UDC 577.176.52

Total Synthesis of *dl*-3α-Acetoxy-5β-pregna-9(11),16-dien-20-one[*1,*2]

Pregna-9(11),16-dien-20-one derivatives are useful materials for the synthesis of natural and synthetic cortical hormones.[1] This communication presents the total synthesis of *dl*-3α-acetoxy-5β-pregna-9(11),16-dien-20-one (XXIV).

The tetracyclic ketone (I)[2] was hydrogenated[3] over palladium-charcoal in an alkaline medium to give the 5β-dihydroketone (II),[*3] m.p. 82~85°,[*4] UV λ_{max}^{EtOH} mμ (ε): 273 (16000), in 82% yield. Stereospecific reduction of the carbonyl group of compound (II) was achieved by lithium tri-*tert*-butoxyaluminum hydride to give the 3α-hydroxy compound (III), m.p. 125~126°, UV λ_{max}^{EtOH} mμ (ε): 273 (16500), in 85% yield. On the modified Birch reduction of Wilds and Nelson,[4] followed by acid hydrolysis, compound (III) was converted into the conjugated tetracyclic ketone (IV), m.p. 170~171°, UV λ_{max}^{EtOH} mμ (ε): 241.3 (16820) in 37% yield, together with a stereoisomeric by-product in about 10% yield.

Introduction of a double bond at the 11,12 position was carried out by the usual method used in steroid chemistry. Enolacetylation of IV with isopropenyl acetate and *p*-toluenesulfonic acid gave the heteroannular dienol diacetate (V), m.p. 97~109°, UV λ_{max}^{EtOH} mμ (ε): 235 (18840). This was converted without purification into the conjugated dienone (VI), m.p. 149~151°, UV λ_{max}^{EtOH} mμ (ε): 285 (28840), by bromination and subsequent dehydrobromination with lithium bromide and lithium carbonate in dimethyl formamide.[5] The overall yield of VI from IV was 34%.

By treatment with ethyl orthoformate in ethanol containing a trace of pyridine hydrochloride, VI was transformed into the trienol ether (VII),[6] m.p. 118~122°/130°, UV λ_{max}^{EtOH} mμ (ε): 321 (20870), which was then converted into an oily monoconjugated dienone (VIII)[*5] by controlled hydrolysis with 50% acetic acid. Hydrocyanation of the crude product of VIII with hydrogen cyanide and triethyl aluminum in tetrahydrofuran[7] proceeded stereospecifically to yield the 13β-cyano ketone (IX), m.p. 249~251°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240, 1726, as the sole product. The overall yield of this cyano ketone (IX) from the conjugated dienone (VI) was 54.5%.

Conversion of this cyano group into a methyl group was achieved by our previously

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*1 Studies on Total Syntheses of Steroids XII.

*2 The greater part of this work was presented at the 14th general meeting of the Pharmaceutical Society of Japan, held at Sapporo in July 1961.

*3 All compounds recorded gave satisfactory compositional analyses.

*4 All melting points were measured on Kofler block and corrected.

*5 The crude reaction product showed an absorption at 235 mμ in UV spectrum, but not any around 321 mμ.

1) *a*) L.F. Fieser, M. Fieser: "Steroids,, p. 600, Reinhold Publishing Corporation (1959). *b*) J.H. Fried, A.N. Nutile: J. Org. Chem., **27**, 914 (1962). *c*) T.R. Carrington, S. Eardley, J. Elks, G.F.H. Green, G.I. Gregory, A.G. Long, J.C.P. Sly: J. Chem. Soc., **1961**, 4560; J. Attenburrow, J.E. Connett, W. Graham, J.F. Oughton, C. Ritchie, P.A. Wilkinson: *Ibid.*, **1961**, 4547. *d*) S. Bernstein, M. Heller, F.J. McEvoy, S.M. Stolar: J. Org. Chem., **26**, 505 (1961). *e*) S. Bernstein, R. Littell: *Ibid.*, **26**, 3610 (1961).

2) *a*) W. Nagata, T. Terasawa, S. Hirai, K. Takeda: Tetrahedron Letters, No. 17, 27 (1960). *b*) W. Nagata, S. Hirai, T. Terasawa, I. Kikkawa, K. Takeda: This Bulletin, **9**, 756 (1961). *c*) J.P. Kutney, Wm. McCrae, A. By: Canad. J. Chem., **40**, 982 (1962).

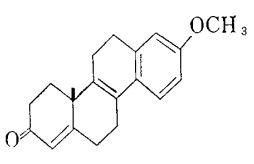
3) cf. W.S. Johnson, E.R. Rogier, J. Szmuszkovics, H.I. Hadler, J. Ackerman, B.K. Bhattacharyya, B.M. Bloom, L. Stalmann, R.A. Clement, B. Bannister, H. Wynberg: J. Am. Chem. Soc., **78**, 6289 (1956).

