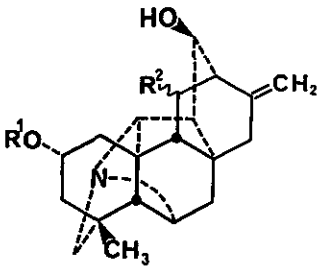
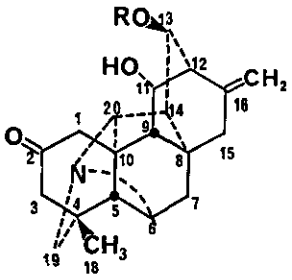
HETISINE DERIVATIVES, PART 1: ACETYLATION AND OXIDATION OF HETISINE

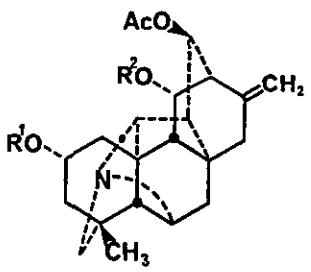
Jan A. Glinski, Balawant S. Joshi, Quing Ping Jiang, and S.William Pelletier*
Institute for Natural Products Research and the Department of Chemistry, School of Chemical Sciences, The University of Georgia, Athens, Georgia 30602, U.S.A.

Abstract — Acetylation of hetisine (1) under drastic conditions afforded 2-acetyl (8), 11-acetyl (9), 13-acetyl (5), 2,11-diacetyl (7), 11,13-diacetyl (2) and 2,11,13-triacetyl (6) hetisines. Sarett oxidation of the compounds (9), (5), (7) and (2) gave 11-acetyl-2,13-didehydro (11), 13-acetyl-2,11-didehydro (12), 13-dehydro-2,11-diacetyl (14) and 2-dehydro-11,13-diacetyl (10) hetisines, respectively. Alkaline hydrolysis of (12) and (2) gave 2,11-didehydrohetisine (13) and 2-dehydrohetisine (hetisinone) (3), respectively. Sarett oxidation of hetisine (1) afforded (13) as the major product besides 11-dehydrohetisine (15). All the compounds have been characterized by their ir, ms, ^1H nmr and ^{13}C nmr data. The location of keto groups in the hetisine derivatives (3), (10), (11), (12), (13), (14) and (15) has been confirmed by CD and ORD measurements.

The C_{20}-diterpenoid alkaloid hetisine (1) is a minor constituent of a number of *Aconitum* and *Delphinium* species.[1] Acetylation of 1 is known to give 11,13-diacetylhetisine (2)[2], which on oxidation with chromium trioxide-acetic acid and subsequent hydrolysis affords







1 R^1 = H; R^2 = α-OH
7 R^1 = Ac; R^2 = α-OAc
8 R^1 = Ac; R^2 = α-OH
9 R^1 = H; R^2 = α-OAc
16 R^1 = H; R^2 = β-OH

3 R = H
4 R = Ac

2 R^1 = H; R^2 = Ac
5 R^1 = R^2 = H
6 R^1 = R^2 = Ac

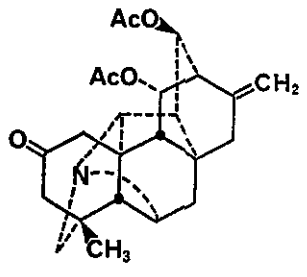
2-dehydrohetisine[3] (hetisinone) (3), a naturally occurring alkaloid of *A. heterophyllum* Wall.[4], *D. cardinale* Hook.[5], *D. cardiopetalum* DC[6], *D. denudatum* Wall.[7], *D. gracile* DC[8], *D. nudicaule* Torr. and Gray[9] and *D. tatsienense* Franch.[10]

Gonzalez *et al* have recently reported the isolation of the alkaloids hetisinone (3) and 13-acetylhetisinone (4) from *Delphinium cardiopetalum* DC.[6] and *D. gracile* DC.[8] Benn and coworkers isolated a new diterpenoid alkaloid, 13-acetylhetisine (5) from *D. nuttalianum* Pritz[11]. In view of the isolation of these alkaloids related to hetisine, we wish to describe herein our work on the synthesis of some hetisine derivatives.

