BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 39 2503—2508 (1966)

The Synthesis of an Etiojervane Analog of Progesterone[1]

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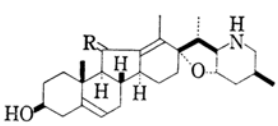
(Received March 25, 1966)

N-Acetyl-22, 27-iminojerva-5, 12-diene-3β, 23α-diol-11-one, prepared from jervine by Masamune et al. (*J. Org. Chem.*, **29**, 2282 (1964)), was submitted to a Birch reduction and then to a modified Wolff-Kishner reduction to yield 22, 27-iminojerv-5-ene-3β, 23α-diol. The compound was then degraded, according to the procedure by Johnson et al. (*Tetrahedron Letters*, **1963**, 545), to a methyl ketone, which was then further oxidized by the Oppenauer method to give 17α-ethyletiojerv-4-ene-3, 20-dione.

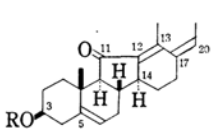
In the past decade considerable attention has been paid to the modification of the basic steroid skeleton of hormones in search of analogs with enhanced or more specific physiological properties. In view of the natural occurrence[2] of the C-nor-D-homosteroid ring system, the synthesis of hormone analogs seemed to be a particularly attractive subject. Etiojervane[3] analogs of testosterone, epiandrosterone and so on have recently been prepared, using the available hecogenin and/or jervine as the starting materials.[4-6] In the present paper we will describe the synthesis of C-nor-D-homoprogesterone.

Jervine (I), one of the most readily-available veratrum alkaloids, was selected as the starting material for our investigation. Two processes for the degradation of I to nitrogen-free compounds have been reported in the literature. One, which was developed by Fried et al.[7] and improved by Okuda et al.[8] and by us,[9] involves the fragmentation of I, by treatment with Lewis acids, to 17-ethyletiojerva-5, 12, 17(20)-terien-3β-ol-11-one (II).

It was deemed efficient to utilize the ethylidene moiety of II to prepare an acetyl side chain of progesterone, and it was attempted to reduce the 12, 13-double bond selectively. The double bond could not be hydrogenated catalytically, however, without a concomitant reduction of the 17, 20-double bond. The Birch reduction of II gave rise to a mixture containing a considerable amount of the starting material (II), from which only a compound, $C_{21}H_{30}O_2$, m. p. 236—237°C, showing a peak at 1730 cm^{-1}, could be isolated in a very low yield. Next, the selective reduction of the 12, 13-double bond in the glycol[10] (III) prepared from II was reexamined under various conditions, as a glycol system would be converted into an acetyl group by the Serini reaction.[11] However, neither the Birch reduction nor the catalytic hydrogenation of III was shown to be of any value in the proposed synthesis.[10] The treatment of the glycol acetate (IIIa) with alkali yielded a multicomponent mixture, from which only etiojerv-5-ene-3, 11, 17-trione 3-ketal[4] (IV), formed by fission of the 17, 20-bond, was isolated, in a moderate yield, by chromatography.



I: R=O
VI: R=H_2



II

1) Part VI of "C-Nor-D-homosteroids and Related Alkaloids"; Part V: T. Masamune, I. Yamazaki and M. Takasugi, This Bulletin, **39**, 1090 (1966).

2) Most of the veratrum alkaloids and the fritillaria alkaloids possess this modified skeleton; C. R. Narayanan, "Progress in the Chemistry of Organic Natural Products," Vol. XX, Springer-Verlag, Wien (1962), p. 298; H, G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie-Verlag, Berlin (1961), p. 758.

3) The designations "etiojervane and jervane" will be used to describe 17aβ-methyl-C-nor-D-homo-18-nor-5α, 13α-androstane and the corresponding cholestane analog respectively; cf. Ref. 4, 5 and 7.

4) S. M. Kupchan and S. D. Levine, *J. Am. Chem. Soc.*, **86**, 701 (1964).

5) W. F. Johns and I. Laos, *J. Org. Chem.*, **30**, 4220 (1965) and the references cited there.

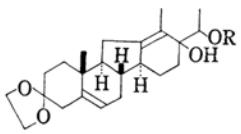
6) H. Mitsuhashi and N. Kawahara, *Tetrahedron*, **21**, 1215 (1965), and the references cited there.

7) J. Fried and A. Klingsberg, *J. Am. Chem. Soc.*, **75**, 4929 (1953).

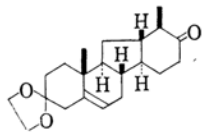
8) S. Okuda, K. Tsuda and H. Kataoka, *Chem. & Ind.*, **1961**, 512.

