Notes

Two New Steroidal Glycoside Sulfates, Longicaudoside-A and -B, from the Mediterranean Ophiuroid *Ophioderma longicaudum*

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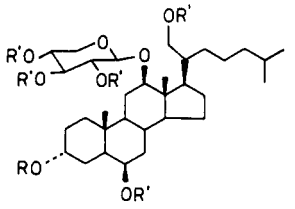
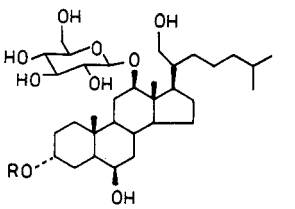
Received July 30, 1985

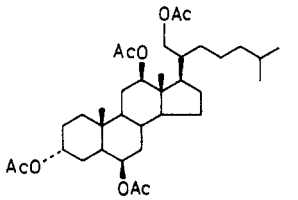
In connection with our investigations of biologically active compounds from echinoderms we have examined the ophiuroid *Ophioderma longicaudum*. We have recently reported the structures of a new carotenoid sulfate and of a group of unusual disulfated 3α,21-dihydroxy steroids along with 5β-cholestane-3α,4α,11β,12β,21-pentol 3,21-disulfate from *O. longicaudum*.[1,2] In this paper we propose structures for two new steroidal glycoside sulfates, designated longicaudoside-A (**1**) and -B (**2**), which were isolated from *O. longicaudum*. These compounds represent the first occurrence of steroidal glycosides in ophiuroids. In the animal kingdom steroidal glycosides are ubiquitous in starfishes,[3] while they are found only rarely in Alcyonarians[4] and as potent shark-repelling compounds in Vertebrata.[5]





1 R= $SO_3^-Na^+$, R'= H
1a R= H, R'= H
1b R= $SO_3^-Na^+$, R'= Ac
1c R= H, R'= Ac

2, R= $SO_3^-Na^+$
2a, R= H



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The methanol extract of *O. longicaudum* (0.7 kg fresh), collected at the Bay of Naples, June 1984, was partitioned into an ethyl acetate/water mixture and the aqueous phase was then extracted with 1-butanol. The 1-butanol-soluble material was chromatographed on Sephadex LH-20, and the glycosyl-containing fractions were further purified by droplet counter current chromatography (DCCC) and HPLC to obtain longicaudoside-A (**1**, 14 mg), $[\alpha]_D$ ±0°, and longicaudoside-B (**2**, 28 mg), $[\alpha]_D$ +3.7°.

The molecular formulae, $C_{32}H_{55}NaO_{11}S$ and $C_{33}H_{57}NaO_{12}S$, for **1** and **2**, respectively, were derived from ^{13}C NMR data (DEPT pulse sequence) and fast atom bombardment (FAB) mass spectra, which gave molecular ion species at m/z 671 (M + H), 693 (M + Na), and 709 (M + K) for **1** and m/z 701 (M + H) and 723 (M + Na) for **2**. M is the molecular weight of the sodium salts. Intense fragments at m/z 573 and 603 in the spectra of **1** and **2**, respectively, were interpreted as due to the loss of $NaHSO_4$ from M + Na. The presence of a sulfate group in both compounds was confirmed by solvolysis of **1** and **2** in a dioxane–pyridine mixture,[6] affording desulfated derivative **1a** and **2a**, which gave molecular ion species in FAB–MS at m/z 569 (M + H) and 591 (M + Na) and m/z 599 (M + H) and 621 (M + Na), respectively. Finally, the ^1H and ^{13}C NMR spectra of the native **1** and **2** on comparison with those of **1a** and **2a** are consistent with a sulfate function. Acid methanolysis of **1** gave methyl xyloside, while acid methanolysis of **2** liberated methyl glucoside. An analysis of ^1H NMR data for **1** (Tables I and II) assisted by decoupling techniques allowed the signals due to the xylopyranoside moiety to be assigned and suggested the $^4C_1$ conformation with β-linkage. Similarly the presence of a β-glucopyranoside moiety in **2** (Table II) was established. Further features of ^1H and ^{13}C NMR spectra (Table I) indicated that both longicaudosides share the same steroidal aglycone. Having established the presence of the sodium sulfate and xylosyl (in **1**) or glucosyl (in **2**) residues, the molecular formula for the aglycone of both **1** and **2** is $C_{27}H_{48}O_4$, corresponding to a saturated cholestane with four hydroxyl groups (three secondary and one primary; DEPT ^{13}C NMR). The analysis of spectral data is continued for longicaudoside A (**1**). The ^1H NMR (CD_3OD) spectrum contained signals for four of the five methyl groups typical of a sterol at δ 0.85 (s, 3 H), 0.92 (d, J = 7 Hz, 6 H), and 1.08 (s, 3 H). Although one methyl doublet was absent, an A portion of an ABX system at δ 3.78 (dd, J = 11.0, 3.2 Hz, 1-H) was observed and assigned to a $HOH_2C(21)$ group, a common feature among the steroids isolated from *O. longicaudum*. The B portion of the ABX system overlaps under the methanol signal (decoupling), but when we measured the spectrum in pyridine-d_5 (Table II) the resonance frequency of the two geminal protons were observed as isolated signals at δ 3.68 (br, $W_{1/2}$ = 20 Hz, 1 H) and 4.17 (br d, J = 12.5 Hz, 1 H). Decoupling proved that the two protons are coupled by 12.5 Hz. Hydroxylation at C-26 or C-27 could be ruled out primarily on the basis of the presence in the ^{13}C NMR spectrum of the typical signals for C-26 and -27 at 23.0 and 23.1 ppm.[7] Reinforcing evidence cames from the values of the shifts of the side-chain carbons and comparison with those of