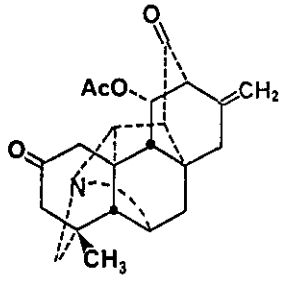
Acetylation of hetisine (1) in chloroform with Ac_2O under reflux gave a mixture of acetylated products which were separated by chromatography on alumina. The fully acetylated 2,11,13-triacetylhetisine (6) was least polar and was obtained as a resin. 11,13-Diacetylhetisine (2), mp 225-227°C, was obtained as the major product of acetylation. 2,11-Diacetylhetisine (7), mp 270-272°C, eluted faster than (2) (Al_2O_3, toluene:2.5% MeOH). All three possible monoacetylhetisines, viz: 2-acetyl (8), mp 245-247°C; 11-acetyl (9), mp 264-266°C; and 13-acetyl (5), mp 241-243°C, were isolated by chromatography.

Acetylation of (1) in acetic anhydride-pyridine at -6°C afforded a mixture of (2), (5) and (9) which was separated on a "Chromatotron".[12]

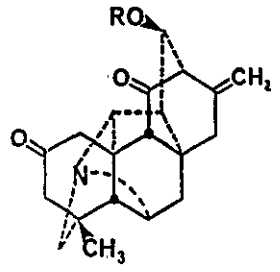
Oxidation of 2 with chromium trioxide-pyridine (Sarett's reagent) gave 2-dehydro-11,13-diacetylhetisine (10) as an amorphous compound. Alkaline hydrolysis of 10 gave hetisinone (3). Similarly, Sarett oxidation of 11-acetylhetisine (9) and 13-acetylhetisine (5) afforded the corresponding dehydroderivatives (11) and (12), respectively. Alkaline hydrolysis of 13-Acetyl-2,11-didehydrohetisine (12) gave 2,11-didehydrohetisine (13), mp 237-240°C. 13-Dehydro-2,11-diacetylhetisine (14) was obtained by similar oxidation of 2,11-diacetylhetisine (7).



10

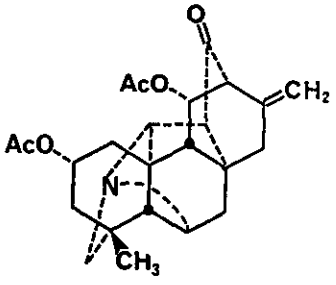


11

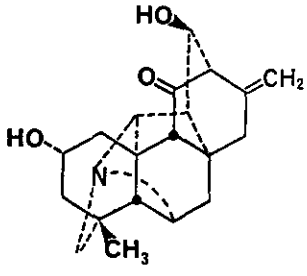


12 R = Ac
13 R = H

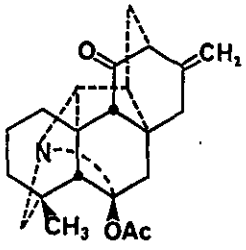
Sarett oxidation of hetisine (1) afforded 2,11-didehydro hetisine (13) as the major product. Acetylation of 13 gave 12, identical with the compound obtained earlier by the oxidation of 13-acetylhetisine (5). By chromatographic separation of the oxidation product, 11-dehydrohetisine (15) was also isolated. Reduction of 11-dehydrohetisine (15) with sodium borohydride gave the C(11)-β-epimer (16) of hetisine. Compound (16) was used in the sulfuric acid rearrangement products studied earlier[13].



14



15



17

^{13}C nmr spectra were determined for all the hetisine derivatives and are recorded in Table 1. The assignments were made by chemical shift comparison of published spectral data[14] taking into account known substituent effects[15].

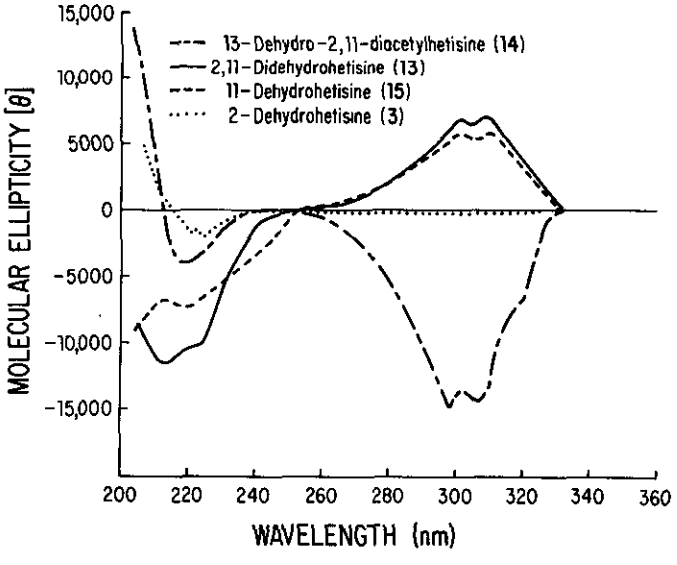


Figure 1.

