles) of SO_2Cl_2 in dry Et_2O. In this case, $CHCl_3$ (2.5 ml.) was added to make a homogeneous solution. The resulting residue was recrystallized from Me_2CO-hexane to XVIII (230 mg.) as colorless needles, m.p. 209~210° (decomp.). Several recrystallization from the same solvent gave an analytical sample as colorless plates, m.p. 217.5~218° (decomp.), $[\alpha]_D^{21}$ +72° (c=1.15). *Anal.* Calcd. for $C_{21}H_{28}O_3Cl_2$: C, 63.15; H, 7.07. Found: C, 62.69; H, 7.02.

b) From 2α,6β-Dichlorotestosterone Acetate (XIII)——A suspension of XIII (500 mg.) in AcOH (25 ml.) and conc. HCl (1.2 ml.) was stirred at room temperature until it become homogeneous (ca. 2 hr.). The solution set aside for 2 days at room temperature. The precipitate was collected, washed with H_2O and dissolved in Et_2O. The ethereal solution was washed with 4% NaOH and H_2O, dried with Na_2SO_4 and condensed to a small volume. Thus 280 mg. of colorless scales, m.p. 211~212° (decomp.), was obtained. Recrystallization from Me_2CO gave an analytical sample which was identical with XVIII obtained as above.

2,2,6β-Trichlorotestosterone Acetate (XIV)——XV (2 g.) was treated as described in p. 1222. The washed and dried ethereal solution was evaporated to dryness with caution of over-heating. The oily residue*9 was subjected to procedure (3) with excess (4 moles) of SO_2Cl_2 in dry Et_2O for 2 hr. at 5~10°. Colorless needles were deposited near the end of reaction. The crystals were collected by filtration and washed with Et_2O, H_2O and Et_2O. Recrystallization from Me_2CO gave XIV (630 mg.) as colorless prisms, m.p. 211~212° (decomp.). Several recrystallization from the same solvent afforded an analytical sample as colorless prisms, m.p. 214.5~216.5° (decomp.), $[\alpha]_D^{21}$ −22.4° (c=1.25). *Anal.* Calcd. for $C_{21}H_{27}O_3Cl_3$: C : 58.14; H, 6.27. Found : C, 58.06; H, 6.48.

Further crops of XIV (470 mg., m.p. 212~213° (decomp.) were obtained by treatment of the ethereal filtrate. XIII could not be obtained from the mother liquors.

Dechlorination*10 of 2α,4-Dichlorotestosterone Acetate (X)——A mixture of X (50 mg.), Zn dust (200 mg.), MeOH (2 ml.) and AcOH (1 ml.) was refluxed for 30 min. The solid was filtered off and washed with Me_2CO. The filtrate was poured into ice-floating 10% NaOH. The precipitate was collected, washed with H_2O, dried in vacuum and recrystallized from Me_2CO to X (30 mg., m.p. 225~227°), which was identical with the authentic sample.[6]

Dechlorination*10 of 2,2,6β-Trichlorotestosterone Acetate (XIV)——XIV (20 mg.) was treated as described above. Recrystallization from MeOH gave XII (m.p. 137~140°), which was identical with the authentic sample.

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*7 Measured in $CHCl_3$ containing 2% pyridine.
*8 Measured in MeOH containing 2% dioxane. λ_{max} changed to 241 mμ during 10 min. because of decomposition.
*9 Usually became crystalline after a while.
*10 The method of Kirk and Petrow (J. Chem. Soc., **1958**, 1334).

Summary

Some 2-ethoxalyl-4-en-3-one was treated with N-halo-succinimide in pyridine to give the corresponding 2α-halo-4-en-3-one in a good yield. Direct chlorination of testosterone acetate with sulfuryl chloride (1 mole) gave a small amount of 2α-chlorotestosterone acetate in dry benzene or dry ether, and with sulfuryl chloride (excess) gave mainly 2α,4-dichlorotestosterone acetate in dry benzene and mainly 2α,6β-dichlorotestosterone acetate in dry ether. These observations were confirmed by the syntheses of their related compounds through the unequivocal routes.

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170. Hiromu Mori: Studies on Steroidal Compounds. XII.*1 Stereochemistry of 1,4-Addition of Grignard Reagent for α,β-Unsaturated Steroidal Ketones. Grignard Reaction of 3β-Hydroxycholest-4-en-6-one.

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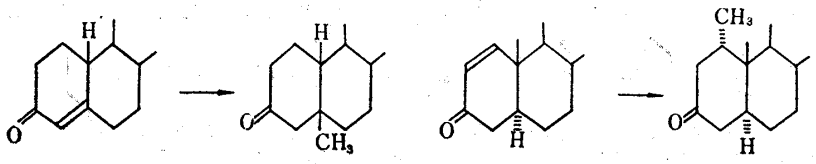
In the preceding papers, the Grignard reactions of 19-nor-3-oxo-4-ene (I) and 3-oxo-1-ene (II) steroids were described.[1,2] 1,4-Addition product was isolated in each case, when Grignard reaction was taken place in the presence of cuprous chloride: 5β-methyl-3-oxo (III) and 1α-methyl-3-oxo (IV) compound were obtained respectively as shown in Chart 1. The stereochemical course of the reaction was explained by stereochemical



I III II IV

Chart 1.

interaction. This paper describes further study of stereochemistry of Grignard reaction, in which the reaction of 3β-hydroxycholest-4-en-6-one (V) will be reported, and discussion will be made concerning the stereochemistry of 1,4-addition of Grignard reagent for α,β-unsaturated ketones.

When 3β-hydroxycholest-4-en-6-one (V)[3] was treated with methyl magnesium iodide in the presence of cuprous chloride or cupric acetate, there was obtained a new compound (VI), m.p. 175.5~177.5° with no characteristic absorption in ultraviolet spectrum.

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*1 H. Mori, J. Yamada: This Bulletin, **11**, 1418 (1963).
*2 1604 Shimosakunobe, Kawasaki-shi (森 弘).
1) H. Mori: This Bulletin, **10**, 382 (1962).
2) *Idem*: *Ibid.*, **10**, 386 (1962).
3) I. M. Heilbron, E. R. H. Jones, F. S. Spring: J. Chem. Soc., **1937**, 801.