The Transformation of Jervine into 18-Functional *C*-Nor-*D*-homosteroids[1)]

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(Received June 2, 1979)

N,O-Diacetyldeoxojervine, obtained by the Wolff-Kishner reduction of jervine followed by acetylation, has been catalytically hydrogenated to (22*S*,25*S*)-*N*,3-*O*-diacetyl-5α-veratranine-3β,23β-diol. Irradiation in benzene containing mercury(II) oxide and iodine afforded 20-formyl-17β-ethyl-12α-etiojervan-3β-ol 3-acetate which was converted into 17β-ethyl-3β-hydroxy-12α-etiojervan-20-one 3-acetate by dye-sensitized photo-oxygenation of the corresponding morpholine enamine. Reduction to 17β-ethyl-12α-etiojervane-3β,20β-diol 3-acetate with sodium borohydride followed by irradiation in benzene in the presence of mercury(II) oxide and iodine afforded an 18-functional *C*-nor-*D*-homosteroid, (20*R*)-18,20-epoxy-17β-ethyl-12α-etiojervane-3β,20β-diol. The configuration of the methyl group on the tetrahydrofuran ring has been shown to be α on the basis of the NMR spectrum, confirming a previous assignment.

In a previous paper, the transformation of deoxojervine, a jerveratrum alkaloid, into an 18-functional *C*-nor-*D*-homosteroid was reported.[2)] The transformation involved the catalytic hydrogenolysis of deoxojervine[3)] to a veratranin-23β-ol (**5**), removal of the piperidine ring by a procedure devised by Franck and Johnson to afford 17β-ethyl-3β-hydroxy-12α-etiojervan-20-one, reduction to 17β-ethyl-12α-etiojervane-3β,20β-diol 3-acetate (**10**) with sodium borohydride, and a functionalization of the inactive 13β-methyl group by an intramolecular radical process.

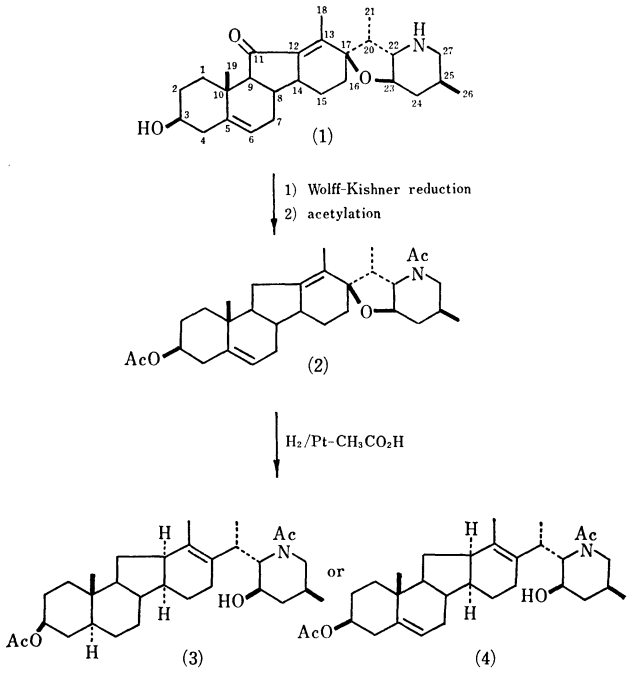
In this paper, an alternative method for the transformation of deoxojervine derived from jervine into the 18-functional *C*-nor-*D*-homosteroid (**11**) is described which utilizes photo-induced reactions as the key steps.

Results

Jervine (**1**), an abundantly available jerveratrum alkaloid, was used as the starting material. The previous severe conditions for the removal of the hindered 11-oxo group[3)] was found to be unnecessary and the 11-oxo group was smoothly removed either by the Huang-Minlon or by the Nagata-Itasaki[4)] modification of the Wolff-Kishner reduction to yield deoxojervine (approximate yield 50%).

