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AN ACID-CATALYZED ISOMERIZATION OF ISOATISINE

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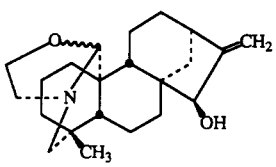
ABSTRACT.—An acid-catalyzed isomerization of isoatisine [**3**] at room temperature gives a hydrate **6** as the major product as well as a mixture of the methyl ketones **4** and **5**. The structure of compound **6** was determined by its spectral data, including nOe difference and 2D COSY nmr spectra. The formation of **6** suggests that the carbocation **9** is an intermediate in the formation of the methyl ketones **4** and **5** during the acid-catalyzed isomerization of isoatisine.

An acid-catalyzed allylic rearrangement of the diterpenoid alkaloids garryfoline [**1**], napelline, etc., which have a [3.2.1]bicyclooctane ring system, occurs at room temperature; the product in the case of **1**, i.e., cuauchichicine [**2**], is a single methyl ketone in which the C-16 methyl has a β orientation (1).

An acid-catalyzed isomerization of isoatisine [**3**] containing a [2.2.2]bicyclooctane ring system, by refluxing in ethanolic HCl, gives a mixture of two epimeric methyl ketones **4** and **5** (2). A pure sample of compound **4** was available (2), but a pure sample of compound **5** was not available. All the fractions containing compound **5** were found to be mixtures of **4** and **5**. In order to obtain pure samples of **4** and **5** for further study, we carried out an acid-catalyzed isomerization of isoatisine at room temperature.

A solution of isoatisine [**3**] in ca. 7% aqueous HCl was stirred for 7 days at



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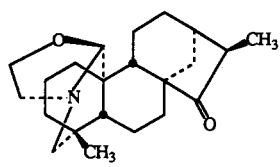

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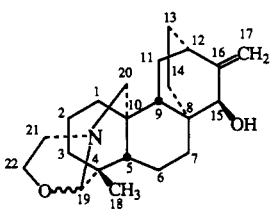

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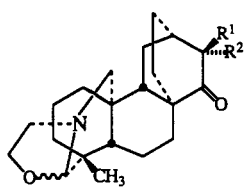
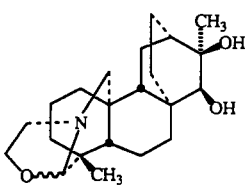


4 R^1=Me, R^2=H
5 R^1=H, R^2=Me



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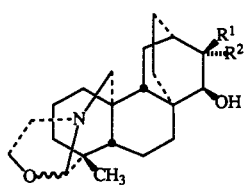


7 R^1=Me, R^2=H
8 R^1=H, R^2=Me

room temperature. The mixture of products was fractionated on an alumina rotor of a Chromatotron (3). Compound **4** could be isolated pure, but **5** could not, even after repeated crystallization. Besides these compounds, a highly polar product **6**, mp 102–105°, was also isolated in a yield of 50%.

In an attempt to obtain a pure sample of **5** and to confirm the structure of **4**, compounds **7** and **8** were synthesized using the reported procedures starting with α- and β-tetrahydroatisines (4). The structure of β-tetrahydroatisine has been confirmed by a single-crystal X-ray analysis (4). Oxidation of **7** with pyridinium chlorochromate (PCC) gave compound **4** (mp 158–160°); its tlc, mp, ir, and ^{1}H-nmr spectra were identical with those reported for **4** (2). The structure of **4** was further supported by its ^{13}C-nmr spectrum (not reported earlier). The chemical shifts (Table 1) were assigned on the basis of DEPT experiments and by comparing them with those of isoatisine (5) and related compounds. Oxidation of **8** with PCC, however, did not furnish a pure sample of **5**. Compound **5** epimerized rapidly in contact with alumina; hence its purification was carried out on a silica plate. However, its ^{13}C-nmr spectrum still showed the presence of signals due to contamination with compound **4**. The ^{13}C-nmr chemical shifts for **5** were assigned from the major peaks of the spectrum and are given in Table 1.

