This observation indicated that the configurational relationship between two hydroxyl groups at C_8 and C_{15} in serratanidine is *trans*. However, it is still obscure which hydroxyl group is situated in the β configuration. This ambiguity was solved by the following experiment.

Treatment of serratanidine (IV) with phosgene in pyridine afforded serratanidine carbonate (XIII), mp 277—278°, $C_{17}H_{23}O_5N$, IR ν_{max} cm^{-1}: 3050 (OH), 1747 (C=O). IR spectral data showed that the carbonyl group in this carbonate ester is situated on the six membered ring or larger. The formulae (XIII) and (XIV) for serratanidine carbonate are still possible but the latter was excluded by the following NMR observations. The NMR spectrum of the carbonate in DMSO revealed three signals at 6.28 (1H, br. d., J=4 cps, >C<u>H</u>–OH), 5.55 (1H, br. d., J=4.3 cps, >C<u>H</u>–OCO–), 4.26 (1H, d., J=4 cps, –O<u>H</u>) and the last signal disappeared by treatment with D_2O, suggesting that the free hydroxyl group in the carbonate is the secondary one. The double resonance technique supported also the correctness of this assignment. These observations show clearly the *cis* relationship between the C_{13} and C_{15} hydroxyl group.

Since the absolute configuration of serratinine (I) which was correlated with serratanidine through the compound (VI) with the original hydroxyl group at C_{13} intact, has been firmly established, the absolute stereostructure of serratanidine should be represented by the formula (IV) and *cis*–diol–A which seems to arise from (VIII) by attack of OsO_4 from the less hindered α side, is depicted by the formula (IX).

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Synthesis of Ecdysone

Insect moulting hormone ecdysone (I) was isolated in pure state in 1954 by Butenandt and Karlson[1] and its chemical structure was elucidated as 2β,3β,14α,22β_F, 25–pentahydroxy–5β–cholest–7–en–6–one (I) by X–ray analysis in 1965.[2] Only one year after establishment of structure, two groups[3,4] succeeded in the synthesis of ecdysone. In our program to synthesize ecdysone, its chemical structure was divided in three partial structures, namely, A–ring (II), B,C–ring (III) and side chian (IV) structure, and novel and improved methods of preparation of these partial structures were developed, two of these methods being already reported. We now succeeded in synthesis of ecdysone by using above–mentioned methods.

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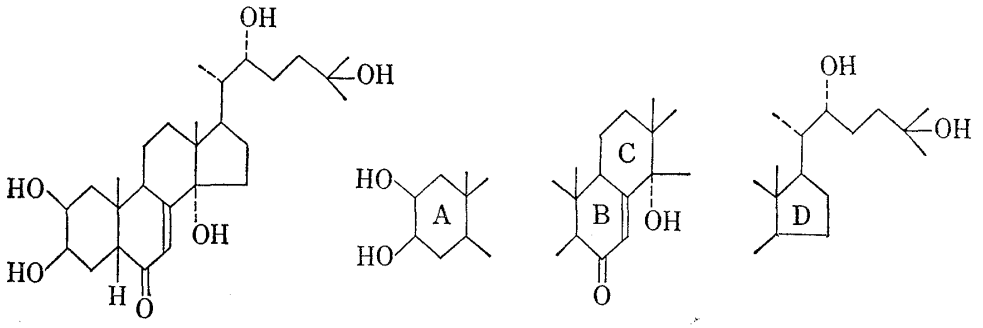
2) R. Huber and W. Hoppe, *Chem. Ber.*, **98**, 2403 (1965).
3) J.B. Siddall, J.P. Marshall, A. Bowers, A.D. Cross, J.A. Edwards, and J.H. Fried, *J. Am. Chem. Soc.*, **88**, 379 (1966). J.B. Siddall, A.D. Cross, J.H. Fried: *ibid.*, **88**, 862 (1966).
4) U. Kerb, P. Hocks, R. Wiechert, A. Furlenmeier, A. Fürst, A. Langemann, and G. Waldvogel, *Tetrahedron Letters*, **1966**, 1387.



ecdysone (I) II III IV

Chart 1

Stigmast-22-ene-3,6-dione (V)[5] was served as a starting material, which was introduced into diketal (VI) (mp 119—121°, $[\alpha]_D^{26}$ −3°) by the usual method. Ozonolysis of VI, followed by treatment with zinc dust in acetic acid,[6] gave diketal aldehyde (VII) (mp 172—175°, $[\alpha]_D^{31}$ −2°). Reaction of VII with ethynylmagnesium bromide afforded ethynyl compound (VIII) as a mixture of 22-isomers, which was treated with methylmagnesium bromide and then shaken with carbon dioxide to give unsaturated acid (IX). Without isolation of isomeric carboxylic acids, IX was catalytically hydrogenated with 10% palladium-charcoal and hydrolyzed by 50% acetic acid to a mixture of isomeric dioxolactone. This mixture was again converted into 3,6-diketal, which was treated with hydrochloric acid in mild condition to give a sparlingly soluble 3-monoketal of dioxolactone (X) (mp 314—317°, $[\alpha]_D^{16}$—9°). This mono ketal (X) was found to be 22β_F-lactone[7] and, accordingly, an important key intermediate in ecdysone synthesis. From mother liquor, another isomeric dioxolactone (XXIII) (mp 270—277°, $[\alpha]_D^{31}$ +28°) was isolated as completely hydrolyzed compound (3,6-dione).