In previous experiments, the transformation of deoxojervine into (22*S*,25*S*)-5α-veratranine was achieved in a rather poor yield by catalytic hydrogenation of deoxojervine itself.[2)] This has now been significantly improved by the use of the *N,O*-diacetyl derivative (**2**). Thus, catalytic hydrogenation of the diacetate **2**[3)] in glacial acetic acid in the presence of Adams platinum oxide (25% weight of the substrate) afforded an amorphous product which showed a single spot on TLC and which was identified as (22*S*,25*S*)-*N*,3-*O*-diacetyl-5α-veratr-13(17)-enine-3β,23β-diol (**3**) by NMR analysis (see Experimental). Hydrogenation conducted with less catalyst (10% weight of the substrate) gave (22*S*,25*S*)-*N*-3-*O*-diacetylveratr-5,13(17)-dienine-3β,23β-diol (**4**) as the major product; the product was identified by NMR analysis.

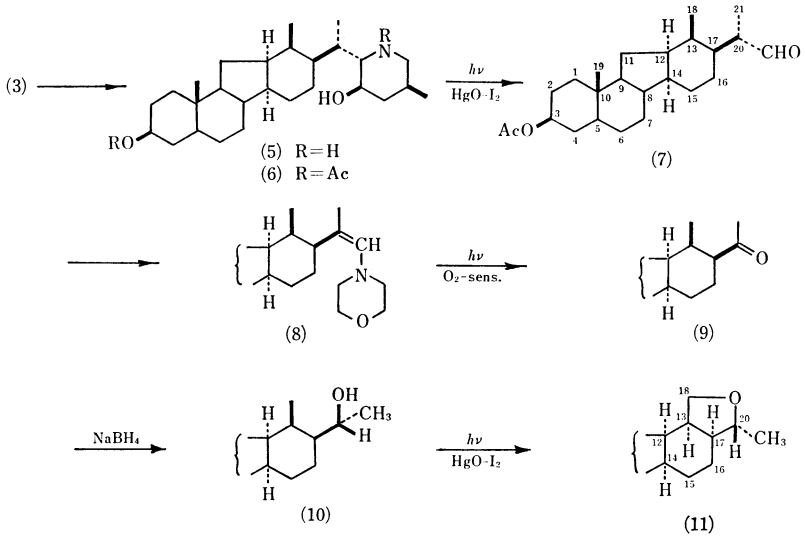
The hindered tetrasubstituted double bond of the 23β-ols **3** or **4** was hydrogenated catalytically using a rhodium–platinum catalyst as reported in a previous paper[2)] to yield an amorphous perhydro derivative (**6**) as the exclusive product. The stereochemistries at the C-13 and the C-17 were identified by its transformation into 17β-ethyl-3β-hydroxy-12α-etiojervan-20-one 3-acetate obtained in previous experiments.[2,5)]



Scheme 1.

The removal of a heterocyclic ring of veratranine **6** was executed by a method involving a radical fragmentation developed by the authors.[6)] Thus, (22*S*,25*S*)-*N*,3-*O*-diacetyl-5α-veratranine-3β,23β-diol (**6**) in benzene containing mercury(II) oxide and iodine was irradiated for 13 h with a high pressure Hg arc. The product was passed through a column of silica gel and the most mobile fraction collected to afford crystalline 20-formyl-17β-ethyl-3β-hydroxy-12α-etiojervan-20-one 3-acetate **7** in 35% yield. As noted previously, this fragmentation reaction is considered to be a radical counterpart of an ionic fragmentation[7)] and is useful in removing the piperidine ring from *N*-acetylveratranine at room temperature under neutral conditions.

The transformation of the aldehyde into 17β-ethyl-3β-hydroxy-12α-etiojervan-20-one 3-acetate (**9**) was conducted by a photochemical method. The aldehyde **7**, obtained as above, was converted into a morpholine enamine (**8**) which was immediately subjected to dye-sensitized photo-oxygenation as reported by Huber[8)]



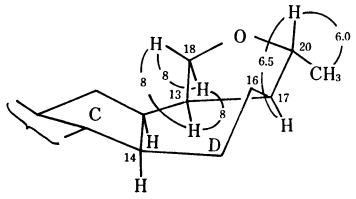
Scheme 2.

and Foote.[9] Irradiation of a benzene solution of the enamine **8** containing Rose Bengal with a 100-W high pressure Hg arc for 10 h with oxygen bubbling slowly through afforded 17β-ethyl-3β-hydroxy-12α-etiojervan-20-one 3-acetate (**9**), identical with a specimen obtained by a nonphotochemical procedure[2] as a single product in 83% yield. As previously reported,[2] reduction of the methyl ketone **9** with sodium borohydride afforded nearly a single alcohol (**10**). The configuration of the 20-hydroxyl group of this compound was assumed to be β on the basis of the consideration of the steric course of the reduction with complex metal hydrides.[2]

Irradiation of 20β-ol **10** in benzene containing mercury(II) oxide and iodine[10] gave an amorphous 18-functional *C*-nor-*D*-homosteroid **11** in 47% yield after purification by column chromatography. The yield was much greater than that in the previous experiments in which lead tetraacetate was used instead of mercury-(II) oxide.