4) A.L. Wilds, N.A. Nelson: *Ibid.*, **75**, 5360 (1953).

5) cf. L. Velluz, B. Goffinet, J. Warnant, G. Amiard: Bull. Soc. chim. France, 1289 (1957).

6) cf. C. Djerassi, G. Rosenkranz, F. Sondheimer: J. Am. Chem. Soc., **76**, 4092 (1954).

7) W. Nagata, M. Yoshioka, S. Hirai: Tetrahedron Letters, No. 11, 461 (1962).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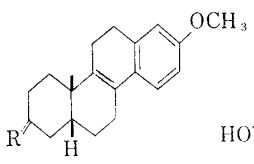
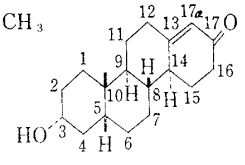

II : R=O
III : R=H, OH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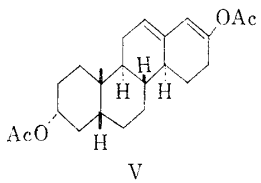
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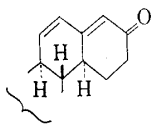
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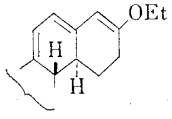
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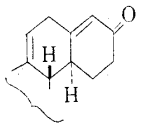
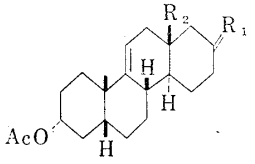
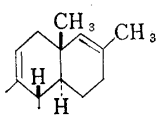

VIII


IX : R_1=O, R_2=CN
X : R_1=ketal, R_2=CN
XI : R_1=ketal, R_2=CHO
(3α-OH instead of OAc)
XII : R_1=ketal, R_2=CH_3
XIII : R_1=O, R_2=CH_3
XIV : R_1=OH, CH_3, R_2=CH_3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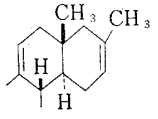
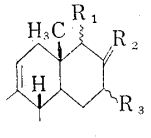
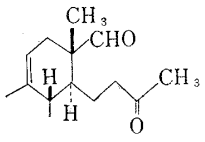
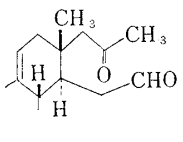
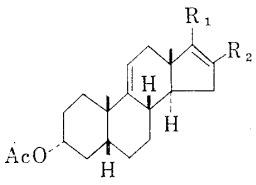

XVI


XVII, XVIII : R_1=OH, R_2=OH, CH_3, R_3=H
XIX, XX : R_1=H, R_2=OH, CH_3, R_3=OH


XXI


XXII


XXIII : R_1=H, R_2=$COCH_3$
XXIV : R_1=$COCH_3$, R_2=H

reported procedure.[2a,8] The cyano ketone (IX) was easily transformed by the usual method into the ketal (X), m.p. 251~252°, IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2248, 1725. Reduction of the latter with lithium aluminum hydride at room temperature, followed by alkaline hydrolysis gave the 13β-formyl compound (XI), which without purification was subjected to Huang-Minlon reduction followed by acetylation to give the 13β-methyl compound (XII), m.p. 125~127°, IR : $\nu_{max}^{CHCl_3}$ 1715 cm^{-1}. The compound (XII) was deketalized with dilute acetic acid to give *dl*-3α-acetoxy-D-homo-5β-androst-9(11)-en-17-one (XIII), m.p. 155~156.5°, IR: $\nu_{max}^{CHCl_3}$ 1710 cm^{-1} (broad). The overall yield of the last comopund (XIII) from the cyano ketone (IX) was 50%.

Contraction of the ring D was performed in the same manner employed by us in the total synthesis of *dl*-3β-hydroxy-5α-pregn-16-en-20-one.[8a,9] Stereoselective addition of methyl magnesium iodide to the ketone (XIII) and subsequent acetylation, gave the methyl carbinol (XIV), m.p. 184~186°, IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3600, 1720, in 76% yield. Treatment of the latter compound with phosphorus oxychloride in pyridine yielded a mixture of the

8) *a*) W. Nagata, I. Kikkawa, K. Takeda : This Bulletin, **9**, 79 (1961). *b*) W. Nagata : Tetrahedron, **13**, 287 (1961). *c*) W. Nagata, S. Hirai, H. Itazaki, K. Takeda : Liebigs Ann. Chem., **641**, 196 (1961).
9) W. Nagata, T. Terasawa, S. Hirai, K. Takeda : Tetrahedron, **13**, 295 (1961).

dehydrated olefines, XV and XVI, in a ratio of about 2.3:1 on the basis of gas-liquid chromatographic analysis.*6 However, a reverse ratio of XV to XVI (1:2.2), favourable to attaining the present object, was obtained by refluxing the mixture in benzene in the presence of *p*-toluenesulfonic acid.[10] Osmium tetroxide hydroxylation of the thus obtained mixture gave four *cis*-glycols, XVII, m.p. 183~185°, XVIII, m.p. 181~183°, XIX, m.p. 205~207°, and XX, m.p. 196~197°, which were separated on alumina. The ratio of the combined yield of the first two glycols, originated from the Δ^{17}-compound (XV), to that of the last two, originated from the isomeric Δ^{16}-derivative (XVI), was about 1:1.8. This ratio agrees well with the above mentioned gas chromatographic result.