9) Footnote 8 of Ref. 4.

10) S. M. Kupchan, T. Masamune and G. W. A. Milne, *J. Org. Chem.*, **29**, 755 (1964).



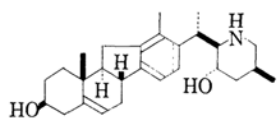
III: R=H
IIIa: R=Ac



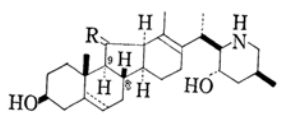
IV

The other degradation process was developed by Johnson et al.;[12] it requires the presence of hydroxyl and secondary amino group in the nitrogen ring as in that of veratramine (V). However, V would not be an appropriate starting material, in view of the yield in isolation from natural plants or in chemical preparations.[13,14] On the other hand, in order to obtain intermediates suitable for degradation from the readily-available alkaloids, jervine (I) or 11-deoxojervine[14] (VI), it was necessary to cleave the ether linkage in those compounds. A reexamination of the references revealed that the fission of the ether linkage took place in several ways.[13-17] The following two reactions appeared to be effective, considering the yields and stabilities of the products; the Birch reduction of I to 8, 9-dihydroisojervine[17] (VII), and the catalytic hydrogenation of VI over platinum in acetic acid to 11-deoxo-5, 6, 8, 9-tetrahydroisojervine[18] (VIII).

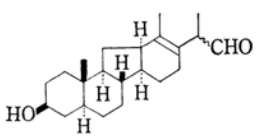
The degradation of VIII was first undertaken, as VIII possessed no oxygen function on C-11 and appeared to be suitable for the present plan. VIII was converted to a *N*-chloro derivative with *N*-chlorosuccinimide, which gave, when treated with sodium methoxide and then hydrolyzed with acid, an aldehyde (IX) in an over-all yield of 89%. The aldehyde was further degraded, with *n*-butyl nitrite and sodium *n*-butoxide in *n*-butanol, to an oxime, which was extracted with 2 N aqueous sodium hydroxide solution and then purified by acetylation with acetic anhydride and pyridine. The acetate, m. p. 139—140°C, obtained in a 35% yield from IX, exhibited, in agreement with the assigned structure of X, strong peaks at 1788 (*N*-acetoxyl) and 1737 cm^{-1} (3-acetoxyl) in the infrared spectrum and five sharp singlets at τ 7.38, 7.71, 7.99, 8.31 and 9.39 in the NMR spectrum. The singlets were attributed to the 21-methyl, *N*-acetoxyl, 3-acetoxyl, 18-methyl and 19-methyl groups respectively. However, an attempted hydrolysis of the oxime to a ketone was unsuccessful; the treatment of the crude oxime with hydrochloric acid in refluxing ethanol gave a compound with a m. p. of 157°C, in a 40% yield; this compound showed no strong absorption in the carbonyl region of the infrared spectrum. It might probably be an isooxazoline derivative. Next, the oxime acetate (X) was heated in glacial acetic acid on a water bath; it yielded a crystalline material, which showed two superimposable spots on thin layer-chromatograms and which resisted further purification. Furthermore, the elemental analysis showed that it contained almost the same percentage of nitrogen as the original acetate, indicating no fission of the C–N bond.



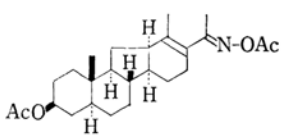
V



VII: R=O, Δ^5
VIII: R=H_2, 5αH



IX



X

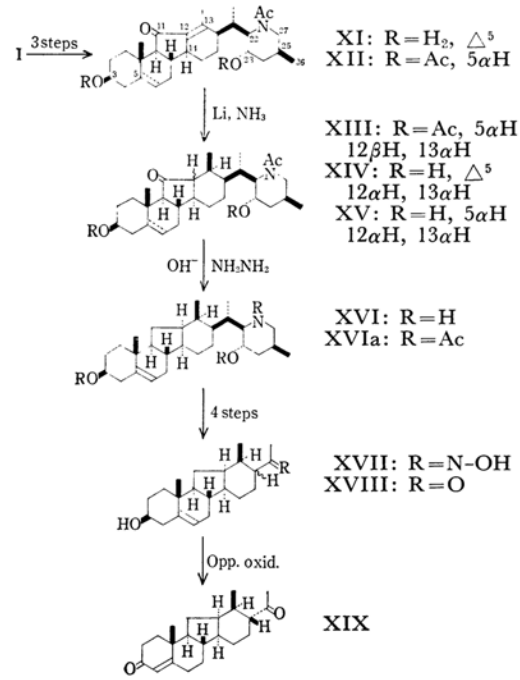
The preparation of 8, 9-dihydroisojervine (VII) by the Birch reduction[17] of I was improved by replacing the dioxane used previously as a solvent by tetrahydrofuran. The acetylation of VII, followed by hydrolysis and isomerization with alkali, proceeded smoothly, and afforded an α, β-unsaturated ketone (XI) in a good yield.[17] The next step in the synthesis required the reduction

11) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publ. Corp., New York, N. Y. (1959), p. 628.
12) R. W. Franck and W. S. Johnson, *Tetrahedron Letters*, **1963**, 545.
13) T. Masamune, Y. Mori, M. Takasugi and A. Murai, ibid., **1964**, 913.
14) T. Masamune, Y. Mori, M. Takasugi, A. Murai, S. Ohuchi, N. Sato and N. Katsui, This Bulletin, **38**, 1374 (1965).
15) a) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **75**, 4938 (1953); O. Wintersteiner and M. Moore and B. M. Iselin, ibid., **76**, 5609 (1954); B. M. Iselin and O. Wintersteiner, ibid., **76**, 5619 (1954); O. Wintersteiner and M. Moore, *J. Org. Chem.*, **29**, 262 (1964). b) O. Wintersteiner and M. Moore, *Tetrahedron*, **21**, 779 (1965).
16) W. G. Dauben, W. W. Epstein, M. Tanabe and B. Weinstein, *J. Org. Chem.*, **28**, 293 (1963).
17) T. Masamune, M. Takasugi, M. Gohda, H. Suzuki, S. Kawahara and T. Irie, ibid., **29**, 2282 (1964).
18) T. Masamune, M. Takasugi and Y. Mori, *Tetrahedron Letters*, **1965**, 489. It was suggested in the reference that a double bond would exist at C-13-C-17. This disposition was confirmed by the transformation of VIII to 11-deoxo-5, 6-dihydrojervine. It will be discussed later (T. Masamune and A. Murai, unpublished results).

of the 12, 13-double bond. Wintersteiner and Moore[15b] observed that the double bond in a 5, 6-dihydro derivative (XII) of XI could be hydrogenated over platinum in acetic acid. However, the product (XIII) was unstable to alkali and readily isomerized.[19] Furthermore, it was supposed that the hydrogenation of the 12, 13-double bond in XI under the aforementioned conditions would accompany the reduction of the 5, 6-double bond. Thus, XI was treated with lithium in liquid ammonia. It produced the corresponding 12, 13-dihydro derivative (XIV), m. p. 148—149°C. The assigned structure was confirmed by a stong absorption at 1737 cm^{-1} in the infrared spectrum and by a broad peak (1H) at τ 4.63 in NMR spectrum. The over-all yield from I to XIV was 40% (4 steps). With the purpose of confirming the stereochemistry, XIV was hydrogenated over platinum in acetic acid. The product, obtained in a good yield, was found to be identical with 22, 27-iminojervane-3β-23α-diol-11-one *N*-acetate (XV), the configuration of which had been established by Wintersteiner and Moore.[19] Thus, both the hydrogens on C-12 and C-13 in XIV were proved to have an α-configuration.

In order to prepare a progesterone analog, the reduction of the 11-carbonyl to methylene group was necessary. A modification of the Huang-Minlon procedure for the Wolff-Kishner reduction of XIV resulted in the removal of the oxygen on C-11, with the concomitant hydrolysis of the *N*-acetyl group; 22, 27-iminojerv-5-ene-3β, 23α-diol (XVI), m. p. 221—223°C, was isolated in a 60% yield after purification. Since XIV was recovered unchanged by reflux with alkali in a mixture of dimethylsulfoxide and diethylene glycol, no epimerization is considered to take place at the carbons adjacent to C-11 during the reduction. A comparison of the NMR spectrum of the triacetate (XVIa), m. p. 155—156°C, with that of XIV supports this conclusion; in the former, the signal due to the 19-methyl protons appeared at τ 9.03, while the corresponding signal of the latter appeared at τ 8.98. The magnitude of the downfield shift caused by the 11-carbonyl function was almost equal to the deshielding effect (0.07 p.p.m.) of a 11-ketonic group found in the study of the NMR spectra of a series of 22, 27-imino-17, 23-oxidojervane derivatives[20]; it was remarkably different from the corresponding effects in compounds possessing a B/C *cis*-fused linkage.[21]