We have shown earlier[16] that the application of the octant rule (CD measurements) is a useful method for deducing the location of the keto group in naturally occurring C_{20}-diterpenoid alkaloids. Thus, deacetylheterophylloidine (deacetylpanicutine) and 13-dehydro-2,11-diacetylhetisine (**14**), exhibit a strong negative Cotton effect, whereas hetisines having a carbonyl group at C(11), e.g. spiradine A acetate (**17**) whose structure has been established by X-ray crystallography[17] and 11-dehydrohetisine (**15**), show a strong positive Cotton effect. The CD curve of 2-dehydrohetisine (**3**) as expected from the octant rule, makes a very small contribution to a negative Cotton effect. Thus 2,11-didehydrohetisine (**13**) shows a strong positive Cotton effect. The CD curves for the compounds **3**, **13**, **14**, and **15** are depicted in Fig. 1.

EXPERIMENTAL

Melting points were determined on a Thomas-Kofler hot stage equipped with a microscope and polarizer and are corrected. ^{1}H nmr spectra were determined in $CDCl_3$ solutions with TMS as an internal reference on a Varian EM-390 spectrometer. ^{13}C nmr spectra were run in $CDCl_3$ solutions with TMS as internal standard at 15.03 MHz in the Fourier mode with a JEOL FX-60 or FX-90Q spectrometer. Mass spectra were recorded on a Finnegan Quadrupole 4023 mass spectrometer at an ionizing voltage of 70 eV. ORD, CD measurements were made on a Jasco J-20 spectropolarimeter. Analytical thin layer chromatography (tlc) was carried out on Merck aluminium oxide PF-254 (type E). Two solvent systems: toluene with 10-25% methanol and ether:methylene chloride (1:1), with 3-10% methanol were used for analytical tlc. Merck aluminium oxide (96 active, 70-230 mesh ASTM) was used for column chromatography.

Hetisine (**1**) — This was isolated from *A. heterophyllum*[2], mp 256-259°C; $C_{20}H_{27}NO_3$, ms: m/z 329 (M^+, 100%), 312(50), 300(10), 283(20); ^{1}H nmr ($CDCl_3$ + CD_3OD): δ 0.99 (3H, s, C(4)-CH_3), 3.80 (1H, br s, C(20)-H), 4.00-4.15 (3H, m, C(2), C(11), C(13)-H), 4.65, 4.90 (each 1H, br s, C(17)-H).

Acetylation of Hetisine — (A) A solution of hetisine (**1**, 900 mg) in chloroform (10 ml) was heated under reflux with acetic anhydride (3 ml) for 15 h. Evaporation under vacuum afforded a gum (1170 mg) which was chromatographed on alumina (activity III; 40 g) and eluted with toluene containing increasing amounts of (0.7-3.7%) methanol. The chromatographic separation was monitored by tlc and the following fractions were collected in their order of elution:

a) 2,11,13-Triacetylhetisine (**6**) — (70 mg), amorphous; $C_{26}H_{33}NO_6$, ms: m/z 455 (M^+, 12%), 412 (6), 396(27), 43(100); ^{1}H nmr: δ 1.00 (3H, s, C(4)-CH_3), 2.06, 2.10, 2.12 (each 3H, s, OAc), 3.55 (1H, s, C(20)-H), 4.85, 5.00 (each 1H, br s, C(17)-H), 5.14, 5.25, 5.25 (each 1H, br s, C(2)-β-H, C(11)-β-H, C(13)-α-H); ir (nujol) ν max 1740, 1730, 1650, 1450, 1370, 1240, 1220, 1180, 1150, 1110, 1020, 960, 905 cm^{-1}

b) 2,11-Diacetylhetisine (**7**) — (70 mg), mp 270-272°C; $C_{24}H_{31}NO_5$, ms: m/z 413 (M^+, 20%), 370 (13), 354(46), 43(100); ^{1}H nmr: δ 1.01 (3H, s, C(4)-CH_3), 2.12 (6H, s, OAc), 3.80 (1H, s, C(20)-H), 4.20 (1H, br d, J = 8 Hz, C(13)-α-H), 4.80, 4.91 (each 1H, br s, C(17)-H), 5.15, 5.25 (each 1H, br s, C(2)-β-H, C(11)-β-H); ir (nujol) ν max 1730, 1650, 1460, 1370, 1352, 1330, 1310, 1240, 1220, 1182, 1165, 1150, 1125, 1110, 1085, 1060, 1035, 1020, 1000, 980, 960, 930, 902, 880, 860 cm^{-1}.