Both glycols, XIX and XX, underwent periodic acid oxidation and gave the same oily keto aldehyde (XXII), IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2700, 1715, showing the original diols were epimeric. Ring closure of this crude keto aldehyde was effected by refluxing it in xylene containing triethylamine acetate to give the expected steroids, *dl*-3α-acetoxy-5β-pregna-9(11),16-dien-20-one (XXIV), m.p. 153~155°, UV λ_{max}^{EtOH} mμ (ε) : 206 (4880), 238 (6960), IR $\nu_{max}^{CS_2}$ cm^{-1}: 1725, 1660. The infrared and ultraviolet spectra of this compound are identical with those of an authentic sample of the natural steroid.[11] Finally, the other two epimeric glycols, XVII and XVIII, were cleaved in the same manner to give the same oily keto aldehyde (XXI), IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2680, 1715, which was then cyclized to *dl*-16-acetyl-5β-androsta-9(11),16-dien-3α-ol acetate (XXIII), m.p. 116~117°, UV λ_{max}^{EtOH} mμ (ε) : 206 (4730), 238 (9690), IR $\nu_{max}^{CS_2}$ cm^{-1} : 1728, 1660.

We wish to thank Dr. K. Takeda for his encouragement and interest in this work.

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March 25, 1963

*6 Gas-liquid chromatographic analysis was carried out by Dr. N. Ikekawa (Institute of Physical and Chemical Research, Tokyo). We express our thanks for this courtesy and for the valuable discussion on the result.

10) cf. L. Velluz, G. Amiard, R. Heymes, B. Goffinet : Bull. Soc. chim. France, 2166 (1961).
11) S.A. Szpilfogel, V. Gerris : Rec. Trav. Chem., **74**, 1462 (1955).

UDC 581.19:582.288

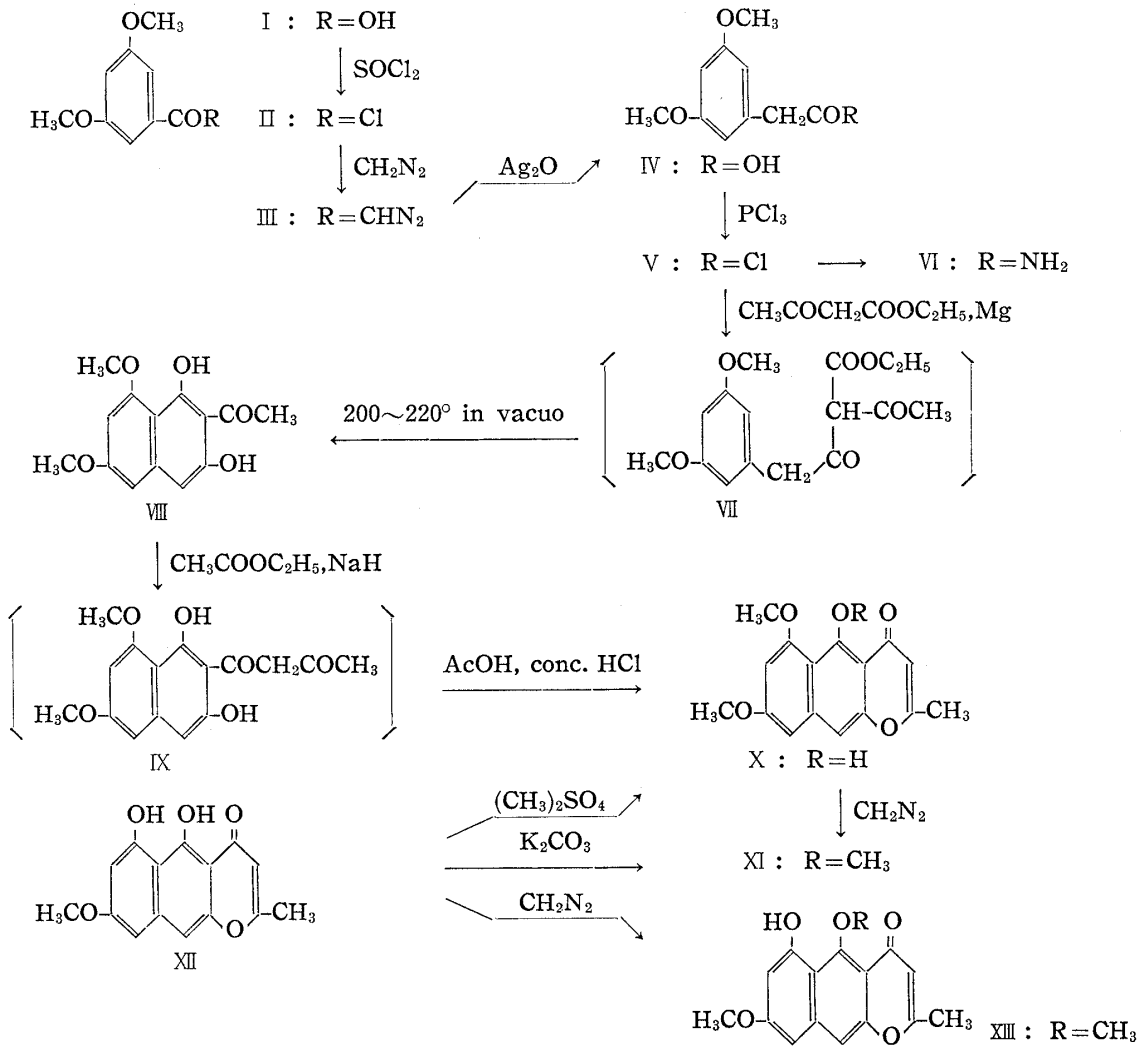
Synthesis of Rubrofusarin Dimethyl Ether