The next step of the synthesis was the degradation of XVI; this was carried out in the way described above to yield an oxime (XVII), m. p. 192—193°C, in a 60% yield from XVI (4 steps). No trouble was encountered in the hydrolysis of XVII; treatment with a mixture of pyruvic acid and acetic acid gave a crude methyl ketone (XVIII) which, in turn, was submitted to the Oppenauer oxidation. Chromatographic purification yielded 17α-ethyletiojerv-4-ene-3, 20-dione (XIX), m. p. 168—169°C, in a 21% yield from XVII (2 steps). In accord with the assigned structure, this C-nor-D-homoprogesterone had prominent peaks at 1715 (20-carbonyl), 1663 (3-carbonyl) and 1616 cm^{-1} (conjugated double bond) in the infrared spectrum, and an absorption maximum at 237 mμ (ε 20200) in the ultraviolet spectrum. It also exhibited two singlets, at τ 8.87 and 7.86 (each 3H, the 19- and 21-methyl groups respectively) and one doublet (3H, J=6 c. p. s., the 18-methyl group) in the NMR spectrum. The acetyl side chain was assigned the α-configuration for the following reasons. The side chain at C-17 of XVI had the β-configuration and was *cis*-oriented relative to the methyl group at C-13. If the acetyl group in XIX had the same (β) configuration, treatment with alkali would cause epimerization at C-17. However, XIX was recovered unchanged after attempts to effect the epimerization by heating XIX under reflux in a 5% methanolic potassium hydroxide solution for 2 hr. This fact indicates that both the methyl at C-13 and the acetyl function at C-17 possess the equatorial conformation and are *trans* to each other. Hence, the acetyl group must have the



19) O. Wintersteiner and M. Moore, *Tetrahedron*, **20**, 1947 (1964).
20) T. Masamune, N. Sato, K. Kobayashi, I. Yamazaki and Y. Mori, ibid., in press. The deshielding effects of the 3β-acetoxyl and 3β-hydroxyl groups are 0.03 and 0.02 p. p. m. respectively.
21) J. P. Kitney, A. By, T. Inaba and S. Y. Leong, *Tetrahedron Letters*, **1965**, 2911; D. M. Bailey, D. P. G. Hamon and W. S. Johnson, ibid., **1963**, 555.

α-configuration, and the epimerization must have taken place during the hydrolysis or the Oppenauer oxidation.

Experimental

The melting points are uncorrected. The optical rotations and the ultraviolet spectra were measured in 95% methanol and 99% ethanol, and the infrared spectra, in Nujol, unless otherwise stated. The NMR spectra were taken in deuterochloroform at 60 Mc., using tetramethylsilane as an internal standard.

The Alkali Treatment of 17-Ethyletiojerva-5, 12-diene-17, 20-diol-3-one 20-Acetate 3-Ethylene Ketal[10] (IIIa).—To dioxane (5 ml.) containing IIIa (0.2 g.), a 1N aqueous sodium hydroxide solution (5 ml.) was added, and then the whole solution was refluxed for 40 min. After the solvent had been removed, the residue was treated with water and three 10 ml. portions of chloroform. The chloroform solution gave, after it had been washed with water, dried with anhydrous sodium sulfate and evaporated to dryness, an oily substance (0.22 g.) which was then chromatographed on alumina (2.0 g.). Fractions eluted with petroleum ether and a mixture of petroleum ether and benzene (1 : 1) crystallized and amounted to 0.15 g. Repeated recrystallizations from *n*-hexane afforded etiojerv-5-ene-3, 11, 17-trione 3-ethylene ketal (IV, 0.05 g.), m. p. 156—157.5°C, which was identical with a sample prepared according to the literature.[4] IR (chloroform): ν_{max} 1738, 1714, 1104 and 1083 cm^{-1}.

Found: C, 73.32; H, 8.30. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19%.

11-Deoxo-5, 6, 8, 9-tetrahydroisojervine (VIII) and the 3, 23, *N*-Triacetyl Derivative. — When 11-deoxojervine[14] (VI; 7.01 g.) was hydrogenated in the presence of pre-reduced Adams' platinum (2.23 g.) at room temperature in acetic acid (140 ml.), 832 ml. of hydrogen (2.05 mol.) was absorbed after 29 hr. After the catalyst and the solvent had then been removed, the residue was treated with water (40 ml.), 6N aqueous ammonia (30 ml.) and chloroform (50 ml.); the chloroform-addition compounds of VIII remained suspended between the aqueous and the chloroform layers. The chloroform compound (7.23 g.), after being collected by filtration, washed with water, and dried, was recrystallized from acetone to yield VIII (4.96 g.), m. p. 143—146°C. Recrystallization from acetone gave an analytical sample (3.64 g.), m. p. 156—157°C; $[\alpha]_D^{20}$ −59.4°; IR; ν_{max} 3300, 1032 and 878 cm^{-1}.