c) 11,13-Diacetylhetisine (2) — (480 mg), mp 225-227°C; $[\alpha]_D$ +26.1 ($CHCl_3$); was obtained as the major acetylation product; Found: C, 69.50; H, 7.62; Ac, 20.19. $C_{24}H_{31}NO_5$ requires: C, 69.73; H, 7.50; Ac, 20.82%. MS: m/z 413 (M^+, 19%), 396(13), 370(6), 354(7), 310(3), 294(8), 276(3), 43-(100); ^1H nmr: δ 1.00 (3H, s, C(4)-CH_3), 2.12, 2.23 (each 3H, s, OAc), 3.62 (1H, s, C(20)-H), 4.20 (1H, br s, C(2)-β-H), 4.82, 5.00 (each 1H, br s, C(17)-H); ir (nujol) ν max 3250, 1735, 1660, 1460, 1430, 1360, 1340, 1312, 1280, 1250, 1225, 1165, 1140, 1130, 1110, 1090, 1060, 1030, 1000, 980, 970, 948, 930, 900, 890, 860, 850 cm^{-1}.

d) 2-Acetylhetisine (8) — (35 mg), mp 245-247°C (from acetone-hexane); $C_{22}H_{29}NO_4$, ms: m/z 371 (M^+, 1%), 354(0.2), 325(0.9), 312(2), 43(100); ^1H nmr: δ 0.98 (3H, s, C(4)-CH_3), 2.03 (3H, s, OAc), 3.68 (1H, s, C(20)-H), 4.17 (2H, dd, J = 8 Hz, C(11)-β-H, C(13)-α-H), 4.64, 4.80 (each 1H, br s, C(17)-H), 5.11 (1H, br s, C(2)-β-H); ir (nujol) ν max 3460, 3420, 1730, 1710, 1655, 1450, 1380, 1365, 1330, 1260, 1250, 1220, 1195, 1180, 1150, 1140, 1115, 1100, 1070, 1040, 1020, 990, 960, 930, 920, 900, 880, 860, 830 cm^{-1}.

e) 13-Acetylhetisine (5) — (140 mg), mp 241-243°C; $C_{22}H_{29}NO_4$; ms: m/z 371 (M^+, 10%), 354(3), 312(18), 282(5), 43(100); ^1H nmr: δ 0.97 (3H, s, C(4)-CH_3), 2.17 (3H, s, OAc), 3.23 (1H, br s, C(6)-β-H), 3.49 (1H, s, C(20)-H), 4.19 (1H, br s, w 1/2 10 Hz, C(2)-β-H), 4.24 (1H, br d, J = 8.5 Hz, C(11)-β-H), 4.72, 4.88 (each 1H, br s, C(17)-H), 5.13 (1H, br d, J = 9 Hz, C(13)-α-H); ir (nujol) ν max 3410, 3070, 1730, 1650, 1460, 1435, 1420, 1375, 1360, 1340, 1300, 1250, 1215, 1180, 1155, 1140, 1115, 1085, 1070, 1055, 1030, 990, 980, 960, 940, 910, 880, 850, 820 cm^{-1}.

f) 11-Acetylhetisine (9) — (95 mg), mp 264-266°C (from acetone-hexane); $C_{22}H_{29}NO_4$, ms: m/z 371 (M^+, 20%), 354(18), 328(15), 294(6), 282(5), 43(100); ^1H nmr: δ 1.00 (3H, s, C(4)-CH_3), 2.10 (3H, s, OAc), 3.82 (1H, br s, C(20)-H), 4.19 (1H, br d, J = 8 Hz, C(13)-α-H), 4,71, 4,91 (each 1H, br s, C(17)-H), 5.13 (1H, d, J=9Hz, C(11)-β-H); ir (nujol) ν max 3420, 3090, 1730, 1650, 1460, 1435, 1420, 1375, 1310, 1340, 1300, 1250, 1215, 1180, 1152, 1140, 1115, 1085, 1070, 1055, 1030, 990, 975, 960, 940, 910, 880, 850, 815 cm^{-1}.

(B) A solution of hetisine (1, 510 mg) in chloroform (7 ml) was treated with acetic anhydride (1 ml), pyridine (2 ml) and kept at -6°C for 53 h. The solution was poured on crushed ice, basified with ammonia (pH 8-9) and extracted with chloroform. This gave a crude product (460 mg). The aqueous layer on basification with 20% sodium hydroxide and extraction with chloroform gave (1, 87 mg). The above mixture (261 mg) was separated on a "Chromatotron" on a 1 mm aluminium oxide rotor (60 PF 254+366) and eluted with ether-hexane (1:1) 200 ml, ether-hexane (7:3) 200 ml, ether 50 ml, ether-methanol (9:1) 200 ml, ether-methanol (4:1) 100 ml and methanol 60 ml. A total of 43 fractions (19 ml each) were collected from which fractions 10-19 gave (2, 30 mg), 23-26 gave (5, 49 mg), 29-36 gave (9, 66 mg) and 37-43 gave (1, 72 mg).