The structure of the highly polar product **6** mentioned above was elucidated on the basis of its spectral data. The molecular formula, $C_{22}H_{33}NO_3$, was derived from the mass spectrum *m/z* $[M+1]^+$ 360 (calcd for $C_{22}H_{33}NO_3$, 359) and the ^{13}C-nmr (DEPT) spectra. The presence of two hydroxyl groups was observed in the ir spectrum (3340, 3300

TABLE 1. ^{13}C Chemical Shifts (in ppm downfield from TMS) and Assignments for Compounds **3–6**.[a]

Carbon	3	4	5	6[b]	6[c]
C-1	40.6	40.5 t	40.5	40.1 t	40.5 t
C-2	22.1	22.2 t	22.2	22.3 t	22.5 t
C-3	40.0	40.0 t	43.4	41.1 t	40.9 t
C-4	38.1	39.5 s	39.4	38.1 s	38.3 s
C-5	48.6	48.5 d	48.5	49.1 d	49.2 d
C-6	19.2	19.0 t	18.9	19.8 t	19.9 t
C-7	31.9	29.4 t	29.7	32.9 t	33.2 t
C-8	37.5	44.6 s	44.5	38.4 s	38.3 s
C-9	39.6	45.1 d	45.5	39.5 d	40.0 d
C-10	35.9	36.0 s	36.0	36.2 s	36.1 s
C-11	28.1	24.6 t	25.3	28.7 t	28.3 t
C-12	36.4	44.4 d	45.4	38.6 d	39.9 d
C-13	27.6	26.6 t	28.0	22.6 t	22.7 t
C-14	26.4	22.2 t	21.1	25.0 t	25.2 t
C-15	76.8	219.0 s	219.0	84.3 d	84.5 d
C-16	156.2	33.4 d	33.3	76.4 s	75.9 s
C-17	109.6	14.5 q	14.8	24.8 q	25.2 q
C-18	24.3	24.2 q	24.2	24.6 q	24.7 q
C-19	98.4	98.4 d	98.4	98.4 d	98.4 d
C-20	49.8	49.4 t	49.5	50.2 t	50.1 t
C-21	54.9	54.9 t	54.8	55.1 t	55.2 t
C-22	58.6	58.2 t	58.7	59.0 t	58.9 t

[a]It has been observed that compounds **3–6** exist as a mixture of C-19 epimers (mixture ~10%) as indicated by their ^{13}C-nmr spectra.

[b]Spectrum recorded in C_6D_6.

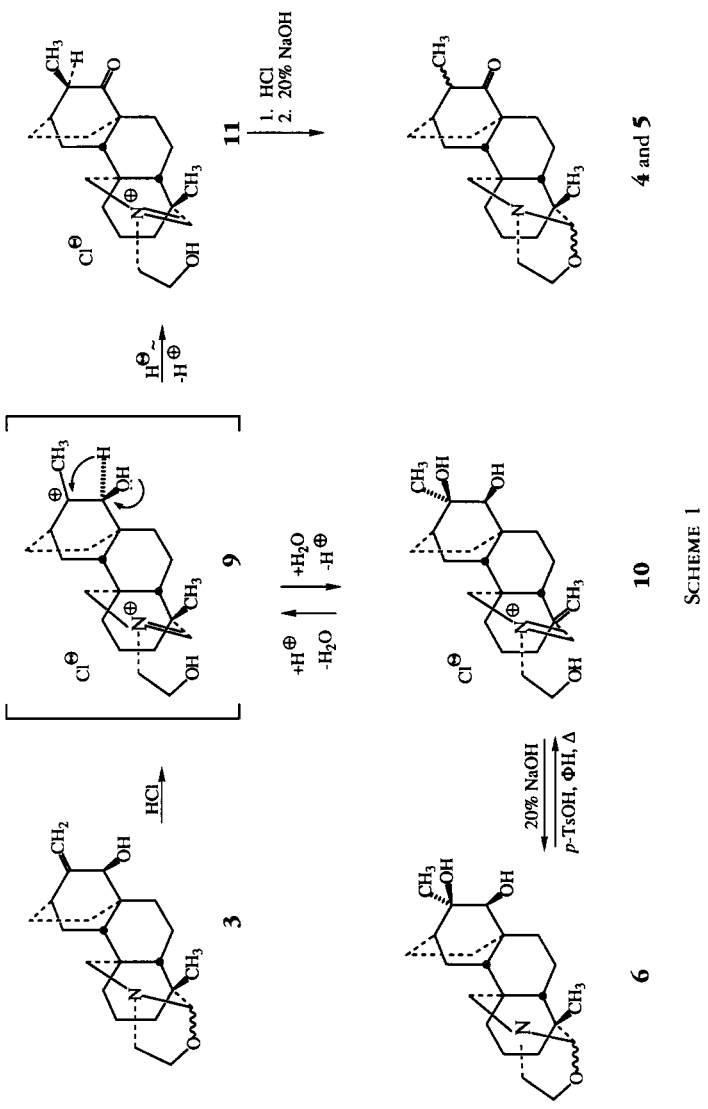
[c]Spectrum recorded in pyridine-d_5.