Found: C, 78.31; H, 10.83; N, 3.33. Calcd. for $C_{27}H_{45}O_2N$: C, 78.02; H, 10.91; N, 3.37%.

Compound VIII (3.37 g.) was acetylated with acetic anhydride (30 ml.) and pyridine (40 ml.) on a steam bath for 2 hr. The residue, obtained after the solvents had been removed by azeotropization with benzene, was crystallized from aqueous methanol; it had a m. p. of 153.5—155°C. Recrystallization from the same solvent afforded a pure sample (3.45 g.) of the triacetyl derivative, m. p. 157—159°C; IR: ν_{max} 1738, 1634 and 1238 cm^{-1}; NMR: a broad multiplet which consisted of three peaks centered at τ 4.93, 5.17 and 5.33 (3H, protons on C-3, C-22 and C-23),[22] a singlet at τ 8.34 3H, 18-methyl protons) and a singlet at τ 9.28 (3H, 19-methyl protons).

Found: C, 73.22; H, 9.40; N, 2.55. Calcd. for $C_{33}H_{51}O_5N$: C, 73.16; H, 9.49; N, 2.59%.

17-Ethyl-20-formyletiojerv-13(17)-en-3β-ol (IX).—A suspended mixture of *N*-chlorosuccinimide (0.50 g.) in ether containing 11-deoxo-5, 6, 8, 9-tetrahydroisojervine (VIII; 1.45 g.) was stirred at room temperature for 1.5 hr. The ether layer was then washed with three 25 ml. portions of water, dried and evaporated to yield a mixture of crystals (1.39 g.). This mixture was used for the next step without further purification, as it colored at room temperature. It was dissolved in methanol (60 ml.); then to the solution there was added a methanol solution containing sodium methoxide (prepared from 0.7 g. of sodium and 30 ml. of methanol) under cooling and in a stream of nitrogen. The solution was allowed to stand at room temperature for 3 hr. and then evaporated below 33°C. The residue was stirred vigorously with 1N hydrochloric acid (120 ml.) at room temperature for 1 or 2 days, until the resinous materials were changed to amorphous powder. The powder (IX) was collected by filtration, washed repeatedly with water, and found to amount to 1.02 g.; UV: only end absorption, ε 1890 at 220 mμ; IR (chloroform); ν_{max} 3575, 3400, 2705 and 1719 cm^{-1}; NMR: a broad peak centered at τ 0.47 (aldehyde proton), a singlet at τ 8.31 (3H, 18-methyl protons), a doublet centered at τ 8.87 (3H, J=7 c. p. s., 21-methyl protons) and a singlet at τ 9.27 (3H, 19-methyl protons).

Found: C, 79.80; H, 10.29. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37%.

17-Ethyl-20-oximinoetiojerv-13(17)-en-3β-ol and the Diacetyl Derivative (X).—To a cooled *n*-butanol solution (2 ml.) containing the aldehyde IX (0.20 g.) and freshly-prepared *n*-butyl nitrite (0.20 g.), was added a 1N sodium *n*-butoxide solution in *n*-butanol (2 ml.), and the whole solution was then kept in a refrigerator for 12 hr. After an excess of dry ice and a small volume of water had been added, the solution was evaporated below 43°C under reduced pressure, and the residue was extracted with chloroform. The chloroform solution was shaken with a 2N aqueous sodium hydroxide solution, which was then neutralized carefully with 2N hydrochloric acid and extracted with chloroform. The chloroform solution gave, after the solvent had been removed, an oxime (0.09 g.) which showed one spot on thin-layer chromatograms but which resisted crystallization; UV: λ_{max} 413 (1760) and 246 mμ (ε 5550); IR (chloroform): ν_{max} 3580, 3290, 1663 and 1602 cm^{-1}.

Found: C, 76.34; H, 10.19; N, 4.02. Calcd. for $C_{21}H_{33}O_2N$; C, 76.09; H, 10.03; N, 4.23%.

The afore-mentioned oxime (0.26 g.) was acetylated with acetic anhydride (1.5 ml.) and pyridine (3 ml.) at room temperature for 14 hr. A crude diacetate, obtained on the removal of the solvents by azeotropization with benzene, crystallized on trituration with isopropyl ether; it was collected by filtration. On recrystallization from acetone-isopropyl ether, the diacetyl derivative (X; 0.22 g.) had a m. p. of 139—140°C; UV: λ_{max} 350 (4660) and 251 mμ (ε 13250); IR: ν_{max} 1788, 1737, 1671 and 1581 cm^{-1}.