13-Acetyl-2,11-didehydrohetisine (12) — a) 13-Acetylhetisine (5, 120 mg) was dissolved in methylene chloride (20 ml) and a freshly prepared solution of Sarett's reagent (1 ml) was added. Usual work-up and purification on a short column of alumina gave (12, 54 mg) as an amorphous compound; $C_{22}H_{25}NO_4$, ms: m/z 367 (M^+, 11%), 339(15), 325(38), 280(75), 252(11), 43(100); ^1H nmr: δ 1.17 (3H, s, C(4)-CH_3), 2.15 (3H, s, OAc), 3.03 (1H, d, J = 3 Hz C(6)-β-H), 3.44 (1H, br s, C(20)-H), 5.07, 5.27 (each 1H, br s, C(17)-H), 5.30 (1H, dd, J = 9 Hz, 3 Hz, C(13)-α-H); ir (nujol) ν max 1730, 1650, 1460, 1375, 1335, 1300, 1280, 1230, 1170, 1130, 1090, 1050, 1030, 1015, 970, 905,

870, 850 cm^{-1}; CD (c, 0.0145, MeOH), $[\theta]_{330}$ +1898, $[\theta]_{320}$ +6327, $[\theta]_{312}$ +10,504, $[\theta]_{308}$ +9871, $[\theta]_{302}$ +10,250, $[\theta]_{280}$ +2404 $[\theta]_{260}$ -506, $[\theta]_{240}$ -2151, $[\theta]_{220}$ -11,010.

b) Compound **12** was also obtained by acetylation of 2,11-didehydrohetisine (**13**) obtained by the oxidation of hetisine (*vide infra*).

2,11-Didehydrohetisine (**13**) — 13-Acetyl-2,11-didehydrohetisine (20 mg) was heated with aq. methanol (5 ml) containing potassium carbonate (10 mg) for 2 h. The hydrolysed product, mp 237-240°C (*from acetone-hexane*), was shown to be identical with **13** prepared by the CrO_3 oxidation of hetisine (*vide infra*).

11-Acetyl-2,13-didehydrohetisine (**11**) — A solution of 11-acetylhetisine (**9**, 87 mg) in methylene chloride (20 ml) was treated with a freshly prepared solution of Sarett's reagent (1 ml) (1g CrO_3 in 10 ml pyridine). Purification of the reaction product on a short alumina column afforded (**11**, 43 mg), mp 285-287°C; ^1H nmr: δ 1.16 (3H, s, C(4)-CH_3), 2.08 (3H, s, OAc), 3.00 (1H, s, C(6)-β-H), 3.36 (1H, br s, C(20)-H), 4.98, 5.10 (each 1H, br s, C(17)-H), 5.25 (1H, d, J = 9 Hz, C(11)-β-H); CD (c, 0.018, MeOH), $[\theta]_{330}$ -1427, $[\theta]_{320}$ -9787, $[\theta]_{308}$ -17,738, $[\theta]_{304}$ -17,331, $[\theta]_{300}$ -17,738, $[\theta]_{280}$ -6524, $[\theta]_{260}$ -1631, $[\theta]_{240}$ -816, $[\theta]_{220}$ -6117.

13-Dehydro-2,11-diacetylhetisine (**14**) — A solution of 2,11-diacetylhetisine (**7**, 391 mg) in methylene chloride was treated with an excess of freshly prepared Sarett's reagent and kept at room temperature for 16 h. A small amount of saturated aq. potassium carbonate was added, the mixture extracted with methylene chloride, and the organic layer was dried and evaporated. The crude product was purified on a short column of alumina to afford **14** (228 mg), mp 222-223°C; $C_{24}H_{29}NO_5$, ms: m/z 411 (M^+, 12%), 369(5), 352(25), 340(2), 324(8), 309(20), 264(10), 43(100); ^1H nmr: δ 1.00 (3H, br s, C(4)-CH_3), 2.04, 2.07 (each 3H, s, OAc), 3.22 (1H, br s, C(6)-β-H), 4.81, 4.92 (each 1H, br s, C(17)-H), 5.15, 5.22 (each 1H, s, C(2)-β-H, C(11)-β-H); ORD (c, 0.0348, MeOH), $[\phi]_{589}$ -82°, $[\phi]_{322}$ -12,042°, $[\phi]_{316}$ -8960°, $[\phi]_{314}$ -9083°, $[\phi]_{280}$ +12,535°, $[\phi]_{235}$ +7932°, $[\phi]_{206}$ + 32,469°; CD (C, 0.0348, MeOH) $[\theta]_{330}$ 0, $[\theta]_{325}$ -1315, $[\theta]_{307}$ -14,426, $[\theta]_{298}$ -14,179, $[\theta]_{240}$ 0, $[\theta]_{218}$ -4027, $[\theta]_{205}$ +17,015.

