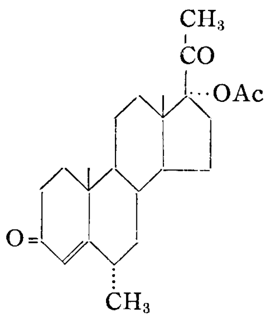
UDC 547.92 : 577.17

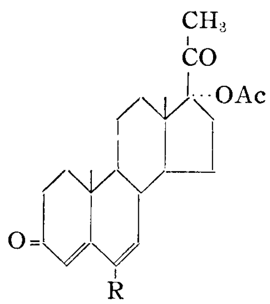
Hiromu Mori : Studies on Steroidal Compounds. IV.[1] Synthesis of 6-Alkoxy-3-oxo-4,6-diene Steroidal Hormones.

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

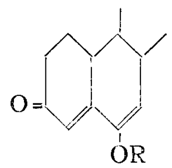
Since it has been reported in 1951 that 19-norprogesterone has high progestational activity,[2] brilliant progress has been made in the field of progestational 19-norsteroids.[3] On the other hand, high progestational activity was reported for 6α-methyl-17α-acetoxypregn-4-ene-3,20-dione (I).[4] Being prompted by this discovery, many substituted 17α-acetoxypregn-4-ene-3,20-dione derivatives having high activity were synthesized[5~7] and a new field was developed in the studies of progestational substances. It was shown by the Syntex group that 6-methyl-17α-acetoxypregna-4,6-diene-3,20-dione[6] (IIa) and 6-chloro-17α-acetoxypregna-4,6-diene-3,20-dione[7] (IIb) are the highest progestational substances known to date.



(I)



(IIa) R=CH_3
(IIb) R=Cl



(III)

It is generally recognized that the substitution of a hydrogen atom at 6-position by some group and simultaneous introduction of the double bond at 6-7 position increase progestational activity of the parent compounds. From this point of view, it seemed of interest to prepare 6-alkoxy-3-oxo-4,6-diene steroidal hormones (III) and the present report concerns the synthesis of such steroidal hormones.

In order to investigate the most suitable method to prepare the above-mentioned structure (III), testosterone acetate derivatives were examined. 6β-Hydroxy-17β-acetoxyandrost-4-en-3-one (IV) was obtained from testosterone acetate by the method of Romo[8] and converted into 17β-acetoxyandrost-4-ene-3,6-dione (V) by oxidation with chromium trioxide