Found: C, 72.31; H, 9.05; N, 3.19. Calcd. for $C_{25}H_{37}O_4N$: C, 72.25; H, 8.98; N, 3.37%.

22, 27-Iminojerva-5, 12-diene-3β, 23α-diol-11-one

22) Footnote 33a of Ref. 17.

***N*-Acetate (XI).**—The Birch reduction of jervine (I) to 8, 9-dihydroisojervine (VII) was carried out according to a procedure reported previously,[17] except that tetrahydrofuran was used as the solvent instead of dioxane; because of the high melting point, the latter was frozen in liquid ammonia, including its starting material, and the yield was sometimes decreased. From 4.0 g. of jervine dissolved in tetrahydrofuran (100 ml.), a crude 8, 9-dihydroisojervine (3.21 g.), m. p. 158—160°C, was obtained. Recrystallization from a mixture of acetone and methanol (9 : 1) afforded the pure sample of VII (3.01 g.), m. p. 161—163°C.

The acetylation of VII proceeded much as has been described in the literature;[17] 5.0 g. of 8, 9-dihydroisojervine was converted to 5.81 g. of the triacetyl derivative, m. p. 163—164°; $[\alpha]_D^{20}$ +95.0°; NMR: a broad peak centered at τ 4.62 (1H, proton on C-6), a broad multiplet which consisted of three peaks centered at τ 4.98, 5.18 and 5.37 (3H, protons on C-3, C-22 and C-23), singlet at τ 8.15 (3H, 18-methyl protons), a doublet centered at τ 8.92 (6H, J=6 c. p. s., 21- and 26-methyl protons), a singlet at τ 9.03 (3H, 19-methyl protons).

Found: C, 71.49; H, 8.34; N, 2.26. Calcd. for $C_{33}H_{47}O_6N$: C, 71.58; H, 8.56; N, 2.53.

A solution of the triacetyl derivative (4.14 g.) in methanol (160 ml.) containing 5% potassium hydroxide was refluxed for 40 min. in a stream of nitrogen. The solution was then evaporated, diluted with water (100 ml.), stirred at room temperature overnight, and filtrered. The precipitates thus collected crystallized, after being dried, on trituration with acetone; then those had a m. p. of 214—217°C. Recrystallization from a mixture of ethanol and acetone (2 : 3) afforded XI (3.17 g.), m. p. 218—219°; $[\alpha]_D^{20}$ −93.0°; UV: λ_{max} 254 mμ (ε 19000); IR: ν_{max} 1701, 1614 and 1055 cm^{-1}; NMR: a broad peak centered at τ 4.63 (1H, proton on C-6), a singlet at τ 7.92 (18-methyl protons), two doublets centered at τ 8.73 and 9.15 (each 3H, J=7 and 6 c. p. s., 21- and 26-methyl protons or vice versa) and a singlet at τ 8.98 (3H, 19-methyl protons).

Found: C, 74.26; H, 9.13; N, 2.93. Calcd. for $C_{29}H_{43}O_4N$: C, 74.16; N, 9.23; N, 2.98.

22, 27-Iminojerv-5-ene-3β, 23α-diol-11-one *N*-Acetate (XIV).—To liquid ammonia (350 ml.) cooled with a dry ice - acetone mixture and containing lithium (604 mg.), 22, 27-iminojerv-5, 12-dien-3β, 23α-diol-11-one *N*-acetate (XI, 4.0 g.) was added over a 5-min. period; the whole mixture was then stirred for another 15 min. The blue color of the mixture disappeared on the addition of ammonium chloride (12 g.), and then the ammonia was removed. The residue was extracted with four 40-ml. portions of chloroform, and the chloroform solution was evaporated to dryness after it had been washed with water and dried with anhydrous sodium sulfate. The residue (3.18 g.) crystallized on trituration with acetone; then it was recrystallized from a mixture of acetone and ethanol (3 : 2) to yield XIV (3.04 g.), m. p. 248—249°; $[\alpha]_D^{20}$ −85°; IR: ν_{max} 3425, 1737, 1600 and 1065 cm^{-1}.

Found: C, 73.72; H, 9.59; N, 4.31. Calcd. for $C_{29}H_{45}O_4N$: C, 73.84; H, 9.62; N, 4.23.

