Journal of Natural Products
Vol. 50, No. 4, pp. 642-645, Jul-Aug 1987

ON THE CONFIGURATION OF SOLAQUIDINE

GINA MECCIA and ALFREDO N. USUBILLAGA*

Instituto de Investigacion Quimica, Facultad de Farmacia, Universidad de Los Andes, Merida, Venezuela

ABSTRACT.—*N*-Acetyl-(22*S*,25*R*)-22,26-epimino-5α-cholestan-3-one [**4d**], an acetylated derivative of solaquidine [**5**], was obtained from solasodine [**1a**] by synthesis, showing that the configuration of **5** should be 5α,22*S*,25*R*.

In a previous study (1) solaquidine [**5**], isolated from the green berries of *Solanum pseudoquina* St. Hil. (Solanaceae), was assigned a 3,3-dimethoxy-22,26-epiminocholestane structure, but its configuration at C-5, C-22, and C-25 remained undetermined. To establish the absolute configuration at those chiral centers, the synthesis of **4d**, the acetylated derivative of the natural compound, was undertaken.

A ten-step partial synthesis was performed starting from solasodine [**1a**]. This compound was chosen as starting material because it possesses a well-established 22*R*, 25*R*, configuration, which upon opening the E ring changes to 22*S*, 25*R*; the latter was thought the most probable configuration for a steroidal alkaloid like **5**. To obtain the target compound, it was required to open the E ring, saturate the double bond, and eliminate the oxygen from C-16. Several techniques are available in the literature to perform this task (2,3). It was decided to follow a route similar to that employed by Kusano *et al.* (4). The synthesis of **5** itself was not tried because generation of a 3,3-dimethoxy functionality would require acid catalysis, which would produce isomerization at C-25 (5).

Esterification of **1a** with HOAc gave *O*-acetyl-solasodine [**1b**], which on reduction with $NaBH_4$ produced *O*-acetyl-dihydrosolasodine [**2**]. Hydrogenation of **2** with Adam's catalyst in HOAc yielded **3a**. The saturated compound was diluted in C_6H_6 and treated with benzylchloroformate to obtain the *N*-benzyloxy derivative [**3b**].

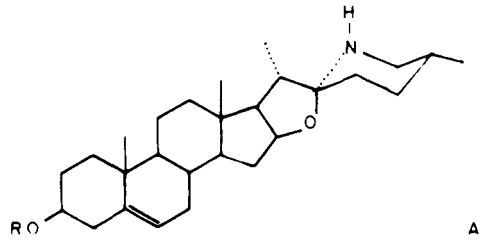
To remove the oxygen from C-16, **3b** was first treated with Kiliani's reagent to obtain the 16-ketone [**3c**]. A solution of this compound in glacial HOAc was stirred during 72 h with *p*-TsOH and 1,2-ethanedithiol to obtain the corresponding dithioketal [**3d**]. The dithioketal derivative was refluxed with Raney Ni in EtOH, producing the simultaneous removal of the benzyloxy group and desulfuration to yield **4a**.

Acetylation of **4a** with Ac_2O/pyridine followed by mild hydrolysis produced **4c**, which was treated with Jones's reagent to yield the desired end product **4d**. This compound was found to be identical to the acetylated product of solaquidine (mmp, tlc, ir, ^1H nmr, and ms). It was, therefore, concluded that the natural product has a 5α, 22*S*, 25*R* configuration, because none of the reactions used in the sequence would modify the configuration of those chiral centers.

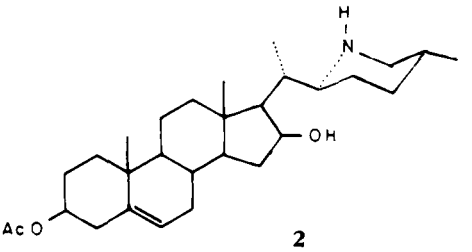
The final product was obtained in an overall yield of 6%. The lowest yield was obtained in the thioketalization reaction (about 42%).