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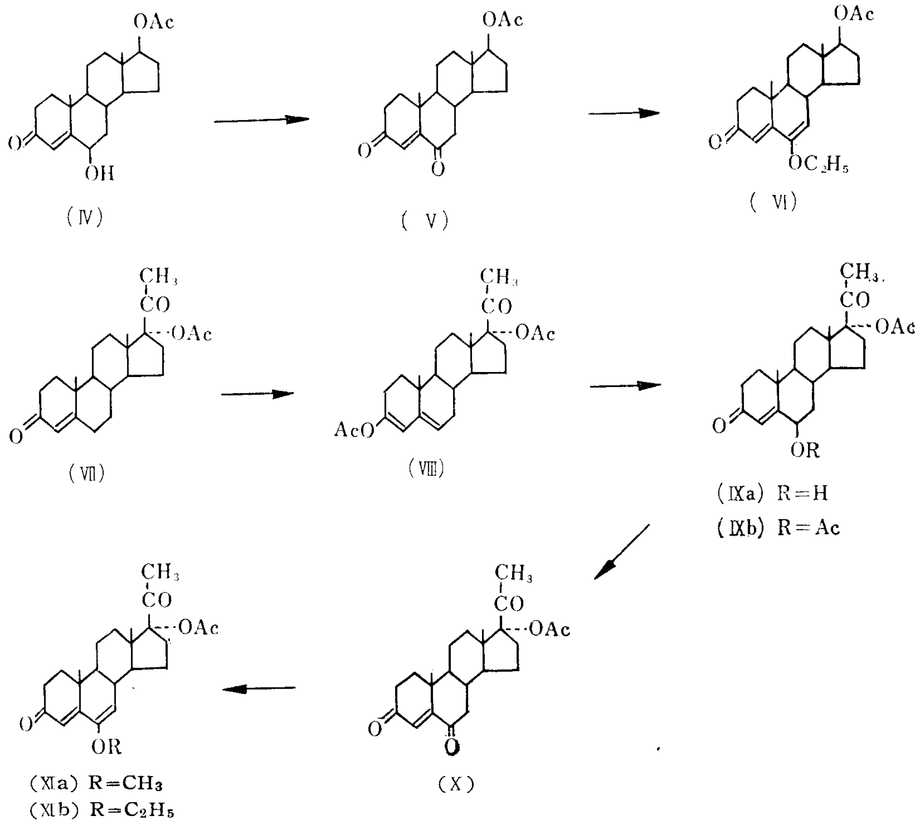
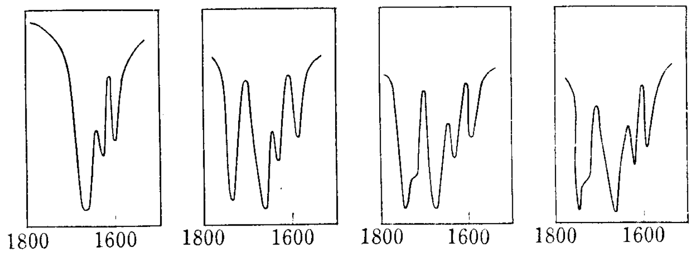
1) Part III. Yakugaku Zasshi, **80**, 330 (1960).
2) C. Djerassi, L. Miramontes, G. Rosenkranz : J. Am. Chem. Soc., **73**, 3540 (1951); **75**, 4440 (1953).
3) C. Djerassi, L. Miramontes, G. Rosenkranz, F. Sondheimer : *Ibid.*, **76**, 4092 (1954); H. J. Ringold, G. Rosenkranz, F. Sondheimer : *Ibid.*, **78**, 2477 (1956); D. A. McGinty, C. Djerassi : Ann. N. Y. Acad. Sci., **71**, 500 (1958).
4) J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes, W. E. Dulin : J. Am. Chem. Soc., **80**, 2904 (1958).
5) A. Bowers, H. J. Ringold : *Ibid.*, **80**, 4423 (1958); J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson, J. Campbell : Chem. & Ind. (London), **1958**, 1002; A. David, F. Hartley, D. R. Millson, J. Petrow : J. Pharm. Pharmacol., **9**, 929 (1957); F. Mukawa : Nippon Kagaku Zasshi, **81**, 331 (1960).
6) H. J. Ringold, J. P. Ruelas, E. Batres, C. Djerassi : J. Am. Chem. Soc., **81**, 3712 (1959).
7) H. J. Ringold, E. Batres, A. Bowers, J. Edwards, J. Zderic : *Ibid.*, **81**, 3485 (1959).
8) J. Romo, G. Rosenkranz, C. Djerassi, F. Sondheimer : J. Org. Chem., **19**, 1509 (1954).



in acetic acid. In a classical paper of 1904, Windaus[9] showed that cholest-4-ene-3,6-dione was convertible by ethanol and hydrogen chloride into an enol ethyl ether, which was prepared also by Nakanishi[10] in 1953 and identified as 6-ethoxycholesta-4,6-dien-3-one by Fieser.[11] In the case of (V), however, milder condition is desirable to prevent hydrolysis of 17β-acetoxyl group. The desired enol ethyl ether (VI) of m.p. 157.5~159° was obtained by stirring the diketone (V) in ethanol at room temperature in the presence of a large amount of *p*-toluenesulfonic acid monohydrate. The structural assignment of the enol ethyl ether as 6-ethoxy-17β-acetoxyandrosta-4,6-dien-3-one (VI) was based on ultraviolet and infrared absorption spectra and elementary analysis. (VI) showed strong absorption at 304 mμ in its ultraviolet spectrum and it is known that 6-ethoxycholesta-4,6-dien-3-one shows absorption at 302 mμ.[12] The infrared absorption spectrum of (VI) did not show the



