Tetrahedron. Vol. 27, pp. 3387 to 3394. Pergamon Press 1971. Printed in Great Britain

THE CONVERSION OF VERATRAMINE INTO VERARINE*

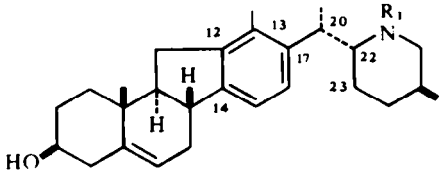
T. MASAMUNE, I. YAMAZAKI, K. ORITO and M. TAKASUGI

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, Japan

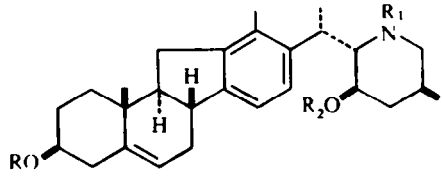
(*Received in Japan* 15 *February* 1971; *Received in the UK for publication* 13 *April* 1971)

Abstract—The transformation of veratramine (II) to vararine (I) by a five-stage process, confirming the configuration of I, is described. The NMR spectra of a series of etiojerva-12,14,16-trienes are also presented and discussed.

THE ALKALOID verarine (I) was isolated[1] from *Veratrum album subsp. lobelianum* (Bernh.) Suessenguth and formulated as 23-desoxyveratramine[2] on the basis of the chemical and spectral data by Tomko *et al.* However, no details were available of the steric configuration. We have recently reported, in preliminary form,[3,4] the conversion of veratramine[5] (II) into I, confirming the structure and configuration as well as completing the synthesis. The present paper describes the details of these experiments. After publication of our work, the total synthesis of I has been presented by Kutney and his collaborators.[6]



I : R_1 = H
Ia: R_1 = Ac

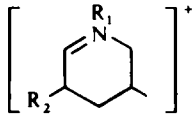


II : R = R_1 = R_2 = H
IIa: R = R_1 = R_2 = Ac
IIb: R = R_1 = Ac, R_2 = H
IIc: R = R_2 = H, R_1 = Ac

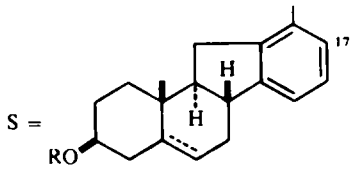
Treatment of veratramine (II) with acetic anhydride (3 mol) and pyridine at room temp, followed by chromatography, afforded the 3-O,23-O,N-triacetyl[7,8] (IIa) and 3-O,N-diacetyl derivatives (IIb), m.p. 265–266°, in 29 and 56% yields, respectively. The structure of the latter was confirmed by the IR (ν_{max} 1725, 1620 and 1027 cm^{-1}) and Mass spectra (a prominent peak at *m/e* 156 due to III[9]). On oxidation with Jones reagent[10] IIb was converted into 3-O,N-diacetyl-23-dehydroveratramine (IV), m.p. 196–198°, in 82% yield. Treatment by NaOMe in refluxing MeOH and subsequent acetylation led to formation of a mixture of IV and the isomeric ketone (V), from which the latter, m.p. 261–262°, was isolated in a pure state in 68% yield. The ratio of

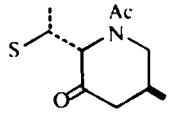
* Part XVIII of C-Nor-D-homosteroids and Related Alkaloids; Part XVII.[5a]

IV to V after equilibration proved to be about 1 to 3.* Since the benzyl part at C_{22} and Me group at C_{25} have been established to be *trans*-oriented in II,[12] those groups in IV and V must possess *trans*- and *cis*-configurations, respectively. Accordingly, IV exhibited a strong negative Cotton effect in the ORD curve like the corresponding 5α,6-dihydro derivative (VI),[5a] while V showed a weak, complex Cotton effect like the epimer[5a] (VII) of VI.