An analysis of the NMR spectrum of the cyclic ether **11** with the aid of spin-decoupling confirmed the structure to be (20*R*)-18,20-epoxy-17β-ethyl-12α-etiojervane-3β,20β-diol acetate **11**, confirming the β-configuration of the C-20 hydroxyl of the starting C-20-ol **10**. Thus, the epoxide **11** showed a 3H singlet at τ 9.27 (19-H), a 3H doublet centered at τ 8.79 (J=6.0 Hz, C-20-methyl), a 3H singlet at τ 8.01 and a broad signal centered at τ 5.34 due to 3α-H. Besides these signals, the spectrum exhibited signals attributable to a methine and methylene protons adjacent to the oxygen of a tetrahydrofuran ring. The methine proton appeared as a 1H broad octet centered at τ 6.39 and the methylene proton as two triplets at τ 6.06 (J= 8 Hz) and 6.58 (J=8 Hz). Irradiation at the center of the doublet at τ 8.79 due to C-20 methyl caused a collapse of the broad octet to a doublet (J=6.5 Hz). Inspection of the Dreiding molecular model indicated that the dihedral angle between the 17α-H and the 20β-H is approximately 130° in epoxide (**11**) having 20 (*R*) configuration. The observed coupling constant is in agreement with this configuration.

Irradiation at τ 7.42 corresponding to a signal due to 13α-H caused a collapse of two triplets into two doublets with J=8 Hz. This decoupling defines the couplings between 13α-H and 18β-H as well as 13α-H and 18α-H to be approximately the same and 8 Hz. These results are summarized in a formula (**12**).



(**12**)

Experimental

All melting points were determined with a hot-plate apparatus (Yanagimoto micro melting point apparatus) and are uncorrected. Unless stated otherwise, IR spectra were determined in Nujol with a JASCO model IR-E spectrophotometer. NMR spectra were determined with a JEOL PS-100 high-resolution spectrometer (solvent $CDCl_3$; Me_4Si as internal reference). TLC was conducted on Wakogel B-5. Mass spectra and elemental analyses were taken by the staff of the Faculty of Pharmaceutical Sciences of this University, the MS with a Hitachi RMU-6E spectrometer.

Reduction of Jervine **1** *to Deoxojervine. i) By Nagata-Itazaki Procedure*:[4] Jervine (30 g) in triethylene glycol (900 ml) containing hydrazine hydrochloride (54 g) and 80% hydrazine hydrate (216 ml) was refluxed for 3 h and the solution cooled to room temperature. To this solution, potassium hydroxide (81 g) was added and the solution concentrated and refluxed for a further 3 h (bath temp 240—260 °C) and poured into water. The crystals, collected by filtration, were dissolved in chloroform and the chloroform solution washed with water and dried (Na_2SO_4). The residue was recrystallized from methanol to yield deoxojervine (14.4 g, 49%) in three crops.

ii) By Huang-Minlon Procedure: Jervine **1** (2 g) in triethylene glycol (60 ml) containing hydrazine hydrate (12 ml) and potassium hydroxide (5.4 g) was refluxed for 1 h (bath temp

120 °C). To the solution, triethylene glycol (100 ml) was added and the solution refluxed for 1 h. The solution was concentrated at bath temperature 200 °C and refluxed for 3 h. The solution was poured into water and extracted with chloroform and the chloroform solution worked up in the usual way. The residue was recrystallized from methanol to yield deoxojervine (0.98 g, 51%) in three crops.