EXPERIMENTAL

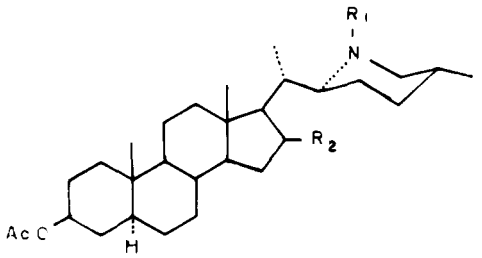
GENERAL EXPERIMENTAL PROCEDURES.—Tlc was performed on Si gel G plates, and the spots were visualized with I_2 vapors. Melting points were determined on a Fisher-Johns hot-stage and are uncorrected. Optical rotations were measured on a Rudolph Research automatic polarimeter, model Autopol III. The ir spectra were recorded in a Perkin-Elmer model 377 spectrometer as KBr disks. The ^1H-nmr spectra were determined in $CDCl_3$ solution with TMS as internal standard, and the chemical shifts are expressed in δ-values; a Varian Ft-80A apparatus was used. The ms spectra were performed at Universidad Central (Caracas) on a Hewlett-Packard 5995 spectrometer. Microanalyses were made at Simon Bolivar University (Caracas).



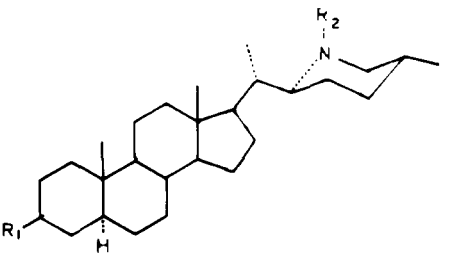
1a R=H
1b R=Ac



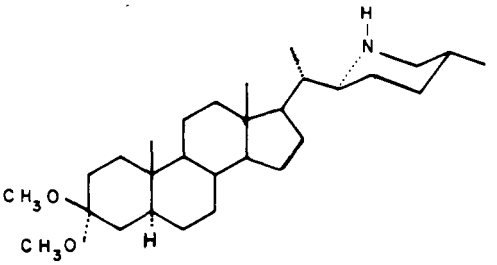
2



	R_1	R_2
3a	H	OH
3b	Cbz	OH
3c	Cbz	=O
3d	Cbz	$=S_2C_2H_4$



	R_1	R_2
4a	OAc	H
4b	OAc	Ac
4c	OH	Ac
4d	=O	Ac



5

(22*R*,25*R*)-22,26-EPIMINO-CHOLEST-5-ENE-3β-OL-ACETATE [**1b**].—To a solution of 15 g of **1a** in 0.85 liters of HOAc, 16 g of *p*-TsOH was added while stirring at room temperature. After 2 h, an additional amount of 5.3 g of *p*-TsOH was added. The mixture was left to react at room temperature for 50 h, after which time 4 liters of a 1% NaCl solution was added, and the mixture was left to stand overnight. The following morning the precipitate was filtered and dissolved in $CHCl_3$. The organic layer was shaken with a 2% solution of NaOH and H_2O. The $CHCl_3$ extract was dried over anhydrous Na_2SO_4 and taken to dryness. The product appeared on tlc mixed with **1a**; it was, therefore, purified over a Si gel column. C_6H_6-EtOAc (5:1) eluted 12.7 g of **1b**, mp 190-192°; $[\alpha]^{22}D$ −102.8° (*c* 0.25, $CHCl_3$). Calcd for $C_{29}H_{45}NO_3$: C 76.43, H 9.95, N 3.07; Found: C 76.17, H 10.23, N 3.01; ir ν max 3400, 1720, 1250 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 0.84 (3H, s, C-18 Me), 1.05 (3H, s, C-19 Me), 0.95 (3H, d, *J*=7 Hz, C-21 Me), 0.85 (3H, d, *J*=7 Hz, C-27 Me), 2.01 (3H, s, OAc), 4.15 (1H, t, *J*=6 Hz, 16α-H), 4.55 (1H, m, 3α-H), 5.3 (1H, d, *J*=4 Hz, C6-H).

3β-*O*-ACETYL-(22*S*,25*R*)-22,26-EPIMINO-CHOLEST-5-ENE-16β-OL [**2**].—To a solution of 12.0 g of **1b** in 600 ml of a mixture of MeOH-CH_2Cl_2 (5:1), 4.8 g of $NaBH_4$ was added while stirring in an ice bath. After 2 h, 1 liter of cold H_2O was added, the aqueous phase was extracted twice with $CHCl_3$, and the $CHCl_3$ phase was taken to dryness. The product (9.85 g) crystallized from EtOAc, mp 210-211°; $[\alpha]^{22}D$ −66.4 (*c* 0.25, $CHCl_3$); calcd. for $C_{29}H_{47}NO_3$: C 76.10, H 10.35, N 3.06; Found: C 76.39, H 10.23, N 3.17; ir ν max 1720, 1250 cm^{-1}; ^{1}H nmr (80 MHz, $CDCl_3$) δ 0.93 (3H, s, C-18 Me), 1.04 (3H, s, C-19 Me), 1.06 (3H, d, *J*=7 Hz, C-21 Me), 0.93 (3H, d, *J*=7 Hz, C-27 Me), 2.01 (3H, s, OAc), 4.35 (1H, dd, *J*=14; 6 Hz, 16α-H), 4.55 (1H, m, 3α-H), 5.3 (1H, d, *J*=4 Hz, C6-H).