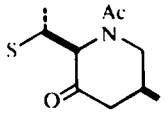


III : R_1 = Ac, R_2 = OH
XIII: R_1 = Ac, R_2 = H
XIV: R_1 = R_2 = H





IV: Δ^5, R = Ac
VI: 5αH, R = Ac

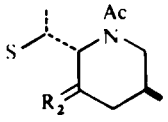


V : Δ^5, R = Ac
VII: 5αH, R = Ac

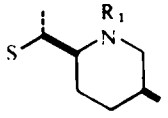
An attempted transformation of IV, *via* 23-tosylhydrazone (VIII), m.p. 201–203°, into the 23-deoxo derivative with configurational retention at C_{22} failed: treatment of VIII with sodium borohydride (NBH)[13] produced a multi-component mixture. This transformation was achieved by the process *via* 23-ethylenethioketal. Reaction of IV with ethane-1,2-dithiol (IX) in the presence of 70% perchloric acid (C_6H_6, room temp, 12 hr)[14] or BF_3 (40°, 4 hr)[15] led to recovery of the starting material or formation of a tarry, intractable mixture, respectively. However, treatment of IV with IX at 0° in MeOH saturated with HCl[16] yielded a crystalline product in 78% yield, which proved to be a 1:1 mixture (TLC). The fraction with the large R_f value gave 23-ethylenethioketal (X), m.p. 155–156°, while that with the small R_f value again showed the two spots in question on TLC. Having available the facile conversion of the latter, which would be 23-hemithioketal (XI), ketal X could be isolated in 62% yield by repeated preparative TLC. It would be reasonable to consider that this ketalization proceded with configurational retention at C_{22}, because hydrolysis of IV under the same acidic conditions as the thioketalization, followed by acetylation, resulted in recovery in good yield of starting material (IV, at 0°, crude 90% and pure 70%, and at room temp, crude 80% and pure 60%; V, at 0°, less than 7%, and at room temp, less than 17%). Further treatment of X with Raney Ni in refluxing EtOH effected desulfurization, giving a N-acetyl-23-desoxy compound, m.p. 195–197°,

* This ratio appears to depend on substituents on the N atom; the value in N-acetyl compounds is 1 to 3[11] or 1 to 2.[5a] while that in N-benzoyl derivatives about 1 to 1.[12] The ratio (1 to 10) reported previously[3] should be revised to 1 to 3.

(64%), which, fortunately, could be obtained in the same yield from the mixture of X and XI as mentioned above. This compound on hydrolysis with base in diethylene glycol (DEG) containing hydrazine afforded the N-deacetyl derivative, m.p. 174–176°, (60%). These substances have been found to be identical with N-acetylverarine[2] (Ia) and verarine.[1] respectively, in all respects.



VIII: Δ^5, R = Ac, R_2 = $=NNHSO_2C_6H_4CH_3$
X : Δ^5, R = H, R_2 = $-SC_2H_4S-$
XI : Δ^5, R = H, R_2 = —OH, $—SC_2H_4SH$



XII : Δ^5, R = R_1 = H
XIIa: Δ^5, R = H, R_1 = Ac

Recently α-halogenation[17] or α-epimerization[18] of ketonic groups protected as ketals under acidic conditions have been reported. However, during the desulfurization epimerization at C_{22} of X would be very improbable, and this was supported by the following. The Huang-Minlon reduction[19] of IV led to removal of the 23-oxo group, producing an isomeric N-acetyl-23-desoxy compound (XIIa), m.p. 240–242°, and its N-deacetyl derivative (XII), m.p. 210–211°, in 61 and 14% yields, respectively. Both Ia and XIIa exhibited strong peaks at *m/e* 140 due to a fragment XIII in the mass spectra, indicating the compounds to be C_{22} epimers. In view of the process of the Huang-Minlon reaction, it is evident that the former Ia possesses the same configuration as IV. Since the configurations of all the asymmetric carbon atoms in II and hence in IV have been established,[20] the present transformation completes the stereochemistry of verarine as well as its synthesis.

In connection with this work we describe collectively the NMR spectra of etiojerva-12,14,16-trienes with an aromatic D ring as well as with *trans*-fused B/C junction (8 βH and 9 αH). In Table 1 the chemical shifts of 19-Me protons of 35 compounds are summarized, including those reported in our previous papers[5a,21] and by Johnson *et al.*[12,22,23] These data are confined to the correlation of the chemical shifts with changes of substituents at C_3, C_5, C_{11} and C_{17}, and the following comments are presented. (1) The observed chemical shifts are in good agreement (within 0·02 ppm), with few exceptions (footnotes *d–h*), with the values calculated, using the shielding effects of various functional groups on the A, B and C rings applied to etiojervane and iminojervane derivatives[24] and assuming the reference chemical shift to be τ 9·08 for the A/B *trans*-fused compounds (including those with an unsaturated carbon at C_5) and that τ 8·93 for the A/B *cis*-fused. This indicates that "the additivity principle" holds for the 19-Me protons of etiojerva-12,14,16-trienes and also that the deshielding effect of an aromatic D ring amounts to *ca* 0·19 ppm, comparing the reference chemical shifts with those of C/D *trans*-fused etiojervanes.[24] (2) The 17-substituents display only negligible effects: for example, 8 compounds at line 2 (3β-OAc), 5αH and 11-H_2) involve those having an electronegative $CH_3CO—$, an electropositive $CH_3CH(OH)—$ or a complex S_1 or S_2 (Table 2) group, but the chemical shifts fall within the narrow range (τ 9·05 ± 0·02 ppm).*

* Two remarkably exceptional examples (footnotes [e] and [h]) are reported.