2-Dehydro-11,13-diacetylhetisine (**10**) — A solution of 11,13-diacetylhetisine (**2**, 80 mg) in methylene chloride (10 ml) was treated with a freshly prepared solution of Sarett's reagent (1.5 ml) and kept for a short time. The solvent was evaporated under vacuum, a saturated solution of potassium carbonate added and the mixture extracted with methylene chloride. This process gave a gum which was purified on a short column of alumina to afford **10** (50 mg); $C_{24}H_{29}NO_5$, ms: m/z 411 (M^+, 23%), 383(4), 368(7), 352(12), 43(100); ^1H nmr: δ 1.13 (3H, s, C(4)-CH_3), 2.06, 2.25 (each 3H, s, OAc), 3.30 (1H, br s, C(6)-β-H), 4.82, 5.00 (each 1H, br s, C(17)-H), 5.10, 5.19 (each 1H, br s, C(11)-β-H, C(13)-α-H); CD (c, 0.019, MeOH), $[\theta]_{326}$ +324, $[\theta]_{320}$ +216, $[\theta]_{298}$ +541, $[\theta]_{290}$ +541, $[\theta]_{280}$ -433, $[\theta]_{260}$ -541, $[\theta]_{240}$ -433, $[\theta]_{220}$ -3245.

2-Dehydrohetisine (Hetisinone) (**3**) — 11,13-Diacetyl-2-dehydrohetisine (**10**) (150 mg) was heated with aq. methanol and potassium carbonate for 20 min. Usual work-up gave a residue (145 mg) which was chromatographed on a short column of grade III alumina. 2-Dehydrohetisine (**3**) (130 mg), mp 195-197°C, was obtained by crystallization from methanol; ^1H nmr: δ 1.17 (3H, s, C(4)-CH_3), 3.29 (2H, br s, OH), 4.21 (2H, d, J = 8.6 Hz, C(11)-β-H, C(13)-α-H), 4.70, 4.88 (each 1H, s, C(17)-

TABLE 1. ^{13}C Chemical Shifts and Assignments for Hetisine and its Derivatives **1-3** and **5-15***.

Carbon	1	8	9	5	7	2	6	12	13	11	14	10	3	15
1	34.3	30.8	32.6	33.8	29.6	32.0	29.6	43.5	43.1	44.5	31.2	43.8	45.2	32.4
2	66.9	70.0	66.8	66.7	69.8	66.5	70.1	210.1	210.8	210.1	69.7	211.7	214.3	67.8
3	38.8	36.3	39.1	40.3	36.2	40.6	36.5	50.7	50.4	49.7	36.2	50.2	49.9	38.7
4	36.8	36.7	36.5	36.6	36.7	36.8	36.6	42.9	42.6	42.4	36.6	42.8	42.4	36.4
5	61.4	61.2	61.3	61.5	60.9	61.4	61.1	59.3	59.1	60.8	60.6	60.5	60.4	61.8
6	64.3	64.1	64.4	64.3	64.2	64.3	64.2	65.5	65.6	65.6	64.6	65.2	65.2	66.5
7	36.4	36.6	36.5	36.0	36.7	36.1	36.1	34.5	34.8	34.5	33.3	35.8	36.1	32.4
8	43.5	43.5	43.9	43.6	43.9	43.9	44.1	45.0	45.0	45.2	43.6	44.8	44.4	44.6
9	55.5	55.2	53.3	55.2	53.1	53.1	53.1	64.8	64.8	54.8	52.9	52.6	55.0	56.9
10	50.7	50.7	50.4	50.6	50.5	50.6	50.4	50.5	52.4	52.6	50.1	55.4	55.7	49.0
11	76.5	76.2	76.7	75.6	76.4	75.9	75.7	207.8	209.7	72.3	72.6	75.3	75.6	215.4
12	50.9	51.5	48.1	48.5	49.1	45.1	44.9	58.5	62.6	60.1	61.1	44.8	50.8	62.8
13	72.4	72.2	70.9	74.5	70.8	73.0	73.2	69.6	67.4	206.5	207.6	72.4	71.5	67.2
14	52.2	52.2	52.8	50.4	51.9	50.2	50.2	49.6	51.8	58.9	59.1	49.8	52.0	50.6
15	34.1	34.2	34.1	33.5	34.0	34.0	34.0	33.1	33.2	33.1	34.6	33.6	33.9	33.2
16	146.1	145.7	146.1	144.8	145.4	144.0	143.3	138.1	139.9	138.4	138.8	142.9	145.4	140.1
17	107.7	107.8	108.1	108.7	108.4	109.6	110.0	114.3	112.7	113.5	113.1	110.4	108.2	115.1
18	29.9	29.6	29.8	29.7	29.6	29.8	29.8	28.3	28.4	28.6	29.4	28.6	28.7	29.2
19	63.3	63.4	63.6	63.2	63.5	63.6	63.6	65.0	64.8	64.2	63.1	64.8	64.4	64.8
20	68.1	67.9	67.9	68.6	67.6	68.5	68.7	70.6	69.8	71.7	68.7	70.5	70.3	69.0
CO	-	170.5	171.1	170.3	170.9, 170.4	179.8, 170.5	170.6,170.2, 170.1	169.6	-	170.2	170.3, 170.1	170.6, 170.2	-	-.
CH_3	-	21.8	21.6	21.2	21.7, 21.5	21.5, 21.2	21.9,21.6, 21.1	20.7	-	21.2	21.7, 21.3	21.4, 21.1	-	-