Catalytic Hydrogenation of N,O-*Diacetyldeoxojervine* **2** *in the Presence of Adams Platinum Oxide.* i) *N*,3-*O*-Diacetyl-11-deoxojervine (1 g) in acetic acid (10 ml) containing platinum oxide (250 mg) was hydrogenated under atmospheric pressure until absorption of hydrogen gas ceased. After removal of the catalyst and the solvent, the residue was neutralized with aq sodium hydrogencarbonate and extracted with chloroform. The chloroform solution was washed with water and dried (Na_2SO_4). The residue (1.01 g) showed a single spot on TLC. Crystallization could not be induced and the solution was immediately used for the next step. IR 3387 (OH), 1740 (OAc), 1620 (NAc), 1239, 1027, and 762 cm^{-1}; NMR 9.29 (1H, s, 19-H), 8.94 (3H, d, J=6.8, 26-H), 8.79 (3H, d, J=6.8, 21-H), 8.34 (3H, s, 18-H), 7.98 and 7.93 (each 3H, s, NAc and OAc), 7.03 (1H, m, 2-H), 6.74 (2H, br. s, 27-H), 5.92 (1H, br. s, $W_{1/2}$=8.4, 23β-H), 5.33 (1H, d, J=10.5, 22β-H) and 5.33 (1H, br. overlapped with 22α-H).

ii) *N*,3-*O*-Diacetyl-11-deoxojervine **2** (1 g) in acetic acid (10 ml) containing platinum oxide (100 mg) was hydrogenated as described above until absorption of hydrogen gas ceased. Work-up of the solution afforded (22*S*,25*S*)-*N*,3-*O*-diacetylveratr-5,13(17)-dienine-3β,23β-diol **4**. Crystallization of the diol was not possible. IR 3394 (OH), 1743 (OAc), 1618 (NAc), 1239, and 1029 cm^{-1}. NMR τ 9.08 (3H, s, 19-H), 8.95 (3H, d, J=7.5, 26-H), 8.65 (3H, d, J=7.5, 21-H), 8.32 (3H, s, 18-H), 7.98 (6H, s, NAc, and OAc), 6.74 (2H, s, br. s, 27-H), 5.93 (1H, br. s, $W_{1/2}$= 9.0, 23β-H), 5.34 (1H, d, J=11.9, 22β-H), and 4.64 (1H, br. s, 6-H).

This diacetate was immediately used for the next step.

Catalytic Hydrogenation of (22S,25S)-N-3-O-Diacetylveratr-13-(17)-enine-3β,23β-diol (3) in the Presence of Rhodium–Platinum Catalyst. The rhodium–platinum catalyst (800 mg) in glacial acetic acid (10 ml) was hydrogenated until approximately 200 ml of hydrogen gas were absorbed. To this solution, 400 mg of (22*S*,25*S*)-*N*,3-*O*-diacetylveratr-13(17)-enine-3β,23β-diol (**3**) was added and the solution hydrogenated for 91 h under atmospheric pressure. The usual work-up of the solution afforded an amorphous (22*S*,25*S*)-*N*,3-*O*-diacetyl-5α-veratranine-3β,23β-diol (**6**) (410 mg). IR 3367 (OH), 1739 (OAc), 1617 (NAc), 1238, 1025, and 775 cm^{-1}; NMR 9.26 (3H, s, 19-H), 9.26 (3H, d, J=6.9), 9.10 (3H, d, J=6.0), and 8.92 (3H, d, J=6.9) (three secondary methyl groups at C-13, C-20, and C-25), 8.03 (3H, s, NAc), 7.91 (3H, s, OAc), 6.80 (1H, d, 22β-H), 6.00 (1H, br. s, 23α-H), and 5.47 (1H, br. 3α-H).

Preparation of 20-Formyl-17β-ethyl-12α-etiojervan-3β-ol Acetate by Irradiation of 23β-ol **6** *in Benzene in the Presence of Mercury-(II) Oxide and Iodine.* (22*S*,25*S*)-*N*,3-*O*-Diacetyl-5α-veratranine-3β,23β-diol (**6**) (1 g) in dry benzene (50 ml) containing mercury(II) oxide (1.3 g) and iodine (2.4 g) was placed in a Pyrex vessel and the solution irradiated with a 100-W high pressure Hg arc under an atmosphere of argon for 13 h. After removal of the inorganic materials by filtration, the solvent was evaporated and the residue subjected to column chromatography (Wakogel C-200). Elution with benzene afforded a residue which was dissolved in dichloromethane. The solution was washed with aq sodium thiosulfate and water successively and dried (Na_2SO_4). Evaporation of the solvent left the crystalline aldehyde **7** (259 mg). NMR 9.19 (3H, s, 19-H), 9.21 (3H, d, J=6.9, 18-H), 8.98 (3H, d, J=7.2, 21-H), 7.99 (3H, s, OAc), 5.34 (1H, broad signal, 3α-H), and 0.49 (1H, d, J=4.1, CHO). In this reaction, a tarry polymerized material accompanied the aldehyde.