The 3-mono ketal (X) was hydrolyzed with *p*-toluenesulfonic acid in aqueous acetone to 3,6-dione (XI) (mp 243—246°, $[\alpha]_{578}^{20}$ +6°), which was partially reduced with one equivalent volume of sodium borohydride in ethanol-methylene chloride at −5° for 30 minutes to give 3β-hydroxy-6-one (XII) (mp 222—223°, $[\alpha]_{578}^{20}$ −7°). Ketalization of XII into oily 6-ketal (XIII), followed by oxidation with pyridine-chromium trioxide complex, led to 6-monoketal of 3,6-dione (XIV) (mp 224—228°, $[\alpha]_{578}^{20}$ +28°).

Introduction of 2β,3β-dihydroxyl grouping in this lactone series was made according to the method reported already from this laboratory.[8] Autoxidation of XIV in the presence of potassium *tert*-butoxide in *tert*-butanol afforded a mixture of two possible enol compounds of 2,3-dione (XV) as oily substance. Reduction of enol mixture (XV) with sodium borohydride in methanol, followed by treatment with *p*-toluenesulfonic acid in methanol, led to a mixture of 2,3-diol, from which pure 2β,3β-dihydroxy-6-one (XVI) (mp 254—258°, $[\alpha]_{578}^{20}$ 0°) was isolated in pure state by preparative thin-layer chromatography in satisfactory yield. The proof of the structure depends upon the fact that this diol (XVI) could be converted easily into an acetonide (XXIV) (mp 238—241°, $[\alpha]_{578}^{20}$ +17°), which on hydrolysis recovered the starting material (XVI), and analogy with chemical transformations in the corresponding cholestane series.[8] Acetylation of XVI with hot acetic anhydride gave the diacetate (XVII) (mp 230—233°, $[\alpha]_{578}^{20}$ +4°).

Bromination of XVII with one equivalent volume of bromine in acetic acid and successive warming at 50° for 2 hours afforded crude 7-bromo compound (XVIII). Crude XVIII

5) E. Fernholz, *Ann.*, **508**, 215 (1934).
6) G. Slomp, Jr. and J.L. Johnson, *J. Am. Chem. Soc.*, **80**, 915 (1958).
7) The assignment of the configuration of C-22 hydroxyl group in X and XXIII was based upon the fact that ecdysone and isoecdysone were synthesized from X and XXIII, respectively.
8) H. Mori, K. Shibata, K. Tsuneda, and M. Sawai, *Chem. Pharm. Bull.* (Tokyo), **15**, 460 (1967). H. Mori, K. Tsuneda, K. Shibata, and M. Sawai, *ibid.*, **15**, 466 (1967).