cm^{-1}). The ^{13}C-nmr spectrum (C_6D_6, Table 1) of compound **6** showed 22 lines for the 22 carbon atoms of the molecule as well as small peaks for the C-19 epimer. The DEPT spectra indicated the presence of four quaternary carbons (76.4, 38.4, 38.1, and 36.2 ppm), five methine carbons (98.4, 84.2, 49.1, 39.5, and 38.5 ppm), eleven methylene carbons (59.0, 55.1, 50.1, 41.0, 40.5, 32.9, 28.2, 25.0, 22.6, 22.3, and 19.8 ppm), and two methyl carbons (24.8 and 24.6 ppm). A new oxygenated quaternary carbon at 76.4 and a new methyl group at 24.8 ppm appeared in the ^{13}C-nmr spectrum of **6**, and the signals due to the exocyclic double bond of the starting material (5) disappeared. This result indicated that one molecule of H_2O had been added to the exocyclic double bond of isoatisine. The ^1H-nmr spectrum (300 MHz, pyridine-d_5) showed the presence of two methyl groups at δ 1.14 and 1.78 ppm (3H each, s), assigned to 4-Me and 16-Me, respectively, and an AB-system at δ 2.88 and 2.98 ppm (1H each, d, $J = 11.7$ Hz) attributed to the 2H-20. A sharp singlet at δ 3.98 ppm was assigned for the H-19, because it showed an nOe enhancement (6.9%) to the 4β-Me in an nOe difference experiment. The H-15α appeared at δ 3.69 ppm as a doublet ($J = 5.4$ Hz) owing to coupling with the 15β-OH (δ 6.44 ppm, d, $J = 5.6$ Hz), as indicated in a 2D COSY spectrum. After addition of D_2O, the 15β-OH and 16-OH (δ 5.74 ppm, 1H, s) disappeared, and the H-15α became a singlet. The four proton signals of the isooxazolidine ring were located at δ 2.96, 3.10, 3.44, and 3.68 ppm (1H each, m), and their complex coupling relationships were shown in the 2D COSY spectrum. The stereochemistry of the groups on C-16 was deduced from the nOe difference experiment. Thus, when the 16-Me was irradiated, the H-15α showed an nOe enhancement (6.5%). Therefore, the C-16 methyl group is most likely in the α position, which is close in space to the H-15α. Hence, compound **6** has a *cis*-diol moiety. Attempts to prepare an acetonide adduct of **6** met with failure, probably because of the presence of a tertiary OH group on C-16. An attempt to methylenate the *cis*-diol **6** according to our published procedure (6) gave a product identified by its ^{13}C-nmr spectrum as a mixture of the methyl ketones **4** and **5**.

A plausible mechanism for the isomerizations is proposed in Scheme 1. Protonation of the exocyclic double bond of isoatisine [**3**] generates a carbocation **9**. At room temperature, this intermediate is attacked by H_2O to give **10**, which upon the basic workup affords the diol **6** as a major product. However, under refluxing conditions intermediate **9** undergoes exclusively a pinacol-type hydride shift from the α face to **11**, which upon epimerization via an enol in acidic medium and basic workup gives two methyl ketones **4** and **5**. This well-documented epimerization is confirmed in our experiment; thus, submitting pure **4** at room temperature to the action of 7% aqueous HCl led to the formation of a mixture of **4** and **5**, as revealed by the ^{13}C-nmr spectrum. The formation of the diol **6** clearly indicates that carbocation **9** is a key intermediate in the isomerization. This study shows that the mechanism of the acid-catalyzed isomerization of a [2.2.2]bicyclooctane ring system is different from that of a [3.2.1]bicyclooctane ring system, which proceeds via enol formation followed by exo-protonation (1).

EXPERIMENTAL

Melting points are corrected and were taken on a Thomas-Kofler hot stage equipped with a microscope and a polarizer. Ir spectra were recorded on a Perkin-Elmer model 1420 spectrophotometer. ^1H- and ^{13}C-nmr spectra were recorded on JEOL FT models FX-60 and FX-270 spectrometers. 2D-COSY and nOe difference spectra were recorded on a Bruker WM 300 spectrometer. Mass spectra were determined on a Finnegan Quadrupole 4023 instrument.