6-Ethoxycholesta-4,6-dien-3-one[3] (VI) (XIa) (XIb)

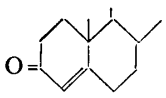
Fig. 1. Infrared Absorption Spectra of 6-Alkoxy-4,6-dien-3-ones (in $CHCl_3$)

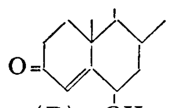
9) A. Windaus: Ber., **39**, 2249 (1906).
10) K. Nakanishi: Unpublished work.
11) L.F. Fieser: J. Am. Chem. Soc., **75**, 4386 (1953).
12) L.F. Fieser, M. Fieser: "Steroids," 45 (1959). Reinhold Publishing Corp., New York.

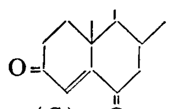
hydroxyl band but acetoxyl band was observed at $1725\,cm^{-1}$, and the spectral curve in the region of $1600\sim1700\,cm^{-1}$ was identical with that of 6-ethoxycholesta-4,6-dien-3-one[13] (Fig. 1).

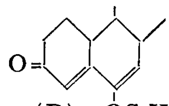
Attempt was made to prepare 6-alkoxy-17α-acetoxypregna-4,6-diene-3,20-dione (XI) via 17α-acetoxypregn-4-ene-3,6,20-trione (X). The synthesis of (X) was made in accordance with the modified method of Romo.[8] The 3-enol acetate (VIII) prepared from 17α-acetoxypregn-4-ene-3,20-dione (VII) by reaction with isopropenyl acetate was oxidized with monoperphthalic acid to 6β-hydroxy-17α-acetoxypregn-4-ene-3,20-dione (IXa). Oxidation of (IXa) with chromium trioxide in acetic acid led to 17α-acetoxypregn-4-ene-3,6,20-trione (X). Table I shows molecular rotation differences by introduction of β-hydroxyl, keto, and 6-ethoxy-6-ene group in 6-position of 3-oxo-4-ene steroids.

Table I. Molecular Rotation Differences of 6-Oxygenated Steroids


(A)


(B) OH


(C) O


(D) OC_2H_5

	MDA	MDB	MDC	MDD	MDA−MDB	MDA−MDC	MDA−MDD
5α-Cholestane	+342[a]	+108[b]	−140[8]		+234	+482	
17β-Acetoxy-5α-androstane	+288[c]	+ 94[8]	−162[d]	−102	+194	+450	+390
Pregnan-20-one	+557[e]	+354[8]	+100[8]		+203	+457	
17α-Acetoxypregnan-20-one	+209[f]	+ 27	−208	−147	+182	+417	+356

a) A. Butenandt, A. Wolff: Ber., **68**, 2091 (1935).
b) L.F. Fieser: J. Am. Chem. Soc., **75**, 4377 (1953).
c) Codex Français, 933 (1949).
d) A. Butenandt, B. Riegel: Ber., **69**, 1163 (1936).
e) L.F. Fieser, M. Fieser: "Steroids," 541 (1959). Reinhold Publ. Corp., Now York.
f) R.B. Turner: J. Am. Chem. Soc., **75**, 3489 (1953).

Treatment of triketone (X) with ethanol and *p*-toluenesulfonic acid monohydrate gave 6-ethoxy-17α-acetoxypregna-4,6-diene-3,20-dione (XIa). By the use of methanol instead of ethanol, 6-methoxy-17α-acetoxypregna-4,6-diene-3,20-dione (XIb) was obtained.

(X) and (XIb) were inactive in Clauberg test when assayed in a dose of 1 mg. From Burn's hypothesis[14] that inactivation of steroidal hormones would also occur through metabolic oxygenation at 6-position, it is reasonable that (X) is inactive in Clauberg test. In the case of (XIb), the inactivity will probably be due to its easy hydrolysis. (VI) was also inactive in androgenic and anabolic tests using a mouse in a total dose of 14 mg. (2mg. per day).