Morpholine Enamine **8** *of Aldehyde* **7**. The aldehyde **7** as obtained above (210 mg) together with morpholine (0.5 ml) and *p*-toluenesulfonic acid (10 mg) in benzene (40 ml) were refluxed for 3 h in a vessel equipped with a Dean-Stark apparatus. The solvent was removed by a rotary evaporator and the residue dissolved in dichloromethane. The solution was washed with 5% aq sodium hydrogencarbonate solution and water successively and dried (Na_2SO_4). Evaporation of the solvent by a rotatory evaporator left an amorphous enamine **8** (250 mg) which was immediately used for the next step. NMR 9.38 (3H, d, J=7.5, 18-H), 9.26 (3H, s, 19-H), 8.41 (3H, s, CH_3–C=C–N), 8.07 (3H, s, OAc), 7.35 (4H, m, $-CH_2-O-CH_2-$), 6.36 (4H, m, $-CH_2-N-CH_2-$), 5.38 (1H, broad signal, 3α-H), and 5.79 (1H, d, J=2.7, C=CH–N–).

Preparation of 17β-Ethyl-3β-hydroxy-12α-etiojervan-20-one Acetate from Enamine **8** *by Dye-sensitized Oxygenation.* Morpholine enamine **8** (250 mg) in dry benzene (35 ml) containing Rose Bengal (6 mg) in a Pyrex vessel was irradiated with a 100-W high pressure Hg arc through a Pyrex filter for 10 h while oxygen was bubbled slowly though. After removal of the solvent, the residue was dissolved in dichloromethane and the solution worked up in the usual way. The residue was subjected to column chromatography (alumina) to remove the Rose Bengal. Elutions with a 6:1 mixture of benzene and diethyl ether afforded a crude 17β-ethyl-3β-hydroxy-12α-etiojervan-20-one acetate (**9**) which was recrystallized from methanol to afford the pure acetate (171 mg). This was identical with the specimen obtained by a non-photochemical procedure.

Reduction of 17β-Ethyl-3β-hydroxy-12α-etiojervan-20-one Acetate (9) with Sodium Borohydride. 17β-Ethyl-3β-hydroxy-12α-etiojervan-20-one acetate **9** (1.56 g) and sodium borohydride (640 mg) in ethanol containing ethyl acetate (6 ml) were stirred for 4 h at room temperature. After the addition of acetic acid, the solvent was evaporated and the residue extracted with dichloromethane. The solution was washed with water and dried to afford an amorphous alcohol (1.44 g) which was virtually a single compound. This was recrystallized from a hexane–diethyl ether mixture.

The Hypoiodite Reaction of 17β-Ethyl-12α-etiojervane-3β,20β-diol 3-Acetate (10) with Mercury(II) Oxide and Iodine. Etiojervan-20β-ol **10** (550 mg) in dry benzene (100 ml) containing mercury(II) oxide (825 mg) and iodine (1.1 g) was irradiated with a high pressure mercury arc generated by Rayonet RPR-208 preparative photochemical reactor through Pyrex for 3 h under an argon atmosphere with stirring. The solution was filtered and a further amount of benzene added. The solution was washed with 5% sodium thiosulfate and water successively and dried. The amorphous residue (575 mg) was subjected to column chromatography (silica gel). Elution with a 20:1 mixture of benzene and diethyl ether afforded an amorphous 18,20-epoxide **11** (260 mg) identical with a specimen obtained previously.[2] It had mp 80.5—81.5 °C after recrystallization from methanol. For NMR spectrum see text.

The authors would like to thank Mrs. Tomoko Okayama of this laboratory for the NMR measurements and spin-decoupling.

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