3β-*O*-ACETYL-(22*S*,25*R*)-22,26-EPIMINO-5α-CHOLESTAN-16β-OL [**3a**].—Acetyl-dihydrosolasodine (9.0 g) dissolved in 200 ml of glacial HOAc was hydrogenated catalytically with 1.0 g of PtO_2 at 60 psig for 3 days. The catalyst was filtered off, and the filtrate was evaporated to a small volume. H_2O was added, the solution made alkaline by the addition of NH_4OH and shaken twice with $CHCl_3$. The organic phase was washed with H_2O, dried over anhydrous Na_2SO_4, and taken to dryness. Crystallization from EtOAc yielded 8.85 g of **3a**, mp 183-185°, $[\alpha]^{22}D$ −13.2° (*c* 0.25, $CHCl_3$); ir ν max 3410, 1720, 1250 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ 0.83 (3H, s, C-18 Me), 0.90 (3H, s, C-19 Me), 1.02 (3H, d, *J*=7 Hz, C-21 Me), 0.80 (3H, d, *J*=7 Hz, C-27 Me), 2.01 (3H, s, OAc), 2.95 (1H, d, *J*=12 Hz, 22-H), 4.35 (1H, dd, *J*=12; 7 Hz, 16α-H), 4.6 (1H, m, 3α-H).

3β-*O*-ACETYL-*N*-BENZYLOXY-(22*S*,25*R*)-22,26-EPIMINO-5α-CHOLESTAN-16β-OL [**3b**].—To a solution of 8.5 g of **3a** in 1 liter of C_6H_6, 500 ml of a 5% solution of $NaHCO_3$ and 12.32 g of a solution of benzyl chloroformate (Cbz-Cl) in toluene were added. The latter was equivalent to 6.16 g of Cbz-Cl and was prepared according to Carter *et al.* (6). After 4 h of shaking the mixture at ambient temperature, an additional 6.1 g of Cbz-Cl soln was added and left standing overnight. The organic layer was separated, washed several times with H_2O, dried over Na_2SO_4, and taken to dryness. The residue was chromatographed over a Si gel column. C_6H_6-EtOAc (10:1) eluted 8.3 g of **3b**, which crystallized from EtOAc, mp 114-115°; $[\alpha]^{22}D$ −9.6° (*c* 0.25, $CHCl_3$); ir ν max 3440, 1710, 1660, 1250 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ 0.80 (6H, s, C-18 and C-19 Me), 0.94 (3H, d, *J*=7 Hz, C-21 Me), 0.98 (3H, d, *J*=7 Hz, C-27 Me), 2.02 (3H, s, OAc), 3.10 (1H, dd, *J*=14; 6 Hz, 26β-H); 3.81 (1H, d, *J*=12 Hz, 26α-H), 4.12 (1H, t, *J*=4 Hz, 16α-H), 4.40 (1H, m, 22-H), 4.69 (1H, m, 3α-H), 5.01 and 5.21 (2H, ABq, *J*=12 Hz, Bz-H_2), 7.34 (5H, bs, aromatic H).

3β-*O*-ACETYL-*N*-BENZYLOXY-(22*S*,25*R*)-22,26-EPIMINO-5α-CHOLESTAN-16-ONE [**3c**].—To a solution of 8.0 g of **3b** in 250 ml of Me_2CO, small portions of Kiliani's reagent were added at 5°. After addition of 14 ml of reagent, the mixture was stirred overnight at room temperature. The following day 20 ml of MeOH and 250 ml of H_2O were added, and the mixture was shaken twice with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated to dryness under vacuum. The residue was purified over a Si gel column. C_6H_6-EtOAc (100:1) eluted **3c** (7.05 g) which crystallized from C_6H_{12}/C_6H_6 mp 148-150°; $[\alpha]^{22}D$ −74° (*c* 0.25, $CHCl_3$). Calcd for $C_{37}H_{53}NO_5$: C 75.09, H 9.03, N 2.37; Found: C 75.28, H 9.08, N 2.31; ir ν max 1735, 1720, 1250, 1680 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ 0.82 (6H, s, C-18 and C-19 Me), 0.92 (3H, d, *J*=7 Hz, C-21 Me), 0.77 (3H, d, *J*=7 Hz, C-27 Me), 2.01 (3H, s, OAc), 2.95 (1H, m, 26β-H), 3.75 (1H, m, 26α-H), 4.48 (1H, m, 22-H), 4.70 (1H, m, 3α-H), 5.01 and 5.21 (2H, ABq, *J*=12 Hz, Bz-H_2), 7.30 (5H, bs, aromatic H).