Experimental*2

17β-Acetoxyandrost-4-ene-3,6-dione (V)——17β-Acetoxy-6β-hydroxyandrost-4-en-3-one[8] (IV) (500 mg.) dissolved in AcOH (15 cc.) was oxidized with CrO_3 (250 mg.) in H_2O (1 cc.) for 15 min. at room temperature. It was diluted with H_2O and the product was extracted with Et_2O. The organic layer was washed with 5% Na_2CO_3 and H_2O, dried over Na_2SO_4, and the solvent was evaporated. Recrystallization from Et_2O-hexane mixture gave pale yellow prisms, m.p. 204~207°; yield, 350 mg. (reported[d] m.p. 198~201°, $[\alpha]_D^{22}$ −47.2°±1.4° (Me_2CO).

6-Ethoxy-17β-acetoxyandrosta-4,6-dien-3-one (VI)——To a solution of 17β-acetoxyandrost-4-ene-3,6-dione (V) (290 mg.) in dehyd. EtOH (100 cc.), *p*-toluenesulfonic acid monohydrate (2.0 g.) was added and the solution was stirred at room temperature for 5 hr. It was diluted with H_2O and the product was extracted with Et_2O. The organic fraction was washed with 5% Na_2CO_3 and H_2O, dried

*2 All m.p.s are uncorrected.
13) K. Nakanishi: Jikken Kagaku Koza, **1**, [I], 358 (1957). Maruzen Co. Ltd., Tokyo.
14) D. Burn, B. Ellis, V. Petrow, I.A. Stuart-Webb, D.M. Williamson: J. Chem. Soc., **1957**, 4092.

over Na_2SO_4, and the solvent was evaporated. Recrystallization from MeOH containing one drop of pyridine gave (VI), m.p. 156～161°; yield, 250 mg. Further recrystallization from the same solvent gave white needles, m.p. 160～162°, $[\alpha]_D^{20}$ −27° (c=0.946, $CHCl_3$), UV : λ_{max}^{EtOH} 304 mμ (log ε 4.18), IR $\nu_{max}^{CHCl_3}$ cm^{-1} : (no hydroxyl band); 1725 (17-AcO), 1655～1650, 1621, 1586 ($\Delta^{4,6}$-3-CO). ν_{max}^{KBr} cm^{-1} : (no hydroxyl band), 1729 (17-AcO), 1662, 1624, 1586 ($\Delta^{4,6}$-3-CO). *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found : C, 74.02; H, 8.38.

6β-Hydroxy-17α-acetoxypregn-4-ene-3,20-dione (IXa)——A solution of 17α-acetoxypregn-4-ene-3,20-dione (12.0 g.) and *p*-toluenesulfonic acid monohydrate (2.0 g.) was refluxed gently for 3 hr. After cool, Et_2O was added and the solution was washed with ice-cold 5% $NaHCO_3$ and H_2O. After drying over Na_2SO_4 and evaporation of the solvent, the residue was crystallized from MeOH to 3,17α-diacetoxypregna-3,5-dien-20-one (VIII), m.p. 192～202°; yield, 11.4 g.

The crude enol acetate (VIII) (8.0 g.) was dissolved in Et_2O (800 cc.), a solution of monoperphthalic acid in Et_2O (59.0 cc., 0.077 g./cc., 1.3 equivalent to 8.0 g. of (VIII)) was added and the solution was allowed to stand at room temperature in the dark for 3 days. After washing with ice-cold 5% $NaHCO_3$ and H_2O, and drying over Na_2SO_4, the solvent was evaporated. Recrystallization of the residue from Me_2CO-hexane mixture gave (IXa), m.p. 235～241°; yield, 4.78 g. Further recrystallization from the same solvent gave white needles, m.p. 239～243°, $[\alpha]_D^{20}$ +7° (c=0.867, dioxane), UV: λ_{max}^{EtOH} 238 mμ (log ε 4.20). *Anal.* Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found : C, 71.13; H, 8.46.