The Hydrogenation of 22, 27-Iminojerv-5-ene-3β, 23α-diol-11-one *N*-Acetate (XIV).—Compound XIV (0.10 g.) was hydrogenated in the presence of prereduced Adams' platinum (62 mg.) at room temperature in acetic acid (12 ml.); 7 ml. of hydrogen was absorbed in 20 min. After the catalyst and the solvent had then been removed, the residue was treated with three 30-ml. portions of chloroform and a 5% aqueous sodium carbonate solution (5 ml.). The chloroform solution was washed with water, dried, and then evaporated to dryness. The residue (97 mg.) was crystallized from acetone, and then recrystallized from 90% aqueous ethanol. The product (92 mg.), m. p. 271—274°C, was identified as a known compound, 22, 27-iminojervane 3β, 23α-diol-11-one *N*-acetate[19] (XV), by a mixed-melting-point determination and by a comparison of the infrared and NMR spectra with those of XV.

The Alkali Treatment of 22, 27-Iminojerv-5-ene-3β, 23α-diol-11-one *N*-Acetate (XIV).—Compound XV (0.1 g.) was suspended in a mixture of diethylene glycol (50 ml.), water (0.5 ml.), and dimethylsulfoxide (10 ml.) containing potassium hydroxide (1.0 g.). The mixture was refluxed at 205°C for 2 hr. in a stream of nitrogen when it was homogenous. To the cooled solution, water (35 ml.) was added, and then the whole mixture was stirred for a while and filtered. The precipitates (62 mg.) thus collected were treated with 1 N hydrochloric acid (7 ml.) and chloroform (45 ml.). The chloroform solution gave a crystalline compound, which had a m. p. of 247—248.5°C and which amounted to 45 mg. after recrystallization from a mixture of acetone and ethanol (3 : 2). It was proved identical with the starting material (XIV) by a comparison of the infrared spectra and by thin-layer chromatography on silica gel (methanol-benzene, 4 : 1). On the other hand, the acidic layer was made alkaline and extracted with chloroform. From the chloroform solution, nothing remained after the solvent had been removed.

22, 27-Iminojerv-5-ene-3β, 23α-diol (XVI) and the 3, 23, *N*-Triacetyl Derivative (XVIa).—To freshly-distilled diethylene glycol (130 ml.), sodium (3.0 g.) was added; the mixture was then heated for a while and cooled. To this solution anhydrous hydrazine[23] (18 ml.) was added, and the mixture was refluxed for 30 min. and cooled. After the addition of 22, 27-iminojerv-5-ene-3β, 23α-diol-11-one *N*-acetate (XIV, 2.0 g.), the entire mixture was heated at 180°C for 48 hr., heated further to 210°C to remove the excess hydrazine, and again refluxed for another 24 hr. To the cooled solution, water (200 ml.) was added, and the mixture was stirred at room temperature overnight. The precipitates thus formed were collected by filtration and dried to yield a crude deoxo derivative (XVI; 1.52 g.). Repeated recrystallizations, each fraction being checked by paper chromatography,[24] afforded a pure sample (1.05 g.) of XVI, m. p. 221—223°C; IR: no absorption near 1700 cm^{-1}.

Found: C, 78.20; H, 10.81; N, 3.08. Calcd. for $C_{27}H_{45}O_2N$: C, 78.02; H, 10.91; N, 3.37.

Compound XVI (0.15 g.) was acetylated with acetic anhydride (1 ml.) and pyridine (2.5 ml.) at room temperature overnight. The solution was poured into ice water (200 ml.), stirred for 4 hr., and then filtered. The crude triacetate (XVIa; 198 mg.), m. p. 153—155°C, obtained after the washing and drying of the

23) L. I. Smith and K. L. Howard, *Org. Synth.*, **24**, 53 (1944).

24) Footnote 40 of Ref. 17.

precipitates, was recrystallized from aqueous methanol to yield pure sample of 22, 27-iminojerv-5-ene-3β, 23α-diol 3, 23, *N*-triacetate, m. p. 155—156°C; $[\alpha]_D^{20}$ −75.0°; IR: ν_{max} 1742, 1732, 1641, 1244, and 1025 cm^{-1}.

Found: C, 73.18; H, 9.66; N, 2.50. Calcd. for $C_{33}H_{51}O_5N$: C, 73.16; H, 9.49; N, 2.59.