In Table 2 are listed the chemical shift data of the Me protons on the D and piperidine rings in verarine and related compounds. The signals due to 18-Me, NAc and OAc protons could be readily distinguished in most spectra. On the contrary, secondary Me protons (21- and 26-Me) appeared as indistinctly resolved doublets or

TABLE 1. THE CHEMICAL SHIFT OF THE 19-ME PROTONS OF 17-SUBSTITUTED ETIOJERVA-12,14,16-TRIENES[a]

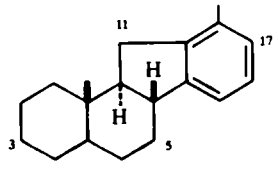
Substituents at 3	5	11	No. of examples[b]	Chemical shift	(τ)[c]
β-OH	αH	H_2	6 (5a, 12, 21)	9·05 ~ 9·07	(9·06)
β-OAc	αH	H_2	8 (5a, 21)	9·03 ~ 9·06	(9·05)
β-OH	Δ^5	H_2	6[d,e] (5a, 22)	8·83 ~ 8·87	(8·85)
β-OAc	Δ^5	H_2	4	8·83	(8·84)
β-OAc	Δ^5	O	1[f]	8·77	(8·77)
O	αH	H_2	1	8·88	(8·865)
O	Δ^4	H_2	2[g]	8·68, 8·70	(8·68)
O	Δ^4	O	1 (23)	8·62	(8·61)
OAc, Δ^3,	Δ^5	H_2	1	8·83	
β-OH	βH	H_2	3 (21)	8·89 ~ 8·92	(8·91)
β-OAc	βH	H_2	1 (21)	8·91	(8·90)
O	βH	H_2	1[h] (21)	8·84	(8·83)

[a] Reference compounds (XV); solvent, $CDCl_3$; internal reference, TMS.

[b] The figures in the parentheses denote the relevant references except the present paper.

[c] The figures in the parentheses refer to the calculated values.

[d-h] The reported values for (d) verarine (I), (e) 17-acetyletiojerva-5,12,14,16-tetraen-3β-ol, (f) N-acetyl-11-oxoveratramine, (g) "N-acetylveratramin-3-one," and (h) N-acetyl-3-dehydro-5β,6-dihydro-11-oxoveratramine are τ 8·82[2] (cal. 8·85), 8·90[22] (8·85), 8·81[23] (cal. 8·78), 8·71[23] (8·68), and 8·81[23] (8·75), respectively.



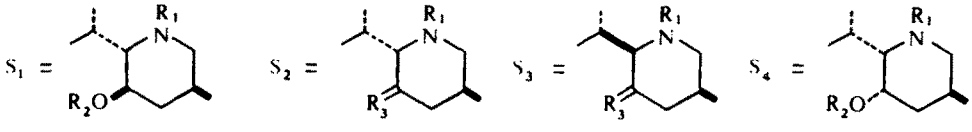
XV

overlapping signals above the background of methylene and methine protons, and were only discernible with difficulty in many cases, especially in the N- and/or 23-O-acetylated derivatives. Nevertheless, by careful comparison of closely related compounds, we made the assignment shown in Table 2, in which the following is to be noted. In most of the N-acetylated (R_1 = Ac) and all the N- and 23-O-acetylated derivatives (R_1 = R_2 = Ac), signals due to 18-Me, NAc and OAc protons, each of which is usually observed as a single singlet, appeared as double or sometimes triple sharp peaks. This suggested the presence of at least two conformers, which would be caused by ring inversion of the piperidine ring[25] and/or by restricted rotation of the bond between C_{17} and C_{20}. This made the assignment difficult, and no definite conclusions could be drawn from the available data concerning their conformations.

TABLE 2. THE CHEMICAL SHIFTS OF THE ME PROTONS OF VERARINE AND RELATED COMPOUNDS [a]

