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METABOLITES OF THE GORGONIAN *ISIS HIPPURIS* FROM INDIA

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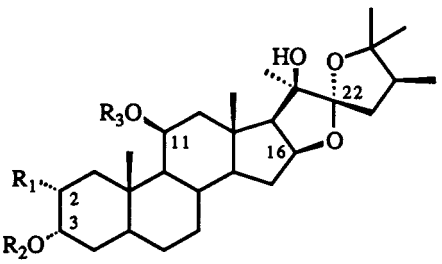
ABSTRACT.—Five new hippurins, 3,11-diacetyl-22-*epi*-hippurin-1 [**4**], 3-acetyl-22-*epi*-hippurin-1 [**5**], 3-acetyl-2-desacetyl-22-*epi*-hippurin-1 [**6**], 2-desacetyl-22-*epi*-hippurin-1 [**7**], and 3,11-diacetylhippurin-1 [**8**], and a new polyhydroxylated sterol, gorgostane-1α,3β,5α,6β,11α-pentaol [**9**], were isolated from a specimen of *Isis hippuris* collected at the Andaman Islands, India. The structures of the new compounds were elucidated by interpretation of spectral data.

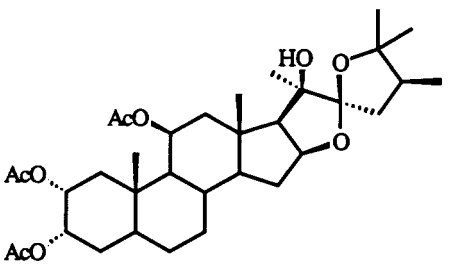
As part of a collaborative program to investigate the metabolites of marine organisms from Indian waters, we have examined the metabolites of the unusual gorgonian *Isis hippuris* L. (Gorgonaceae). In physical appearance, *I. hippuris* more closely resembles a soft coral than the familiar seawhip or sea fan gorgonians. The natural products chemistry of *I. hippuris* features an interesting group of highly oxygenated sterols called hippurins (1,2), which may contain either a 22*R*- or 22*S*-ketal functionality. In this paper, we report the isolation of five new hippurins and one new polyhydroxylated gorgosterol derivative from an Indian specimen of *I. hippuris*.

RESULTS AND DISCUSSION

The gorgonian *Isis hippuris* was collected at the Andaman Islands (3) and was extracted with EtOH. The EtOAc-soluble material from the EtOH extract was chromatographed on Si gel using solvents of increasing polarity from petroleum ether to EtOAc to obtain a series of polyhydroxylated sterols, most of which were in the hippurin series (1,2). Three known metabolites, 22-*epi*-hippurin-1 [**1**], 22-*epi*-hippuristanol [**2**], and 3,11-diacetyl-22-*epi*-hippuristanol [**3**] which had been synthesized by acetylation of **2**, were isolated and identified by comparison of spectral data with those



	R_1	R_2	R_3
1	OAc	H	H
2	H	H	H
3	H	Ac	Ac
4	OAc	Ac	Ac
5	OAc	Ac	H
6	OH	Ac	H
7	OH	H	H



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of authentic samples (2).[1] Five new hippurins, 3,11-diacetyl-22-*epi*-hippurin-1 [**4**], 3-acetyl-22-*epi*-hippurin-1 [**5**], 3-acetyl-2-desacetyl-22-*epi*-hippurin-1 [**6**], 2-desacetyl-22-*epi*-hippurin-1 [**7**], and 3,11-diacetylhippurin-1 [**8**], together with gorgostane-1α,3β,5α,6β,11α-pentaol [**9**], were isolated and the structures elucidated by interpretation of spectral data.