THIOKETALIZATION OF **3c**.—To a solution of 6.0 g of **3c** in 60 ml of glacial HOAc, 2 ml of ethanedithiol and 2.6 g of *p*-TsOH were added. The mixture was stirred for 3 days at room temperature. H_2O was then added and the mixture shaken with $CHCl_3$. The organic layer was shaken with a 5% solution of $NaHCO_3$, washed with H_2O, dried over Na_2SO_4, and taken to dryness. The residue was purified on a Si gel column. C_6H_6 eluted 2.85 g of **3d**, mp 98-100° (from EtOH/Me_2CO); $[\alpha]^{22}D$ −52° (*c* 0.25, $CHCl_3$); ir ν max 1715, 1250, 1680 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ 0.80 (6H, s, C-18 and C-19 Me), 0.96 (3H, d, *J*=7 Hz, C-27 Me), 1.03 (3H, d, *J*=7 Hz, C-21 Me), 2.02 (3H, s, O-Ac), 2.95 (1H, m, 26β-H), 3.05, 3.22, and 3.40 (4H, multiplets, $S_2C_2H_4$), 3.80 (1H, m, 26α-H), 4.70 (1H, m, 3α-H), 5.02 and 5.21 (2H, ABq, *J*=12 Hz, Bz-H_2), 7.3 (5H, bs, aromatic H). Elution with C_6H_6-EtOAc (100:1) yielded 2.2 g of **3c**.

(22*S*,25*R*)-22,26-EPIMINO-5α-CHOLESTAN-3β-OL-ACETATE [**4a**].—The thioketal derivative (2.0 g) was dissolved in absolute EtOH and refluxed for 2 h with an excess of Raney Ni. The mixture was left overnight at room temperature; the following morning the catalyst was filtered off carefully, and the filtrate yielded 0.77 g of **4a**, mp 212-214°; $[\alpha]^{22}D$ 13.2° (*c* 0.25, $CHCl_3$). Calcd for $C_{29}H_{49}NO_2$: C 78.50, H 11.13, N 3.16; Found: C 78.32, H 11.25, N 3.08; ir ν max 1715, 1250 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ 0.70 (3H, s, C-18 Me), 0.85 (3H, s, C-19 Me), 0.83 (3H, d, *J*=7 Hz, C-27 Me), 0.92 (3H, d, *J*=7 Hz, C-21 Me), 2.01 (3H, s, O-Ac), 2.90 (1H, d, *J*=12 Hz, C-22H), 4.7 (1H, m, 3α-H); ms *m/z* 443 (M^+, $C_{29}H_{49}NO_2$, 0.1%), 401 (0.1%), 98 ($C_6H_{12}N$, base peak).

(22*S*,25*R*)-22,26-ACETYLEPIMINO-5α-CHOLESTAN-3β-OL-ACETATE [**4b**].—The acetylation of **4a** (0.69 g) was performed in the usual way at room temperature. After addition of cold H_2O, the precipitate was filtered, washed, and crystallized from MeOH. The *O,N*-diacetate (0.53 g) was obtained as fine needles, mp 164-165°; $[\alpha]^{22}D$ 0.25 (*c*, 0.16, $CHCl_3$). Calcd for $C_{27}H_{51}NO_3$: C 76.65, H 10.58, N 2.88; Found: C 76.47, H 10.72, N 2.96; ir ν max 1720, 1250, 1640 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ 0.73 (3H, s, C-18 Me), 0.84 (3H, s, C-19 Me), 0.90 (3H, d, *J*=7 Hz, C-27 Me), 0.99 (3H, d, *J*=7 Hz, C-21 Me), 2.01 (3H, s, O-Ac), 2.08 (3H, s, N-Ac), 3.25 (1H, m, C-22 H), 4.55 (1H, m, 3α-H).