Type of compounds	No. of examples[b]	21-Me	26-Me	Chemical shifts (τ)[c] 18-Me	NAc	23-OAc
S_1(R_1 = R_2 = H)	3 (12, 21)	8·59–8·61[d]	9·17–9·18[d]			
S_1(R_1 = Ac, R_2 = H)	6 (5a, 21)	(*ca* 8·72 and 8·83)[e]		7·63–7·75[f]	8·05–8·11	
S_1(R_1 = R_2 = Ac)	9 (5a, 21)	(*ca* 8·72 and 8·86)[e]		7·68–7·75[g]	8·09–8·15[h]	7·90 7·98[i]
S_1(R_1 = R_2 = Ac)[j]	1	(8·70 and 8·86)		7·34	8·16	7·95
S_2(R_1 = H, R_3 = H_2)	1[k]	8·86[k]	9·20[k]	7·77		
S_2(R_1 = Ac, R_3 = H_2)	1	(8·78 and 9·01)		7·68	8·18	
S_2(R_1 = Ac, R_3 = O)	2 (5a)	(*ca* 8·82 and 9·04)		(*ca* 7·73, 7·78, 8·09 and 8·48)		
S_3(R_1 = Ac, R_3 = H_2)	1	8·98[l]		7·73	7·86[m]	
S_3(R_1 = Ac, R_3 = O)	2 (5a)	(*ca* 8·74 and 8·98)		(*ca* 7·76 and 7·83)		
S_4(R_1 = Ac, R_2 = H)	1 (5a)	(8·65 and 9·05)		7·75	8·20	

[a] Solvent, $CDCl_3$, internal reference, TMS.
[b] The figures in the parentheses denote the relevant references except the present paper.
[c] The parentheses mean that assignment is impossible.
[d] The assignment is based on the work of Johnson *et al.*[12]
[e] Indistinct doublets.
[f] Sometimes accompanied by a weak and unassignable signal at *ca* 0·10 ppm high field.
[g] Always accompanied by a weak signal at *ca* 0·04 ppm high field in each compound.
[h] Always accompanied by a signal with moderate intensity at *ca* 0·11 ppm high field in each compound.
[i] Sometimes accompanied by a weak but sharp signal at *ca* 0·04 ppm low field.
[j] 3-O,23-O,N-Triacetyl-11-ketoveratramine.[24]
[k] *Cf.*[2]
[l] The signals due to both Me groups coincided.
[m] Accompanied by a signal at τ 7·77.



EXPERIMENTAL

All the m.ps are uncorrected. The homogenity of each compound was checked by TLC on silica gel (Wakogel B-5), developed with cerric sulfate in dil. H_2SO_4 and/or I_2. The optical rotations, ORD curves, UV and IR spectra were measured at room temp in $CHCl_3$, dioxane, 99% EtOH and Nujol, respectively, unless otherwise stated. The NMR spectra were obtained in $CDCl_3$ at 60 and/or 100 Mc and the chemical shifts were given in τ-values, TMS being used as an internal reference.

3-O,N-*Diacetylveratramine* (IIb). (a) Veratramine (II, 300 mg) was treated with Ac_2O (0·2 ml) and pyridine (Py, 2 ml) at 23° for 25 hr. After addition of EtOH (5 ml) the soln was evaporated by azeotropization with C_6H_6 to leave crystalline solid, then dissolved in $CHCl_3$ (20 ml). The $CHCl_3$ soln was washed successively with 1N HCl (10 ml), 1N NaOH aq (10 ml) and H_2O (2 × 20 ml), dried and evaporated to give crystalline residue (365 mg), separated by preparative TLC (17 plates, each 10 g of Wakogel B-5), using a 1:3 mixture of $CHCl_3$ and acetone. A fraction obtained by extraction of the most mobile band (R_f 0·70) with acetone gave crystalline residue (105 mg), recrystallization from ether gave 3-O,23-O,N-triacetylveratramine (IIa, 85 mg), m.p. 199–200°, identical in all respects with an authentic sample.[7,8] A fraction from the least mobile band (R_f 0·19) gave crystalline substance (37 mg), which on recrystallization had m.p. 194–195° and amounted to 27 mg; IR. ν_{max} 3320 and 1600 cm^{-1}. When recrystallized from EtOH aq, this compound had m.p. 173–176° and proved to be N-acetylveratramine (IIc) by comparison of an authentic sample;[7,8] ν_{max} : 3450, 3210, 3040 and 1605 cm^{-1}.

A fraction from the middle band (R_f 0·32) gave crystalline substance (204 mg). recrystallization from acetone afforded IIb (185 mg). m.p. 264·5–265·5°. Further recrystallization gave an analytical sample. m.p. 265–266°; $[\alpha]_D$ −14°; UV. λ_{max} 268 mμ (ε 570) and 277 (550); ν_{max}: 3345. 1725. 1620. 1603 and 1246 cm^{-1}; NMR, τ 8·83 (3H, s, 19-Me), 8·73 (d, J = 6 c/s, 21- and/or 26-Me?), 8·06 (3H, s, NAc), 7·93 (3H, s, OAc), 7·68 (3H. s. 18-Me), 4·47 (1H. br. 6-H), and *ca* 2·94 (2H. br m, aromatic H): Mass, *m/e* 156 (base peak, III), 114 (74%) and 338 (13%), (Found: C, 75·64; H, 8·68; N, 2·67. $C_{31}H_{43}O_4N$ requires: C, 75·42: H, 8·78: N, 2·84%).