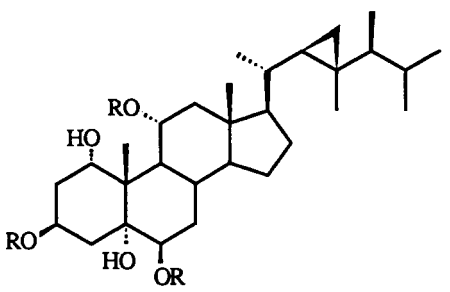
The hippurin derivatives **4–7** were assigned the 22*S* or 22-*epi*-stereochemistry on the basis of the chemical shift of the C-22 signal at $\delta > 118$ in the ^{13}C-nmr spectra (Table 1), the downfield shifts, relative to those for the 22*R* series, of the H-16α and H-24α signals in the ^{1}H-nmr spectra, and the lack of hydrogen bonding between the C-20 hydroxyl and 22,25-oxido oxygen that is apparent in the ir spectra (2). Examination of the ^{1}H-nmr spectra indicated that compounds **4–7** differed from 22-*epi*-hippurin-1 [**1**] only by the pattern of acetylation at the 2-, 3-, and 11-hydroxyl groups. The H-2 signal

TABLE 1. ^{13}C-nmr Spectral Data (50 MHz, $CDCl_3$) for Compounds **1–8**.

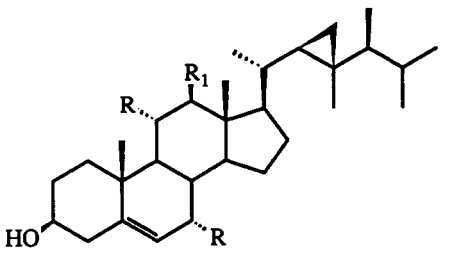
Carbon	Compound							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	36.8	32.3	32.7	37.8	37.7	41.0	39.0	37.7
2	72.8[a]	28.6	25.7	69.0[a]	69.9[a]	67.9[a]	69.2[a]	69.0[a]
3	67.5[a]	66.3[a]	69.6[a]	69.4[a]	69.3[a]	72.8[a]	67.0[a]	69.4[a]
4	33.6[b]	35.3[b]	32.2[b]	31.5[b]	31.6[b]	31.5[b]	33.8[b]	31.8[b]
5	39.0	39.9	41.0	40.3	40.2	40.1	40.5	40.4
6	27.0	27.8	27.6	26.7	26.8	26.8	27.1	26.7
7	32.2[b]	31.5[b]	31.5[d]	32.0[b]	32.1[b]	31.1[b]	32.2[b]	32.2[b]
8	29.7	30.2	30.7	30.2	29.6	29.6	29.7	30.0
9	58.0[c]	58.1[c]	58.0[c]	57.8[c]	58.2[c]	58.1[c]	58.0[c]	56.7[c]
10	37.4	36.3	35.7	39.9	37.3	37.0	37.2	36.9
11	68.0[a]	68.0[a]	69.5[a]	69.5[a]	68.0[a]	67.6[a]	68.1[a]	69.5[a]
12	48.9	48.8	44.6	44.4	48.9	48.7	48.9	44.5
13	42.2	42.1	42.0	42.0	42.2	42.1	42.2	42.1
14	58.3[c]	58.4[c]	56.5[c]	56.5[c]	57.9[c]	57.8[c]	58.3[c]	56.5[c]
15	31.6[b]	31.8[b]	32.1[b]	31.8[b]	31.9[b]	31.7[b]	31.7[b]	33.9[a]
16	79.0	79.0	78.9	78.9	79.0	78.9	79.0	80.0
17	66.4	66.5	66.3	66.3	66.4	66.4	66.5	65.7
18	27.1	27.0	27.2	27.3	27.1	27.1	27.1	28.4
19	13.9[d]	13.9[d]	13.9[d]	13.9[d]	14.0[d]	13.9[d]	13.9[d]	15.2[d]
20	82.6	82.6	82.4	82.5	82.6	82.5	82.7	79.1
21	19.4	19.5	18.9	18.9	19.5	19.3	19.4	17.9
22	118.6	118.6	118.6	118.6	118.6	118.5	118.6	115.3
23	40.0	39.9	39.9	39.9	39.9	39.8	40.0	40.9
24	41.0	41.0	41.0	41.0	41.0	41.0	41.0	41.9
25	84.1	84.2	84.2	84.3	84.2	84.1	84.1	84.6
26	29.1	29.1	29.1	29.1	29.1	29.1	29.1	29.1
27	23.0	23.0	22.9	23.0	23.0	22.9	23.0	23.0
28	15.0[d]	14.1[d]	14.1[d]	15.2[d]	15.3[d]	15.3[d]	15.1[d]	14.7[d]
OAc	21.3		21.8	21.8	21.2	21.3		21.8
			21.5	21.2	21.1			21.2
				21.1				21.1
	170.1		170.5	170.3	170.4	171.5		170.4
			170.0	170.3	170.3			170.4
				170.0				169.8

[a–d]Assignments with the same superscript in the same column may be interchanged.