6β,17α-Diacetoxypregn-4-ene-3,20-dione (IXb)——To a solution of 6β-hydroxy-17α-acetoxypregn-4-ene-3,20-dione (IXa) (500 mg.) in pyridine (10 cc.), Ac_2O (5 cc.) was added and the solution was allowed to stand overnight at room temperature. It was diluted with H_2O and the product was extracted with Et_2O. After washing the Et_2O extract with 5% Na_2CO_3 and H_2O,and drying over Na_2SO_4, the solvent was evaporated. Recrystallization from MeOH gave (IXb), m.p. 239～244°; yield, 330 mg. Further recrystallization from MeOH gave white prisms, m.p. 243～245°, $[\alpha]_D^{20}$ +22° (c=1.119, $CHCl_3$), UV : λ_{max}^{EtOH} 236 mμ (log ε 4.13). *Anal.* Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found : C, 69.90; H, 7.73.

17α-Acetoxypregn-4-ene-3,6,20-trione (X)——6β-Hydroxy-17α-acetoxypregn-4-ene-3,20-dione (IXa) (500 mg.) dissolved in AcOH (20 cc.) was oxidized with CrO_3 (300 mg.) in H_2O (1 cc.) for 15 min. at room temperature. It was diluted with H_2O and the product was extracted with Et_2O. After washing the extract with 5% Na_2CO_3 and H_2O, and drying over Na_2SO_4, the solvent was evaporated. Recrystallization from Me_2CO gave (X), m.p. 214～216.5°; yield, 360 mg. Further recrystallization from Me_2CO gave pale yellow needles, m.p. 215～218°, $[\alpha]_D^{18}$ −54° (c=1.095, $CHCl_3$). UV : λ_{max}^{EtOH} 250 mμ (log ε 4.11). *Anal.* Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82 Found : C, 71.16; H, 7.70.

6-Methoxy-17α-acetoxypregna-4,6-diene-3,20-dione (XIa)——A solution of 17α-acetoxypregn-4-ene-3,6,20-trione (X) (300 mg.) and *p*-toluenesulfonic acid monohydrate (2.0 g.) in MeOH (100 cc.) was stirred at room temperature for 5 hr. It was diluted with H_2O and the product was extracted with Et_2O. After washing Et_2O layer with 5% Na_2CO_3 and H_2O, and drying over Na_2SO_4, the solvent was evaporated. Recrystallization from MeOH containing one drop of pyridine gave (XIa), m.p. 210～213°; yield, 230 mg. Further recrystallization from the same solvent gave white plates, m.p. 215～218°, $[\alpha]_D^{18}$ −39° (c=1.315, $CHCl_3$), UV : λ_{max}^{EtOH} 304 mμ (log ε 4.16). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : (no hydroxyl band), 1732, 1710～1715 (17α-AcO-20-CO), 1658, 1623, 1586 ($\Delta^{4,6}$-3-CO), ν_{max}^{KBr} cm^{-1} : (no hydroxyl band), 1732, 1715 (17α-AcO-20-CO), 1662, 1625, 1589 ($\Delta^{4,6}$-3-CO). *Anal.* Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.05; H, 7.79.