(b) A soln of IIc (150 mg) in Py (3 ml) was treated with Ac_2O (0·05 ml) in Py (0·5 ml) room temp. 37 hr. The soln was worked up as above and gave IIa (28 mg). m.p. 198–200°. IIb (84 mg). m.p. 265–266°. and IIc (15 mg). m.p. 194–195°.

3-O.N-*Diacetyl-23-dehydroveratramine* (IV) *and the* 23-p-*tosylhydrazone* (VIII). To a soln of IIb (458 mg) in acetone. freshly distilled over $KMnO_4$. was added Jones reagent[10] (0·30 ml) at 0°,10 min. stirring. and the mixture further stirred for 50 min. After addition of EtOH (1 ml) and removal of solvent. the residue was shaken with H_2O (50 ml) and $CHCl_3$ (50 ml). The aqueous layer was further extracted with $CHCl_3$ (2 × 50 ml). $CHCl_3$ solns were combined. washed with H_2O (2 × 50 ml). dried and evaporated to leave crystalline residue (441 mg). Recrystallization from ether afforded IV (318 mg) m.p. 196–197° as the 1st crop and that of m.p. 194–195° as the 2nd. Further recrystallization yielded an analytical sample. m.p. 196–198°; $[\alpha]_D$ −90°; λ_{max}: 267 mμ (630). 276 (560) and 302 (250); ν_{max}: 1728. 1663 and 1254 cm^{-1}; ORD. $[\phi]_{332}^{trough}$ −7650°. $[\phi]_{321}^{trough}$ −5400°. $[\phi]_{288}^{peak}$ +4590°. a = −122°; NMR. τ 9·04 and 8·82 (each 3H. d J = 6 and 7 c/s. 21- and 26-Me or *vice versa*). 8·83 (3H. s. 19-Me). 8·44. 8·07. 7·72. 7·69 (each s. NAc and 18-Me). 7·92 (3H. s. OAc). 4·60 (1H. br. 6-H) and *ca* 2·90 (2H. br. aromatic H). (Found: C. 75·83; H. 8·25: N. 2·60. $C_{31}H_{41}O_4N$ requires: C. 75·73; H. 8·41; N. 2·85%).

Compound IV (433 mg) was treated with *p*-tosylhydrazine (850 mg) in refluxing MeOH for 10 hr. Tosylhydrazone VIII crystallized after removal of MeOH. collected by filtration and on recrystallization from MeOH had m.p. 201–203° (340 mg); ν_{max}: 3140. 1730. 1620. 1378. 1300. 1252. 1168 and 815 cm^{-1}. (Found: C. 69·02; H. 7·64; N. 6·16. $C_{38}H_{49}O_5N_3S$ requires: C. 69·15; H. 7·49; N. 6·38%).

To a soln of VIII (51 mg) in dioxane (2·5 ml) was added NBH (100 mg). gas evolved violently and soln became heterogeneous. The suspended mixture was refluxed for 8 hr. cooled and evaporated (red. press). The residue was extracted with ether. washed with 5% $NaHCO_3$aq and H_2O. dried and evaporated to leave amorphous residue (many spots on TLC. resisted further purification).

3-O.N-*Diacetyl-23-dehydro-22-epiveratramine* (V). Compound IV (150 mg) was refluxed in MeOH (15 ml) containing Na (300 mg) for 2·5 hr under N_2. After evaporation of MeOH below 30° the residue was mixed with H_2O (10 ml) and extracted with $CHCl_3$ (3 × 20 ml). The $CHCl_3$ soln was washed with H_2O (2 × 30 ml). dried and evaporated to leave oily substance (147 mg). which was acetylated with Ac_2O (2 ml) and Py (2 ml) at room temp. After solvent removal by azeotropization residue again dissolved in $CHCl_3$ (30 ml). and the $CHCl_3$ soln gave a crystalline mixture (148 mg). which showed two spots and an optical resolution of $[\alpha]_D$ −51·5°. The mixture (118 mg) was separated into two fractions by preparative TLC (9 plates). using a 1:3 mixture of C_6H_6 and acetone. The more mobile fraction (R_f 0·60) gave the starting ketone IV (28 mg). which on recrystallization from ether had m.p. 194–195° (17 mg). The less mobile (R_f 0·40) gave crystalline substance (91 mg). which on recrystallization from acetone afforded 22-epimeric ketone V (81 mg). m.p. 256–258°. Recrystallization gave m.p. 261–262°; $[\alpha]_D$ −40°; λ_{max}: 268 mμ (ε 1000). 277 (900) and 303 (300); ν_{max}: 1726. 1662 and 1248 cm^{-1}; ORD; $[\phi]$ −810°. 0°. −315°. 0°. −270°. 0°. +720°. 0°. +630°. 0°. +360° and +810° at 343. 334. 331. 328. 325. 322. 318. 311. 305. 301 and 293 mμ. respectively; NMR. τ 8·99 and 8·75 (each 3H. d J = 5 and 6 c/s. 21- and 26-Me or *vice versa*). 8·86 (3H. s. 19-Me). 7·98 (3H. s. OAc). 7·88. 7·82. 7·77 (each s. 18-Me and NAc). 4·57 (1H. br. 6-H) and 3·05. 2·91 (2H. q of AB type J = 8 c/s. aromatic H). (Found: C. 75·85; H. 8·40; N. 2·79. $C_{31}H_{41}O_4N$ requires: C. 75·73; H. 8·41; N. 2·85%).