[1] ^{1}H- and ^{13}C-nmr spectra were kindly provided by T. Higa.



9 R=H
12 R=Ac



10 $R=R_1=H$
11 $R=OH, R_1=OAc$

appeared as a doublet of triplets, the H-3 signal as a broad singlet that sharpened on irradiation of the H-2 signal, and the H-11 signal as a second broad singlet, allowing the assignment of the respective signals in each spectrum (Table 2). The familiar downfield shift of >1 ppm for the signals of protons adjacent to an acetate relative to those of protons adjacent to hydroxyl groups allowed assignment of the structures. 3,11-Diacetylhippurin-1 [**8**] was assigned the 22*R* stereochemistry on the basis of the chemical shift of the C-22 signal at δ 115.3 in the ^{13}C-nmr spectrum, a sharp singlet at δ 3.19 in the ^{1}H-nmr spectrum due to the hydrogen bonded C-20 hydroxyl signal, and a ^{1}H-nmr signal at 4.29 (m, 1H) assigned to H-16α. The triacetate **8** is the C-22 epimer of triacetate **4**.

An unrelated sterol, gorgostane-1α,3β,5α,6β,11α-pentaol [**9**], was also isolated from the same extract. The side chain of the gorgostane skeleton, first encountered in gorgosterol (4) [**10**], has a cyclopropane group and four chiral centers, the relative stereochemistry of which was defined by X-ray diffraction (5) studies. A polyhydroxylated gorgostane derivative **11** had previously been isolated from *I. hippuris* (6).

Gorgostane-1α,3β,5α,6β,11α-pentaol [**9**], mp 295–297°, had the molecular formula $C_{30}H_{52}O_5$. The ^{1}H-nmr spectrum ($CD_3OD/CDCl_3$) contained signals at δ −0.25 (t, 1H, J = 5 Hz) and 0.34 (dd, 1H, J = 9, 5 Hz), that were assigned to the C-30 cyclopropyl protons. The C-22 and C-24 protons gave rise to a signal at δ 0.09 (m,

TABLE 2. Selected ^{1}H nmr Data (360 MHz, $CDCl_3$) for Compounds **1–8**.

Proton	1	2	3	4	5	6	7	8	Multiplicity
2β	5.00	—	—	4.91	5.00	3.89	3.82	4.88	br dt, J = 12, 3 Hz
3β	4.04	4.05	4.99	5.26	5.26	5.12	3.95	5.26	br s, $w_{h/2}$ = 10 Hz
9	0.83	0.80	—	—	0.85	0.82	0.81	—	dd, J = 3.5, 11 Hz
11α	4.25	4.31	5.31	5.26	4.26	4.23	4.28	5.26	br s, $w_{h/2}$ = 10 Hz
12α	1.41	—	—	—	1.43	1.41	—	—	br d, J = 14.5 Hz
16α	4.43	4.43	4.44	4.44	4.43	4.44	4.43	4.29	br q, J = 7 Hz
18	1.34[a]	1.34[a]	1.22[a]	1.22[a]	1.35[a]	1.34[a]	1.34[a]	1.18[a]	s
19	1.10[a]	1.04[a]	0.89[a]	0.97[a]	1.12[a]	1.06[a]	1.04[a]	0.95[a]	s
21	1.26[a]	1.30[a]	1.27[a]	1.29[a]	1.32[a]	1.28[a]	1.25[a]	1.28[a]	s
24α	2.25	2.26	2.26	2.27	2.26	2.25	2.25	—	m
26	0.98[a]	0.98[a]	0.98[a]	0.98[a]	0.98[a]	0.98[a]	0.98[a]	1.22[a]	s
27	1.28[a]	1.28[a]	1.28[a]	1.28[a]	1.30[a]	1.30[a]	1.28[a]	1.25[a]	s
28	0.94	0.94	0.94	0.94	0.94	0.94	0.94	0.97	d, J = 6.5 Hz
OAc	2.08	—	2.04	2.08	2.08	2.11	—	2.07	s
	—	—	2.00	2.02	1.98	—	—	2.02	s
	—	—	—	1.97	—	—	—	1.96	s
21OH	—	—	—	—	—	—	—	3.19	s

[a]Methyl signal assignments may be interchanged within a column.