6-Ethoxy-17α-acetoxypregn-4-ene-3,20-dione (XIb)——A solution of 17α-acetoxypregn-4-ene-3,6,20-trione (X) (300 mg.) and *p*-toluenesulfonic acid monohydrate (2.0 g.) in dehyd. EtOH (100 cc.) was stirred at room temperature for 4 hr. It was diluted with H_2O and the product was extracted with Et_2O. After washing Et_2O layer with 5% Na_2CO_3 and H_2O, and drying over Na_2SO_4, the solvent was evaporated. Recrystallization from MeOH containing one drop of pyridine gave (XIb), m.p. 177～179.5; yield, 250 mg. Further recrystallization from the same solvent gave white needles, m.p. 181.5～183°, $[\alpha]_D^{20}$ −35° (c=0.792, $CHCl_3$), UV : λ_{max}^{EtOH} 304 mμ (log ε 4.17). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : (no hydroxyl band), 1730, 1710～1715 (17α-AcO-20-CO), 1650, 1620, 1585 ($\Delta^{4,6}$-3-CO). ν_{max}^{KBr} cm^{-1} : (no hydroxyl band), 1732, 1713 (17α-AcO-20-CO), 1665, 1621, 1588 ($\Delta^{4,6}$-3-CO). *Anal.* Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found : C, 72.70; H, 8.02.

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Summary

Synthesis of some steroidal hormones having 6-alkoxy-4,6-dien-3-one structure was carried out. 17β-Acetoxyandrost-4-ene-3,6-dione (V), prepared by oxidation with chromium trioxide of 6β-hydroxy-17β-acetoxyandrost-4-en-3-one (VI), was treated with ethanol and *p*-toluenesulfonic acid monohydrate to give 6-ethoxy-17β-acetoxyandrosta-4,6-dien-3-one (VI). The treatment of 17α-acetoxypregn-4-ene-3,6,20-trione (X) with ethanol (or methanol) and *p*-toluenesulfonic acid monohydrate gave 6-ethoxy-(or methoxy)-17α-acetoxypregna-4,6-diene-3,20-dione (XIa or XIb). (X) was synthesized from 17α-acetoxypregn-4-ene-3,20-dione (VII) by the modified method of Romo.

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Tatsuo Ohta and Susumu Mihashi : Furoquinolines. XXI.*[1] Synthesis and Alkoxyl Interchange of 4-Ethoxyfuro[2,3-*b*]quinoline and its 2,3-Dihydro Analogs.

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Berinzaghi, Deulofeu, Labriola, and Muruzabal[1] showed that, by the influence of alcoholic alkali, an interchange occurs between the methoxyl group at the 4-position of furoquinoline alkaloid and alkoxyl group of the particular alcohol used. By this means, the ethoxyl and propoxyl analogs of skimmianine (Ia) and ethoxyl analog of γ-fagarine (IIa) were obtained.

The present paper deals with the synthesis of the title compounds and their alkoxyl interchange reaction. Respective refluxing of 4-chloro-3-(2-chloroethyl)carbostyril (I) and its 7-methoxy derivative (II) with ethanolic potassium hydroxide solution gave 4-ethoxy-2,3-dihydrofuro[2,3-*b*]quinoline (III) and its 7-methoxy derivative (IV). Dehydrogenation of (III) with N-bromosuccinimide in the presence of benzoyl peroxide, followed by heating of the product with collidine, yielded 4-ethoxyfuro[2,3-*b*]quinoline (V), identical with the ethoxyl analog[2] of dictamnine obtained previously by alkoxyl interchange of dictamnine.

Reconversion of (V) to dictamnine (VI) with 10% methanolic potassium hydroxide solution was concluded easily but 2,3-dihydrodictamnine (VII), 2,3-dihydroevolitrine (VIII), and 2,3-dihydroskimmianine (IX) did not undergo transformation, except (VII) into (III), into the corresponding ethoxyl analogs with 10% ethanolic potassium hydroxide solution. Further, an attempt was made to obtain (VII) and (VIII) respectively from (III) and (IV) with 10% methanolic potassium hydroxide solution, but it failed in spite of prolonged heating or the reaction in sealed tube.

From these experimental results, it may be concluded that the carbon atom in the 4-position of the furo[2,3-*b*]quinoline ring has small electron density due to the overlapping of the resonance effect of the furan and pyridine ring. Therefore, the alkoxyl group in the 4-position of the furoquinoline alkaloids is quite easily substituted with other alkoxide ions.

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2) T. Ohta, *et al.* : Tokyo Yakka Daigaku Kenkyû Nempô, **4**, 255 (1954).