Epimerization of 23-*ketones* IV *and* V *under basic and acidic conditions.* (a) The experiment described in the preceding section indicated that the ratio of IV to V after epimerization of IV under the basic conditions was about 1 to 3 (1 to 3·3 from the optical rotation of the mixture. and 1 to 3·1 from the yields after preparative TLC).

(b) 22-Epimeric ketone V (45 mg) was treated with refluxing MeOH (5 ml) containing Na (100 mg) for 2·5 hr and worked up as above to yield oily residue (38 mg). which on acetylation with Ac_2O (1 ml) and Py (1 ml) at room temp overnight afforded a crystalline mixture of IV and V. This showed the optical rotation of $[\alpha]_D$ −52·0° and amounted to 43 mg. The mixture was separated by preparative TLC to yield IV (10 mg as crude crystals and 4 mg as pure. m.p. 192–195°) and V (29 mg as crude crystals and 23 mg as pure.

m.p. 257–258°). The result revealed that the ratio of IV to V after epimerization of V was about 1 to 3 (1 to 3·2 from optical rotation, and 1 to 2·9 from isolated yields).

(c) Compound IV (30 mg) was dissolved in MeOH (4 ml) saturated with HCl at 0° and kept in a refrigerator (*ca* 0°) for 2·5 hr (the same acidic conditions as those in the thioketalization). The soln was poured into ice-water and extracted with $CHCl_3$ (3 × 3 ml). The $CHCl_3$ soln was washed with H_2O (3 × 10 ml), dried and evaporated to leave amorphous residue, which was acetylated as mentioned above. The product (26 mg) crystallized on trituration with ether and was submitted to separation by preparative TLC. The recovered starting ketone IV (26 mg as crude crystals) and the epimer V (2 mg as crude) had m.ps 194–196° (21 mg) and 258–260° on recrystallization from ether and acetone, respectively (the ratio of IV to V, 13 to 1).

Compound IV (30 mg) was treated under the same conditions in MeOH (4 ml) saturated with HCl at room temp for 2·5 hr and worked up as above. Amorphous substance (31 mg), obtained after acetylation, was separated in the usual manner and afforded IV (24 mg as crude crystals) and V (5 mg), which on recrystallization had m.ps 194–196° and 259–260° and amounted to 18 and 5 mg, respectively (the ratio of IV to V, 5 to 1).

N-*Acetyl*-23-*dehydroveratramine* 23-*ethylenedithioketal* (X). Into MeOH (2 ml) saturated with HCl were added IV (106 mg) and ethanedithiol (IX, 0·5 ml) at 0° and then HCl gas was passed in at 0° for 1 hr. After being at 0° for 2 hr, the soln was diluted with $CHCl_3$ (10 ml), and solid $NaHCO_3$ added until evolution of CO_2 had ceased. The ppt formed was filtered, the filtrate evaporated and the residue again dissolved in $CHCl_3$. The $CHCl_3$ soln was washed with 2N HCl and H_2O, dried and evaporated to leave a crystalline substance, 83 mg after recrystallization (two spots on TLC). The crystalline mixture was then separated by prep. TLC (ether). The fraction with large R_f value (0·30) afforded ketal X (34 mg) after recrystallization from ether, which had m.p. 155–156° and showed a single spot; $[\alpha]_D$ −77·3° (MeOH); λ_{max}: 268 mμ (ε 1400), 277 (1200) and 306 (shoulder, 250); ν_{max}: 3220, 1655 (shoulder), 1634, 1054 and 810 cm^{-1}. (Found: C, 71·12; H, 8·22; N, 2·58. $C_{31}H_{43}O_2NS_2$ requires: C, 71·09; H, 8·27; N, 2·66%).