Rubrofusarin was isolated first by Raistrick, *et al.*[1] as orange red crystals, m.p. 214.5~215.5°, from *Fusarium culmorum* (W. G. Smith) Sacc. and some related *Fusarium* spp.

The structure of rubrofusarin (XII) was established by Stout and Dreyer[2] in X-ray analysis, and almost the same time by Tanaka and Tamura[3] by chemical reactions.

In the present study, the synthesis of rubrofusarin dimethyl ether has been carried out by the following scheme :

1) J.N. Ashley, B.C. Hobbs, H. Raistrick : Biochem. J., **31**, 385 (1937).
2) G.H. Stout, D.L. Dreyer, L.H. Jensen : Chem. & Ind. (London), 289 (1961); Acta Cryst., **15**, 451 (1962).
3) H. Tanaka, T. Tamura, Y. Ohne, N. Ogawa : Tetrahedron Letters, No. 4, 151 (1961); Agr. Biol. Chem., **27**, 48 (1963).



3,5-Dimethoxybenzoyl chloride[4] (II), m.p. 30~32°, was subjected to the Arndt-Eistert reaction to obtain a diazoketone (III), m.p. 71~72°, which was converted into 3,5-dimethoxyphenyl acetic acid[5] (IV), m.p. 100~101°, by the action of silver oxide. The acid chloride[5] (V) which was characterized as the acid amide (VI), m.p. 126~127°, (*Anal.* Calcd. for $C_{10}H_{13}O_3N$: C, 61.54; H, 6.66; N, 7.18. Found : C, 61.99; H, 6.70; N, 7.13), was reacted with ethyl acetoacetate and magnesium in abs. benzene by the Spassow reaction to yield ethyl 2-(3,5-dimethoxyphenylacetyl)acetoacetate (VII).

On vacuum distillation of VII, 2-acetyl-6,8-dimethoxy-1,3-naphthalenediol (VIII), yellow prisms, m.p. 194°, was afforded (Yield : 16.5%, calcd. from IV) (*Anal.* Calcd. for $C_{14}H_{14}O_5$: C, 64.12; H, 5.34. Found : C, 64.20; H, 5.31. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3320 (OH); 1650 (C=O)), which gave a dark green color with ferric chloride and dark red color with Gibbs' reagent.

The naphthalene derivative (VIII) was subjected to the Claisen condensation with ethyl acetate using sodium hydride to yield 2-acetoacetyl-6,8-dimetoxy-1,3-naphthalenediol (IX) which was cyclized by the action of acetic acid and hydrochloric acid to afford 2-methyl-5-hydroxy-6,8-dimethoxy-4*H*-naphtho[2,3-*b*]pyran-4-one (X), orange yellow needles, m.p. 213° (*Anal.* Calcd. for $C_{16}H_{14}O_5$: C, 67.13; H, 4.89. Found: C, 67.08; H, 4.81) giving a green

4) J.C. Roberts, *et al.* : J. Chem. Soc., **1955**, 2784; *Ibid.*, **1962**, 2063.
5) F. Mauthner : J. prakt. Chem. (2), **110**, 127 (1925); A.J. Birch, *et al.* : Austral. J. Chem., 8, 529 (1955).