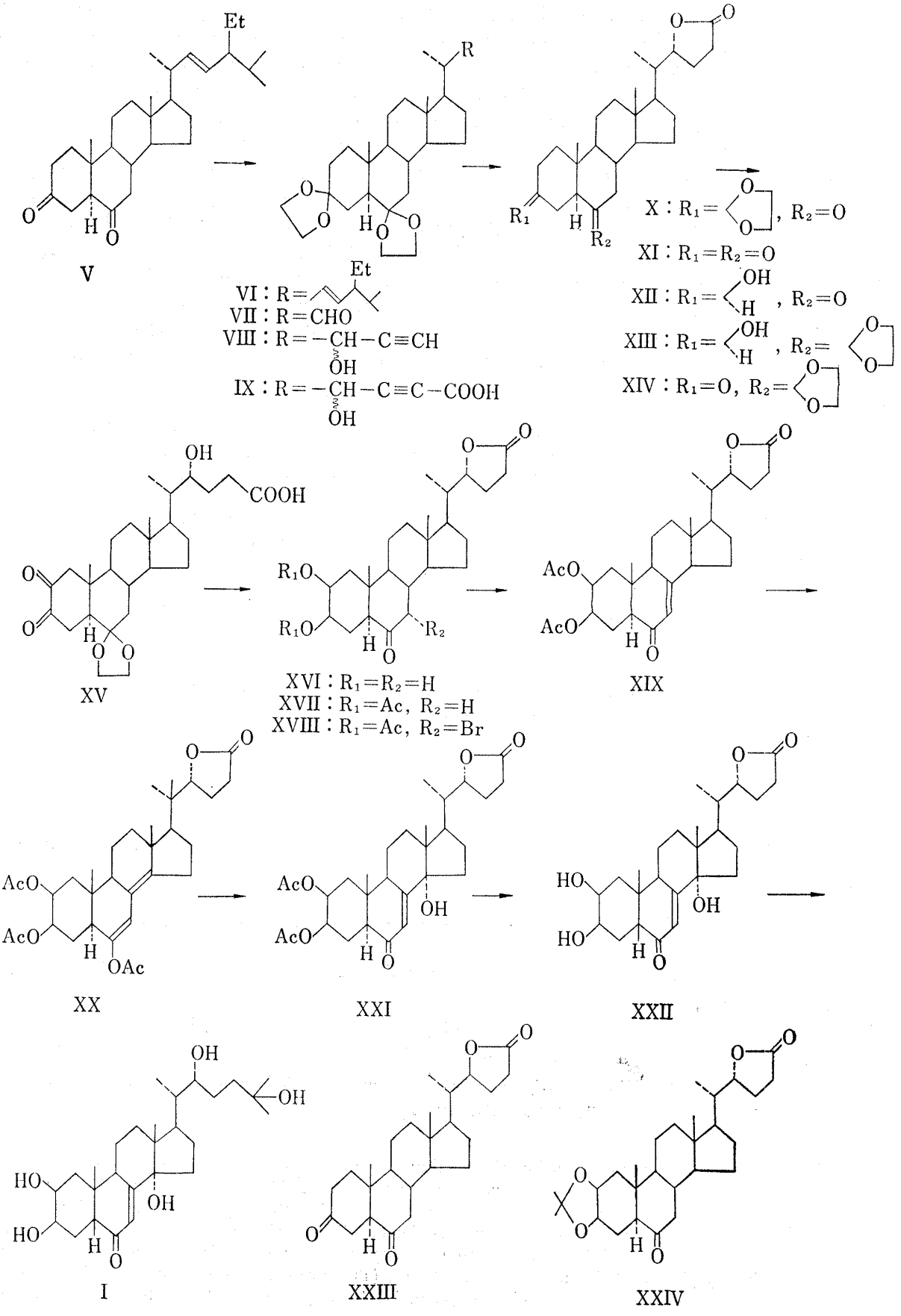


Chart 2

was treated with lithium carbonate in dimethylformamide to afford 7-en-6-one (XIX) (mp 271—274°, $[\alpha]_{578}^{20}$ +20°, UV λ_{max}^{EtOH} (e) 244 mμ (14200)). A hydroxyl group was introduced at C-14 in XIX by a novel method developed in this laboratory,[9] that is, enol acetylation of XIX with acetic anhydride in the presence of a small amount of perchloric acid in ethyl acetate[10] afforded an enol acetate (XX) as an oily substance, which was oxidized with 1.3 equivalent of monoperphthalic acid in ether–tetrahydrofuran mixture to 14α-hydroxy-7-en-6-one (XXI) (mp 269—272°, $[\alpha]_{578}^{20}$ +70°, UV λ_{max}^{EtOH} (e) 240 mμ (12700)).

Hydrolysis and isomerization (at C-5) of XXI with 0.6% potassium carbonate in 90% methanol at reflux temperature for 30 minutes gave 2β,3β,14α-trihydroxy-7-en-6-ones as an equilibrium mixture. From this equilibrium mixture, which consisted of 5β- and 5α-compound at a ratio of 4:1,[11] 5β-isomer (XXII) (mp 264—266°, $[\alpha]_{578}^{20}$ +79°, UV λ_{max}^{EtOH} (e) 243 mμ (10600)) was isolated by preparative thin-layer chromatography. Grignard reaction of XXII with a large excess of methylmagnesium bromide in tetrahydrofuran at 0° for 30 minutes afforded ecdysone (I) (mp 238—239°, $[\alpha]_{578}^{20}$ +62°, UV λ_{max}^{EtOH} (e) 243 mμ (11600)) identical in all physical properties (melting point, optical rotation, UV, IR, NMR and MS) with those reported for the natural product.

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UDC 547.833.3.04

Ferricyanide Oxidation of *dl*-N-Methylisosalsoline and Its Methiodide[1]

In connection with a preceding work,[2] ferricyanide oxidation of *dl*-N-Methylisosalsoline (I) and its methiodide (II) was examined.

To a stirred solution of I (1.56 g, 7.5 mmole) in dioxane (64 ml) and 2.8% aq. NH_4OH (160 ml) was added powdered $K_3Fe(CN)_6$ (5.6 g, 17.0 mmole). After two hr's agitation at room temperature followed by standing for 1 hr, the reaction mixture was treated with K_2CO_3 (powder) and the product was extracted with $CHCl_3$.

1) All melting points were uncorrected using a Yanagimoto micro melting point measuring apparatus. All nuclear magnetic resonance (NMR) spectra were taken with a JNR-C60S spectrometer and the chemical shifts were τ-value measured from DSS as internal standard. Mass spectrometory (MS) spectrum was measured with a Hitachi mass spectrometer Model RMU-6D. Gas liquid chromatography (GLC) was run with a Shimadzu GC-1C gaschromatograph (hydrogen flame ionization detector) on 1.5% OV-17 as stationary phase. Thin-layer chromatography (TLC) were carried out on silicagel G (Merck), developing solvents: *a*) conc. NH_4OH–MeOH (1:20) for tertiary and *b*) 10% HCl–MeOH (1:2) for quaternary amines.
2) B. Umezawa, O. Hoshino, H. Hara, and J. Sakakibara, *Chem. Pharm. Bull.* (Tokyo), **16**, 381 (1968).