The fraction with small R_f value (0·23) amounted to 39 mg but again showed two spots (X and XI) with almost the same intensity, which were again separated by prep. TLC, yielding X (20 mg), m.p. 155–156°, identical with ketal X described above. By repeated chromatography compound X was obtained pure in 62% yield (66 mg).

N-*Acetylverarine* (Ia) *and verarine* (I). (a) A soln of X (100 mg) in EtOH (4 ml) was refluxed with Raney Ni (W-2, 2·0 g) for 10 hr. After removal of catalyst and solvent, the residue (77 mg) was dissolved in $CHCl_3$, the $CHCl_3$ soln washed with 2N HCl, 5% $NaHCO_3$aq and H_2O, dried and evaporated to yield an oily substance. This was crystallized from ether–isopropyl ether, collected by filtration and washed rapidly with ether (53 mg). Further recrystallization from ether–isopropyl ether gave Ia, m.p. 195–197°, identical in all respects with authentic sample derived from natural verarine (I); $[\alpha]_D$ −15·0° (EtOH) and −20·8° ($CHCl_3$); λ_{max}: 267 mμ (930) and 275 (900); ν_{max}: 3410, 1610, 1263, 1150, 1068 and 808 cm^{-1}; NMR; τ 9·01 and 8·78 (each 3H, d J = 7 and 6·5 c/s, 21- and 26-Me or *vice versa*), 8·83 (3H, s, 19-Me), 8·18 (s, NAc), 7·68 (3H, s, 18-Me), 4·45 (1H, br, 6-H) and 3·04, 2·84 (2H, q of AB type J = 8 c/s, aromatic H); Mass, *m/e* 140 (base peak, XIII) and 295 (10%). (Found: C, 79·80; H, 9·65; N, 3·01. $C_{29}H_{41}O_2N$ requires: C, 79·95; H, 9·49; N, 3·22%).

The crystalline mixture (300 mg) of X and XI described before was treated with Raney Ni (6·0 g) in refluxing EtOH (12 ml) for 10 hr. The mixture was worked up as above and gave crude Ia, crystallized on trituration with acetone. Recrystallization from ether–isopropyl ether afforded Ia (149 mg), m.p. 194–195°, identical in all respects with the afore-mentioned sample of Ia.

(b) Na pellets (123 mg) were completely dissolved in DEG (4·6 ml) under heating (*ca* 110°). To the soln were added anhydrous hydrazine[26] (0·65 ml) and Ia (73 mg) at *ca* 90°, and the mixture was heated at 185° for 12 hr. After cooling the soln was mixed with H_2O and extracted with $CHCl_3$ repeatedly. The $CHCl_3$ soln was washed with H_2O, dried and evaporated to leave colorless oily residue (66 mg), which was again dissolved in $CHCl_3$ (5 ml). The soln was shaken with 2N HCl (2 × 5 ml), and the aqueous layer was then basified with 1N NaOHaq, extracted with $CHCl_3$, washed with H_2O and dried. The $CHCl_3$ soln left amorphous substance (41 mg), crystallized from isopropyl ether–ether–acetone. Recrystallization from ether afforded I, m.p. 174–176°, identical with natural verarine (m.m.p., IR and TLC); ν_{max}: 3240, 1055 and 810 cm^{-1}; NMR,[2] τ 9·20 and 8·86 (each 3H, d J = 6 and 7 c/s, 26- and 21-Me^2), 8·87 (3H, s, 19-Me), 7·77 (3H, s, 18-Me), and 4·52 (1H, br, 6-H) and 3·00 (2H, br s, aromatic H).

N-*Acetyl*-22-*epiverarine* (XIIa) *and* 22-*epiverarine* (XII). To DEG (11 ml) containing KOH (1·3 g) and 80% hydrazine (1 ml) was added 23-ketone IV (100 mg) in EtOH (3·5 ml). The soln was refluxed (*ca* 100°) for 1·5 hr and, after removal of the condenser, heated to *ca* 200° to evaporate excess hydrazine, and then

refluxed at 200° for 2 hr. After cooling, the soln was diluted with H_2O (20 ml), extracted with ether repeatedly. The ether soln was washed with H_2O, dried and evaporated to leave amorphous substance, which crystallized on trituration with ether, 105 mg, two spots on TLC. The crystalline mixture was again dissolved in ether (20 ml), and the soln shaken with 2N HCl (20 ml), when insoluble material (HCl salt?) appeared between both the layers. The ether soln was washed with water, dried and evaporated to leave XIIa (54 mg), m.p. 236–239°. Recrystallization gave m.p. 240–242°. (36 mg); $[\alpha]_D$ −28°; λ_{max}: 269 mμ (ε 870) and 278 (810); ν_{max}: 3419, 1622, 1268, 1060 and 810 cm^{-1}; NMR τ 8·98 (6H?, d J = 6 c/s, 21- and 26-Me), 8·87 (3H, s, 19-Me), 7·86, 7·77, 7·73, (each s, 18-Me and NAc), 4·46 (1H, br, 6-H) and 2·95 (2H, br s, aromatic H); Mass, *m/e* 140 (base peak, XIII) and 295 (13%). (Found: C, 80·00; H, 9·19; N, 3·01. $C_{29}H_{41}O_2N$ requires: C, 79·95; H, 9·49; N, 3·22%).