* Chemical shifts in ppm downfield from TMS; solvent deuterochloroform, except for **(15)** taken in H_2SO_4+D_2O.

a These assignments may be interchanged in any vertical column.

H); ORD (c, 0.0669, MeOH), $[\phi]_{589}$ +131°, $[\phi]_{360}$ +360°, $[\phi]_{340}$ +294°, $[\phi]_{330}$ +392°, $-[\phi]_{314}$ +360°, $[\phi]_{280}$ +9385°, $[\phi]_{204}$ +8207°. CD (c, 0.0669, MeOH), $[\theta]_{325}$ 0, $[\theta]_{320}$ -33, $[\theta]_{287}$ -294, $[\theta]_{255}$ -65, $[\theta]_{225}$ -1799, $[\theta]_{222}$ -1668, $[\theta]_{220}$ -1706, $[\theta]_{206}$ +4774.

Oxidation of Hetisine with Sarett's Reagent — A solution of hetisine (2 g) in methylene chloride (300 ml) was cooled to -5°C and Sarett's reagent (5.5 ml) was gradually added. The mixture was placed in the refrigerator and two additional portions (7.5 ml each) of the reagent were added during 3 h. Usual work-up gave a crude product (1.6 g) which was chromatographed on alumina and eluted with toluene containing 0.5-4% methanol. The chromatographic separation was monitored by tlc and the following compounds were isolated in their order of elution:

a) 2,11-Didehydrohetisine **13** — (420 mg), mp 237-240°C (Lit.[5] mp 236-238°C); $C_{20}H_{23}NO_3$, ms: m/z 325 (M^+, 76%), 297(15), 280(85), 157(37), 144(67); ^1H nmr: δ 1.18 (3H, s, C(4)-CH_3), 3.42 (1H, br s, C(20)-H), 4.23 (1H, dd, J = 9.2, 1.2 Hz, C(13)-α-H), 4.89, 5.03 (each 1H, s, C(17)-H); ir (nujol) ν max 3100, 1720, 1705, 1460, 1375, 1330, 1305, 1280, 1250, 1215, 1190, 1150, 1130, 1090, 1070, 1050, 1030, 1000, 970, 950, 925, 910, 900, 890, 858, 835 cm^{-1}; ORD (c, 0.0936, MeOH), $[\phi]_{589}$ +260°, $[\phi]_{325}$ +7215°, $[\phi]_{318}$ +5980°, $[\phi]_{315}$ +6045°, $[\phi]_{285}$ -5557°, $[\phi]_{257}$ -4290°, $[\phi]_{235}$ -7215°, $[\phi]_{205}$ +14,300; CD (c, 0.0936, MeOH), $[\theta]_{340}$ 0, $[\theta]_{330}$ +98, $[\theta]_{310}$ +6955, $[\theta]_{306}$ +6955, $[\theta]_{300}$ +6955, $[\theta]_{213}$ -11,472, $[\theta]_{205}$ -8482.