2H), and the C-21 methyl group appeared as a singlet because it had the same chemical shift as the C-20 proton at 0.90 ppm. These unusual chemical shifts are typical of those previously reported for the gorgostane side chain (7). The ^{13}C-nmr spectrum contained 30 signals of which five [δ 63.7 (d), 67.0 (d), 75.0 (d), 77.7 (d), 78.6 (s)] were assigned to carbon atoms bearing hydroxyl groups.

The positions of the hydroxyl groups were assigned by interpretation of the ^{1}H-nmr spectra. In pyridine solution, a signal was observed at δ 3.02 (t, 1H, J = 12 Hz); this signal is peculiar to H-4β in a 3β,5α,6β-trihydroxy sterol (8). The multiplicities of the signal at δ 4.11 (tt, 1H, J = 10,5 Hz, H-3α) and 3.52 (br s, 1H) in the CD_3OD/$CDCl_3$ spectrum indicated that the 2- and 7-positions are unsubstituted. The H-3α signal at 4.11 ppm was sufficiently deshielded to require two axial hydroxyl groups at C-1 and C-5. The H-1β signal at δ 3.95 (br s, 1H) was not coupled to any other downfield proton signals, an observation that served to eliminate most other possible hydroxylation positions. The remaining downfield signal at δ 3.8 (m, 1H), assigned to H-11β, was partially obscured. However, the corresponding signal in the 3,6,11-triacetate **12** appeared at 5.15 (td, 1H, J = 12, 5.5 Hz), and irradiation of this signal caused the H-12β signal at δ 2.42 (dd, 1H, J = 12, 5.5 Hz) to collapse to a doublet (J = 12 Hz). The ^{13}C-nmr signal at δ 51.3 (t) was typical of C-12 in an 11α-hydroxy sterol (9). Comparison of the ^{13}C-nmr spectrum with those of other polyhydroxylated sterols (10–12) supported a structure in which the D ring was unsubstituted.

EXPERIMENTAL

COLLECTION, EXTRACTION, AND PURIFICATION.—Specimens of the gorgonian *I. hippuris* (dry wt 3.5 kg) were collected off the Andaman coast in the Bay of Bengal, India in December 1985. (This collection represents a significant range extension for *I. hippuris*.[2]) A voucher specimen is on deposit at the Department of Invertebrate Zoology, U.S. National Museum of Natural History, Smithsonian Institution, Washington, DC. The animals were cut into thin slices and stored in EtOH at room temperature. The EtOH extract was concentrated under reduced pressure, redissolved in EtOAc and dried over anhydrous $MgSO_4$. Evaporation of the solvent yielded a dark greenish gum (40 g) that was chromatographed repeatedly on Si gel using solvent mixtures of increasing polarity from petroleum ether (bp 60–80°) through C_6H_6 to EtOAc. Crystallization of selected fractions from suitable solvent mixtures yielded the following steroids: 22-*epi*-hippurin-1 [**1**] (500 mg), 22-*epi*-hippuristanol [**2**] (35 mg), 3,11-diacetyl-22-*epi*-hippuristanol [**3**] (100 mg), 3,11-diacetyl-22-*epi*-hippurin-1 [**4**] (125 mg), 3-acetyl-22-*epi*-hippurin-1 [**5**] (30 mg), 3-acetyl-2-desacetyl-22-*epi*-hippurin-1 [**6**] (250 mg), 2-desacetyl-22-*epi*-hippurin [**7**], (30 mg), 3,11-diacetylhippurin-1 [**8**] (impure, 70 mg), gorgostane-1α,3β,5α,6β,11α-pentaol [**9**] (40 mg). A portion of the impure sample of **8** (25 mg) was chromatographed on normal phase hplc (70% Et_2O/hexane) to yield pure **8** (10 mg).