The afore-mentioned insoluble material and acidic soln were shaken with 10% NaOHaq and ether. The ether soln was washed with H_2O, dried and evaporated to leave resinous residue (22 mg), separated by prep. TLC. The least mobile fraction gave a crystalline substance, recrystallization from ether afforded XII (13 mg), m.p. 210–211°; ν_{max}: 3360, 3165, 1087, 1073 and 805 cm^{-1}; Mass, *m/e* 98 (base peak, XIV) and 295 (10%).

Acknowledgement—The authors are deeply grateful to Doctor J. Tomko, Slovak Academy of Sciencies, for kind donation of verarine as well as identification of N-acetylverarine. They are also indebted to Messrs. S. Shimokawa and Y. Kishio for measurement of the NMR spectra, to Miss G. Maeda and Mrs. T. Tohma for microanalysis, and to Miss Y. Imai for measurement of the Mass spectra.

REFERENCES

[1] J. Tomko and A. Vassová, *Chem. Zvesti* **18**, 266 (1964)
[2] J. Tomko and S. Bauer, *Coll. Czech. Chem. Comm.* **29**, 2570 (1964)
[3] T. Masamune, I. Yamazaki and M. Takasugi, *Bull. Chem. Soc. Japan* **39**, 1090 (1966)
[4] T. Masamune, M. Takasugi, A. Murai and K. Kobayashi, *J. Am. Chem. Soc.* **89**, 4521 (1967)
[5] [a] T. Masamune, M. Takasugi and A. Murai, *Tetrahedron* in press;
[b] W. S. Johnson, H. A. P. deJongh, C. E. Coverdale, J. W. Scott and U. Burckhardt, *J. Am. Chem. Soc.* **89**, 4523 (1967)
[6] J. P. Kutney, J. Cable, W. A. F. Gladstone, H. W. Hanssen, E J. Torupka and W. D. C. Warnock, *Ibid.* **90**, 5332 (1968)
[7] K. Saito, *Bull. Chem. Soc. Japan* **15**, 22 (1940)
[8] W. A. Jacobs and L. C. Craig, *J. Biol. Chem.* **160**, 555 (1945)
[9] H. Budzikiewicz, *Tetrahedron* **20**, 2267 (1964)
[10] A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.* 2548 (1953)
[11] R. L. Augustine, *Chem. Ind. (London)* 1448 (1961)
[12] J. W. Scott, L. J. Durham, H. A. P. deJongh, U. Burckhardt and W. S. Johnson, *Tetrahedron Letters* 2381 (1967)
[13] *Cf.* L. Cagliotti, *Tetrahedron* **19**, 1127 (1963);
L. Cagliotti and P. Grosseli, *Chim. Ind. (Milan)* **46**, 799 (1964)
[14] *Cf.* C. Djerassi, C. H. Robinson and D. B. Thomas, *J. Am. Chem. Soc.* **78**, 5685 (1956)
[15] *Cf.* Y. Sato and N. Ikekawa, *J. Org. Chem.* **24**, 1367 (1959)
[16] *Cf.* S. M. Kupchan, *J. Am. Chem. Soc.* **81**, 1913 (1959)
[17] A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlok, C. Ouannes and J. Jacques, *Bull. Soc. Chim. France*, 1822 (1961)
[18] R. B. Turner, R. B. Miller and Jean-Lee Lin, *J. Am. Chem. Soc.* **90**, 6124 (1969)
[19] Huang-Minlon, *Ibid.* **71**, 3301 (1949)
[20] Ref. 12 in the preceding paper (Ref. 5a)
[21] T. Masamune, K. Kobayashi, M. Takasugi, Y. Mori and A. Murai, *Tetrahedron* **24**, 3461 (1968)
[22] R. W. Franck, G. P. Rizzi and W. S. Johnson, *Steroids* **4**, 463 (1964)
[23] D. M. Bailey, D. P. G. Hamon and W. S. Johnson, *Tetrahedron Letters* 555 (1963)
[24] T. Masamune, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)* **91**, 407 (1970)
[25] H. Paulsen and K. Todt, *Angew. Chem.* **78**, 943 (1966)
[26] L. I. Smith and K. L. Howard, *Org. Syntheses* **24**, 53 (1948)