SCHEME 1

ATISINE [3].—A solution of isoatisine [3] (230.0 mg) in 7% aqueous HCl was kept at room temperature for 7 days. The reaction mixture was cooled in an ice-H_2O bath and basified to pH 14 with 20% NaOH solution. The separated white material was extracted with Et_2O (3 × 30 ml). The Et_2O extract was washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo to give a solid residue (212.0 mg). The residue was fractionated on an alumina rotor (1 mm, EM 1104-3) and eluted with a gradient of hexane, Et_2O, and MeOH. Homogeneous (tlc) fractions were combined. Fractions 1–6 gave a gummy residue A (107.5 mg), and fractions 7–8 gave a gummy residue B (99.5 mg). The latter fractions were eluted with Et_2O containing 2 and 3% MeOH. The ^{13}C-nmr spectrum of residue A indicated that it was a mixture of compounds **4** and **5**. Residue B crystallized from Et_2O to afford compound **6** (50%): mp 102–105°, eims *m/z* $[M+1]^+$ 360 (for $C_{22}H_{33}NO_3$, 359); ir (Nujol) ν max 3340 and 3300 cm^{-1}; ^{1}H nmr (pyridine-d_5) δ 1.14 (3H, s, 4-CH_3), 1.78 (3H, s, 16-CH_3), 3.69 (1H, d, J = 5.4 Hz, H-15α, doublet becomes a singlet on D_2O addition), 3.98 (1H, s, H-19β), 5.77 (1H, s, 16-OH), 6.44 (1H, d, J = 5.4 Hz, 15β-OH) (the last two signals disappeared on addition of D_2O); ^{13}C nmr see Table 1.

OXIDATION OF COMPOUND **7**.—To a solution of **7** (51.1 mg) in CH_2Cl_2 (7 ml), PCC (50 mg) was added with stirring. After 1 h the solution became dark-colored, and tlc showed a very faint spot corresponding to the starting material. $CHCl_3$ (30 ml) was added to the reaction mixture, and the solution was passed over a small column of alumina. The eluted solution was washed with H_2O, and the organic layer was again passed over a small column of alumina. The eluted solution on evaporation gave a brownish residue (43.1 mg) which was fractionated on an alumina rotor (1 mm, EM 1104-3) of a Chromatotron (3). Elution was carried out with hexane with increasing amounts of EtOH. Fractions eluted with hexane/2% EtOH gave a homogeneous compound that crystallized from Me_2CO, mp 158–160° (12.6 mg, 25%). Its tlc, co-tlc, mp, ir, and ^{1}H-nmr spectra were identical with those reported for compound **4** (4). For ^{13}C-nmr chemical shifts assignments see Table 1.

EPIMERIZATION OF **4** IN 7% AQUEOUS HCl.—A solution of compound **4** (32 mg) in 7% HCl was kept at room temperature for 4 days. The ice-cold reaction mixture was basified with Na_2CO_3 solution and then extracted with Et_2O. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to dryness in vacuo. The ^{13}C-nmr spectrum of the residue (31.5 mg) indicated it to be a mixture of methyl ketones **4** and **5** (δ 14.5 and 14.8 ppm).

OXIDATION OF COMPOUND **8** (4).—To a solution of **8** (60.0 mg) in CH_2Cl_2 (7 ml), PCC (60 mg) was added with stirring. After 1.5 h the reaction was worked up as described above. The purification was carried out on a silica plate (20 × 20 cm) using a $CHCl_3$/15% EtOH solvent system. The least polar band gave the oxidized product (31.7 mg; 53.3%), which crystallized from Me_2CO, mp 140–145°. The ^{13}C-nmr spectrum of the product indicated it to be a mixture of methyl ketones **4** and **5**. The major signals were due to compound **5** and are reported in Table 1.

ATTEMPTED PREPARATION OF ACETONIDE OF COMPOUND **6**.—Compound **6** (19.0 mg) was dissolved in dry Me_2CO, and the solution was made acidic (pH 3) with methanolic HCl. The solution was stirred at room temperature for 2 days. Removal of Me_2CO, basification, and extraction of the aqueous solution of the residue with Et_2O gave the starting material. Its ^{13}C-nmr spectrum was identical with that of compound **6**.

METHYLENATION OF COMPOUND **6**.—To a solution of **6** (26.5 mg) in dry C_6H_6 (21 ml) were added diethoxymethane (0.75 ml) and *p*-toluenesulphonic acid (5.0 mg), and the solution was refluxed overnight on a steam bath with a Dean Stark water separator. The reaction mixture was then passed over a small column of alumina (neutral activity III), and the column was washed with C_6H_6/5% MeOH (10 ml). The residue (23.5 mg; 93%) showed a tlc and a ^{13}C-nmr spectrum identical with those of compounds **4** and **5** (the mixture of compounds **4** and **5** gives a single spot on the tlc).

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