22-*epi*-HIPPURIN-1 [**1**].—White solid, mp 257–259°, ir ($CHCl_3$) 2930, 1730, 1025, 970 cm^{-1}; ^{1}H-nmr ($CDCl_3$) see Table 2; ^{13}C nmr ($CDCl_3$) see Table 1; cims *m/z* (rel. int.) $[M]^+$ 520 (1), 505 (2), 462 (6), 374 (27), 359 (10), 332 (10), 331 (13), 299 (33), 271 (31), 169 (100); hrms *m/z* 520.3389, $C_{30}H_{48}O_7$ requires 520.3400.

22-*epi*-HIPPURISTANOL [**2**].—White solid, mp 225–227°; ir ($CHCl_3$) 3620, 3450 (br), 2930, 1450, 1025, 970, 925, 915 cm^{-1}; ^{1}H nmr ($CDCl_3$) see Table 2; ^{13}C nmr ($CDCl_3$) see Table 1; hrms (ci) *m/z* 463.3398 $[M+1]^+$, $C_{28}H_{47}O_5$ requires 463.3425.

3,11-DIACETYL-22-*epi*-HIPPURISTANOL [**3**].—White solid, mp 257–259°; ir ($CHCl_3$) 2930, 1722, 1020, 970, 925 cm^{-1}; ^{1}H nmr ($CDCl_3$) see Table 2; ^{13}C nmr ($CDCl_2$) see Table 1; cims *m/z* (rel. int.) $[M]^+$ 546 (1), 531 (2), 488 (10), 359 (15), 358 (55), 343 (20), 299 (24), 298 (92), 283 (30), 256 (14), 255 (65); hrms *m/z* 546.3562, $C_{32}H_{50}O_7$ requires 546.3557.

3,11-DIACETYL-22-*epi*-HIPPURIN-1 [**4**].—Colorless needles, mp 178–180°; ir ($CHCl_3$) 1732, 1718, 1022, 970, 910 cm^{-1}; ^{1}H nmr ($CDCl_3$) see Table 2; ^{13}C nmr ($CDCl_3$) see Table 1; cims *m/z* (rel. int.) $[M-H_2O]^+$ 586 (2), 546 (5), 416 (13), 314 (10); hrms *m/z* 586.3509, $C_{34}H_{50}O_8$ requires 586.3506.

[2]F.M. Bayer and J. Stefani, personal communication.

3-ACETYL-22-*epi*-HIPPURIN-1 [**5**].—White solid, mp 240–243°; ir ($CHCl_3$) 1732, 1718, 1030, 972, 912 cm^{-1}; ^1H nmr ($CDCl_3$) see Table 2; ^{13}C nmr ($CDCl_3$) see Table 1; cims *m/z* (rel. int.) $[M-H_2O]^+$ 544 (2), 504 (8), 434 (10), 416 (35), 299 (19), 381 (22); hrms *m/z* 544.3388, $C_{32}H_{48}O_7$ requires 544.3400.

3-ACETYL-2-DESACETYL-22-*epi*-HIPPURIN-1 [**6**].—Colorless crystals, mp 248–250°; ir ($CHCl_3$) 1730, 1025, 970, 915 cm^{-1}; ^1H nmr ($CDCl_3$) see Table 2; ^{13}C nmr ($CDCl_3$) see Table 1; cims *m/z* (rel. int.) $[M]^+$ 520 (1), 462 (7), 374 (24), 259 (12), 314 (19), 299 (32), 271 (32), 169 (100); hrms *m/z* 520.3409, $C_{30}H_{48}O_7$ requires 520.3400.

2-DESACETYL-22-*epi*-HIPPURIN-1 [**7**].—Colorless crystals, mp 260–261°; ir ($CHCl_3$) 3610 (s), 3450 (br), 1485, 1040, 972, 992, 912 cm^{-1}; ^1H nmr ($CDCl_3$) see Table 2; ^{13}C nmr ($CDCl_3$) see Table 1; cims *m/z* (rel. int.) $[M+1]^+$ 479 (100), 461 (36), 332 (19), 289 (16), 271 (10); hrms *m/z* 479.3364, $C_{28}H_{47}O_6$ requires 479.3372.