b) 11-Dehydrohetisine **(15)** — (740 mg), mp 292-298°C; $C_{20}H_{25}NO_3$, ms: m/z 327 (M^+, 100%), 310 (7), 299(28), 282(62), 157(30), 144(20), 131(20), 91(30); ^1H nmr: δ 1.01 (3H, s, C(4)-CH_3), 4.20 (2H, brm, C(2)-β-H, C(13)-α-H), 4.98 (2H, br s, C(17)-H); ir (nujol) ν max 3300, 1720, 1640, 1460, 1370, 1340, 1300, 1280, 1260, 1220, 1200, 1170, 1142, 1120, 1110, 1090, 1080, 1040, 990, 960, 940, 880, 860 cm^{-1}; ORD (c, 0.0225, MeOH), $[\phi]_{589}$ +131°, $[\phi]_{323}$ +5101°, $[\phi]_{280}$ -6017°, $[\phi]_{265}$ -5363°, $[\phi]_{260}$ -5363°, $[\phi]_{237}$ -7619°, $[\phi]_{215}$ -294°, $[\phi]_{209}$ -5232°, $[\phi]_{205}$ +1177°; CD (c, 0.0225, MeOH), $[\theta]_{340}$ 0, $[\theta]_{330}$ +131, $[\theta]_{310}$ +5951, $[\theta]_{308}$ +5886, $[\theta]_{302}$ +6115, $[\theta]_{220}$ -7260, $[\theta]_{213}$ -6671, $[\theta]_{205}$ -8730.

ACKNOWLEDGEMENTS

We thank Dr. P. Moser, CIBA-GEIGY LTD, Basle for the ORD-CD measurements.

REFERENCES

1. S.W. Pelletier and L.H. Keith, "The Alkaloids" Ed. R.H.F. Manske, Vol. XII, p. 174, Academic Press, N.Y., (1970); S.W. Pelletier and N.V. Mody, "The Alkaloids" Ed. R.H.F. Manske, Vol. XVIII, p. 133, Academic Press, N.Y.(1981).
2. H.E. Wright, G. Newton, and S.W. Pelletier, *Chem. Comm.* 1969, 507.
3. R.T. Alpin, M.H. Benn, S.W. Pelletier, J. Solo, S.A. Telang, and H. Wright, *Can. J. Chem.*, **46**, 2635 (1968); S.W. Pelletier, *Tetrahedron*, **14**, 76 (1961).
4. S.W. Pelletier, R. Aneja, and K.W. Gopinath, *Phytochemistry*, **7**, 625 (1968).
5. M.H. Benn, *Can. J. Chem.*, **44**, 1 (1966).
6. A.G. Gonzalez, G. de la Fuente, and M. Reina, *Anal. Quim.*, **77C**, 171 (1981).

7. S.W. Pelletier, L.H. Keith, and P.C. Parthasarathy, *J. Amer. Chem. Soc.*, **89**, 4146 (1967).
8. A.G. Gonzalez, G. de la Fuente, R. Reina, and I. Timon, *Heterocycles*, **22**, 667 (1984).
9. P. Kulanthaivel and M. Benn, *Heterocycles*, **23**, 2515 (1985).
10. S.W. Pelletier, J.A. Glinski, B.S. Joshi, and S.Y. Chen, *Heterocycles*, **20**, 1347 (1983).
11. M.H. Benn, J.F. Richardson, and W. Majak, *Heterocycles*, **24**, 1605 (1986).
12. H.K. Desai, B.S. Joshi, A.M. Panu, and S.W. Pelletier, *J. Chromatogr.*, **322**, 223 (1985).
13. S.W. Pelletier, J.A. Glinski, K.I. Varughese, J. Maddry, and N.V. Mody, *Heterocycles*, **20**, 413 (1983).
14. A.G. Gonzalez, G. de la Fuente, M. Reina, R. Diaz, and I. Timon, *Phytochemistry*, **25**, 1971 (1986); M.G. Reinecke and W.H. Watson, *Heterocycles*, **24**, 49 (1986).
15. F.W. Wehrli and T. Wirthlin, in "Interpretation of Carbon-13 NMR Spectra", Heyden, London (1976).
16. S.W. Pelletier, B.S. Joshi, H.K. Desai, A. Panu, and A. Katz, *Heterocycles*, **24**, 1275 (1986).
17. G. Goto, K. Sasaki, N. Sakabe, and Y. Hirata, *Tetrahedron Letters*, 1369 (1968); K. Sasaki, N. Sakabe, and Y. Hirata, *J. Chem. Soc.*, Perkin I, 354 (1971).

Received, 24th August, 1987