(22*S*,25*R*)-22,26-ACETYLEPIMINO-5α-CHOLESTAN-3β-OL [**4c**].—A solution of 450 mg of **4b** in 200

ml of MeOH was mixed with 200 mg of K_2CO_3 dissolved in 5 ml of H_2O and let stand overnight at room temperature. The following morning the mixture was shaken with $CHCl_3$. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue (410 mg) was crystallized from MeOH as colorless needles, mp 258-260°; $[\alpha]^{22}D$ 10.8° (*c* 0.25, $CHCl_3$). Calcd for $C_{29}H_{49}NO_2$: C 78.50, H 11.13, N 3.16; Found: C 78.37, H 11.30, N 3.25; ir ν max 3420, 1640 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ 0.72 (3H, s, C-18 Me), 0.82 (3H, s, C-19 Me), 0.85 (3H, d, J=7 Hz, C-27 Me), 0.95 (3H, d, J=7 Hz, C-21 Me), 2.08 (3H, s, N-Ac), 3.60 (1H, m, 3α-H); ms *m/z* 443 (M^+, $C_{29}H_{49}NO_2$, 0.1%), 140 (base peak), 98 (38.9%).

(22*S*,25*R*)-22,26-ACETYLEPIMINO-5α-CHOLESTAN-3-ONE [**4d**].—To a solution of **4c** (300 mg) in Me_2CO, Jones reagent was added dropwise at room temperature. After 15 min a few drops of i-PrOH were added to destroy excess reagent. The solution was mixed with an excess of H_2O and extracted with $CHCl_3$. The organic layer was shaken with H_2O, dried over anhydrous Na_2SO_4, and evaporated to dryness. The product (220 mg) was purified over a small basic alumina column and crystallized in Me_2CO (152 mg), mp 131-135°; $[\alpha]^{22}D$ 21.8° (*c* 0.078, $CHCl_3$). Calcd for $C_{29}H_{47}NO_2$: C 78.86, H 10.72, N 3.17; Found: C 78.60, H 10.85, N 3.08; ir ν max 1710, 1630 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ 0.72 (3H, s, C-18 Me), 0.99 (3H, s, C-19 Me), 0.86 (3H, d, J=7 Hz, C-21 Me), 0.92 (3H, d, J=7 Hz, C-27 Me), 2.10 (3H, s, N-Ac), 3.25 (1H, m, C-22 H); ms *m/z* 441 (M^+, $C_{29}H_{47}NO_2$, 0.9%), 440 (1.5%), 427 (1.6%), 398 (1.3%), 300 (1.4%), 140 (98%), 98 ($C_6H_{12}N$, base peak). These spectroscopic properties of **4d** are identical to those of the acetylated derivative of **5**. Both substances co-chromatographed on Si gel G plates using $CHCl_3$-MeOH (20:1) Rf, 0.80, and C_6H_6-EtOAc (1:1) Rf, 0.62. No depression was observed in the mp of **4d** upon mixing with a small amount of the acetylated derivative of **5**.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the support of Consejo de Desarrollo Cientifico, Humanistico y Tecnologico (ULA), Grant Fa-34, of Fundayacucho for a fellowship to G.M. and a generous gift of solasodine hydrochloride by Diosynth, Oss-Holland.

LITERATURE CITED

1. A. Usubillaga, G. de Castallano, J. Hidalgo, C. Guevara, P. Martinod, and A. Paredes, *Phytochemistry*, **16**, 1861 (1977).
2. H. Ripperger and K. Schreiber, in: "The Alkaloids, Chemistry and Physiology." Ed. by R.H. Manske, Vol. 19, Chap. 2, Academic Press, New York, 1981, pp. 118-142.
3. J.G. Bird, D.J. Collins, F.W. Eastwood, and R.H. Exner, *Aust. J. Chem.*, **32**, 797 (1979).
4. G. Kusano, T. Takemoto, Y. Sato, and D. Johnson, *Chem. Pharm. Bull.*, **24**, 661 (1976).
5. R.E. Marker, A.C. Shabica, and D.L. Turner, *J. Am. Chem. Soc.*, **63**, 2274 (1941).
6. H.E. Carter, R.L. Frank, and H.W. Johnstone, in: "Organic Syntheses." Ed. by E.C. Horning, Collective Vol. 3, John Wiley and Sons, New York, 1955, pp. 167-169.

Received 3 November 1986