3,11-DIACETYLHIPPURIN-1 [**8**].—Oil; ir ($CHCl_3$) 3500 (br), 2970, 2930, 1730, 1450, 1370, 1260, 1040, 1025, 980, 925 cm^{-1}; ^1H nmr ($CDCl_3$) see Table 2; ^{13}C nmr ($CDCl_3$) see Table 1; hrms (ci) *m/z* 605.3685 $[M+1]^+$, $C_{34}H_{53}O_9$ requires 605.3691.

GORGOSTANE-1α,3β,5α,6β,11α-PENTAOL [**9**].—White solid, mp 295–297°; ir ($CHCl_3$) 3600, 3300 (br) cm^{-1}; ^1H nmr ($CD_3OD/CDCl_3$) δ −0.25 (t, 1H, $J=4.9$ Hz), 0.09 (m, 2H), 0.34 (dd, 1H, $J=4.5$, 9.4 Hz), 0.52 (s, 3H), 0.73 (d, 3H, $J=7$ Hz), 0.77 (s, 3H), 0.81 (d, 3H, $J=7$ Hz), 0.82 (d, 3H, $J=7$ Hz), 0.90 (s, 3H), 1.06 (s, 3H), 2.27 (dd, 1H, $J=5.6$, 12 Hz), 3.52 (br s, 1H), ~3.80 (m, 1H), 3.95 (br s, 1H), 4.11 (m, 1H); ^{13}C nmr (C_5D_5N) δ 78.6 (s), 77.7 (d), 75.0 (d), 67.0 (d), 63.7 (d), 58.0 (d), 55.2 (d), 51.3 (t), 50.7 (d), 47.6 (d), 43.7 (s), 42.9 (s), 42.9 (t), 38.7 (t), 36.2 (t), 35.3 (d), 32.2 (d), 32.1 (d), 30.2 (d), 28.6 (t), 25.8 (s), 24.8 (t), 22.2 (q), 21.5 (t), 21.2 (q), 21.2 (t), 16.7 (q), 15.5 (q), 14.2 (q), 12.8 (q); eims *m/z* (rel. int.) $[M-H_2O]^+$ 474 (31), 456 (72), 438 (63), 402 (32), 401 (49), 388 (31), 387 (37), 285 (65); hrms *m/z* 474.3725, $C_{30}H_{50}O_4$ requires 474.3711.

PREPARATION OF TRIACETATE [**12**].—A solution of pentaol **9** (5 mg) in Ac_2O (300 μl) and pyridine (300 μl) was stirred at room temperature overnight. Si gel chromatography of the reaction mixture yielded the triacetate **12** (3 mg) as the major product: colorless oil; ir ($CHCl_3$) 2970, 1735, 1373, 1250, 1035, 901 cm^{-1}; ^1H nmr ($CDCl_3$) δ −0.15 (t, 1H, $J=4.9$ Hz), 0.18 (m, 2H), 0.45 (dd, 1H, $J=4.5$, 9.4 Hz), 0.71 (s, 3H), 0.83 (d, 3H, $J=7$ Hz), 0.87 (s, 3H), 0.95–0.98 (m, 9H), 1.16 (s, 3H), 2.03 (s, 3H), 2.04 (s, 3H), 2.06 (s, 3H), 2.42 (dd, 1H, $J=5.7$, 12 Hz), 3.52 (br s, 1H, ex.), 3.64 (br s 1H, $W_{1/2}=7.5$ Hz), 4.67 (br s, 1H, $W_{1/2}=7$ Hz), 5.15 (dt, 1H, $J=5.5$, 12 Hz), 5.22 (br s, 1H, ex.), 5.36 (m, 1H); eims *m/z* (rel. int.) $[M-HOAc]^+$ 558 (0.5), 540 (3), 480 (23), 438 (25), 420 (100), 402 (48), 305 (43); hrms *m/z* 558.3945, $C_{34}H_{54}O_9$ requires 558.3922.

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