17-Ethyl-20-formyletiojerv-5-en-3β-ol.—Into methanol containing 22, 27-iminomerv-5-ene-3β, 23α-diol (XVI; 1.0 g.) *N*-chlorosuccinimide (385 mg.) was stirred below 30°C, and then the entire mixture was stirred for another 2.5 hr. The solution was concentrated to 50 ml. below 30°C under reduced pressure. Into the solution, cooled with an ice bath, there was stirred in a stream of nitrogen sodium (2.3 g.) dissolved in absolute methanol (50 ml.). The whole solution was allowed to stand at 0°C for 2.5 hr. and then evaporated below 35°C under diminished pressure. The residual oil was mixed with water (50 ml.), and then with 2 N hydrochloric acid (50 ml.). The heterogeneous mixture was vigorously stirred at room temperature overnight and then filtered. The precipitates (835 mg.) had a m. p. of 160—165°C after being washed with water and dried. Two recrystallizations from a mixture of acetone and methanol (4 : 1) yielded 17-ethyl-20-formyletiojerv-5-en-3β-ol (720 mg.), m. p. 173—180°C; IR: ν_{max} 3495, 2735 and 1715 cm^{-1}; NMR: a broad peak centered at τ 4.67 (1H, olefinic proton on C-6), a doublet centered at τ 9.02 (3H, J=7 c. p. s., 21-methyl protons) and a singlet at τ 9.01 (3H, 19-methyl protons).

Found: C, 79.85; H, 10.19. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.39%.

17-Ethyl-20-oximinoetiojerv-5-en-3β-ol (XVII).—To absolute methanol (2.1 ml.) containing *n*-butyl nitrite (0.3 ml.) and the afore-mentioned aldehyde (0.10 g.), there was added, under cooling with ice and in a stream of nitrogen, sodium (96 mg.) dissolved in absolute methanol (2.1 ml.); the whole mixture was then allowed to stand in a refrigerator for 22 hr. The solution was made acidic to pH 4 with concentrated hydrochloric acid and evaporated to dryness. The residue was treated with water and five 20-ml. portions of warm chloroform; the chloroform solution was then shaken with a saturated aqueous sodium chloride solution, dried and evaporated. The residual oil crystallized on trituration with acetone; it had a m. p. of 180—184°C. The collected crystals (65 mg.) were twice recrystallized from a mixture of acetone and methanol (4 : 1) to yield the oxime (XVII; 52 mg.), m. p. 192—193°; $[\alpha]_D^{20}$ −27°; IR: ν_{max} 3340, 1680 and 1060 cm^{-1}.

Found: C, 76.19; H, 10.04; N, 3.86. Calcd. for $C_{21}H_{33}O_2N$: C, 76.09; H, 10.03; N, 4.23%.

17-Ethyletiojerv-5-en-3β-ol-20-one (XVIII) and 17-Ethyletiojerv-4-ene-3, 20-dione (XIX).—17-Ethyl-20-oximinoetiojerv-5-en-3β-ol (XVII; 0.41 g.) was suspended in a mixture of pyruvic acid (1.8 ml.), water (18 ml.) and acetic acid (18 ml.), and then refluxed for 3 hr. under a stream of nitrogen. The mixture became homogeneous on being heated. The cooled solution was diluted with water (40 ml.) and made strongly alkaline with a concentrated aqueous sodium hydroxide solution. After ethanol (30 ml.) had been added, the solution was treated with five 30-ml. portions of ether. The ether solution gave, after being washed with water and dried, an oil (221 mg.) which was crystallized from isopropyl ether to yield the crude methyl ketone (XVIII; 209 mg.), m. p. 96—103°C. This ketone was used for the next step without further purification.

The afore-mentioned methyl ketone (XVIII; 150 mg.) was dissolved in a mixture of toluene (100 ml.) and cyclohexanone (5 ml.); 3 ml. of the toluene was then distilled off in order to remove the water from the system. Aluminum isopropoxide (500 mg.) was added, and the reaction mixture was refluxed for 5 hr. under stirring and then cooled. It was distilled with steam for 5 hr. to remove the organic solvents. The residual mixture was extracted with four 30-ml. portions of ether; the ether layer, after being washed with water and dried, was evaporated to dryness. The residue (158 mg.) was purified by thin-layer chromatography on silica gel (ether-acetone, 3 : 2). The extraction of the main spot with chloroform and the subsequent evaporation of the solvent afforded the crude 17α-ethyletiojerv-4-ene-3, 20-dione (XIX), which was recrystallized from a mixture of acetone-methanol (7 : 3) to yield a pure sample (60 mg.), m. p. 168—169°C; $[\alpha]_D^{20}$ +129°.

Found: C, 80.20; H, 9.52. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62%.

The authors wish to express their thanks to Professor Toshi Irie for his encouragment, and also to Professor Shigenobu Okuda, the University of Tokyo, and to Dr. Issei Iwai, Sankyo Co., Ltd., for providing them with crude jervine. They are also indebted to Dr. Toshio Sato and to Mr. Shigezo Shimokawa for the measurement of the NMR spectra.