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0022-3263/86/1951-0533$01.50/0

Table I. NMR Data of Compounds 1 and 2 (in CD_3OD)[a]

^{13}C NMR, δ			^1H NMR							
				1			2			
C	1[b]	2[b]	H	δ	mult	J, Hz	δ	mult	J, Hz	
1	35.6	35.6								
2	28.0	28.0								
3	76.7	76.7	3	4.72	br s	($W_{1/2}$ = 7.5 Hz)	4.73	br s	($W_{1/2}$ = 7 Hz)	
4	32.1	32.1								
5	43.7	43.7								
6	72.3	72.4	6	3.72	q	3	*d*			
7	40.4	40.4								
8	30.6	30.6								
9	54.8	54.6								
10	37.4	37.0								
11	27.1	27.2								
12	86.7	86.3	12	3.55	dd	11, 4.1	*d*			
13	49.0	49.0								
14	55.8	55.8								
15	25.2	25.0								
16	27.0	27.0								
17	52.2	51.9								
18	9.7	9.8	18	0.85	s		0.87	s		
19	15.3	15.3	19	1.08	s		1.08	s		
20	41.9	41.4								
21	66.1	66.3	21	3.78 (1 H)	dd	11, 3.2	*d*			
				c			*c*			
22	30.4	30.2								
23	25.0	24.1								
24	40.7	40.7								
25	29.1	29.1								
26	23.1	23.1	26							
				0.92 (6 H)	d	7	0.92 (6 H)	d	7	
27	23.0	23.0	27							
1′	102.1	101.3	1′	4.38	d	7.5	4.43	d	7.5	
2′	75.1	75.2	2′	3.20	dd	9, 7.5	3.22	dd	7.5, 9	
3′	78.2	78.2	3′	*c*			3.40	t	9	
4′	71.2	71.8	4′	3.48	ddd	10, 8, 5.5	*c*			
5′	67.0	77.8	5′	3.24 (a)	dd	11, 10	*d*			
				3.85 (e)	dd	11, 5.5	*d*			
6′		62.7	6′				3.89	dd	11.5, 1.5	

[a] ^1H NMR spectra were determined at 500 MHz. ^{13}C NMR spectra were determined at 62.9 MHz. [b] Assignments were made by using the DEPT technique, the assignments reported for 5α-cholestan-3α-ol,[7] methyl β-D-xylopyranoside,[12] and methyl β-D-glucopyranoside,[12] the substituent effects that have been published for hydroxy steroids,[9] the glycosidation shifts,[11] and the comparison with the data for **1a** and **2a** (Experimental Section). [c] Signals under methanol signal. [d] Nonassignable proton resonances. Overlapping signals spread out from δ 3.5 to 3.73 (5 H) are observed in the spectrum.

Table II. 500-MHz ^1H NMR Data (δ) of Compounds 1 and 2 (in Pyridine-d_5)[a]

	1	2
H-3β	5.31 (br t, $W_{1/2}$ = 7.5 Hz)	5.31 (br t, $W_{1/2}$ = 7.5 Hz)
H-6α	3.90 (q, J = 3 Hz)	3.90 (q, J = 3 Hz)
H-12α	3.83 (dd, J = 10.5, 5 Hz)	3.86 (dd, J = 11, 4.5 Hz)
H-21	3.68 (b, $W_{1/2}$ = 20 Hz)	3.58 (dd, J = 11, 8 Hz)
	4.17 (br d, 12.5)	4.06
H_3-18	0.82 (s)	0.82 (s)
H_3-19	1.19 (s)	1.18 (s)
H_3-26,27	0.80 (d, J = 7 Hz)	0.80 (d, J = 7 Hz)
H-1′	4.96 (d, J = 7.5 Hz)	5.01 (d, J = 7.5 Hz)
H-2′	4.06 (dd, J = 8, 7.5 Hz)	4.06
H-3′	4.24 (dd, J = 8 Hz)	4.21 (t, J = 9 Hz)
H-5′	3.85 (5′$_a$, dd, J = 11, 10 Hz)	4.06
	4.43 (5′$_e$, dd, J = 11, 5 Hz)	
H-6′		4.40 (dd, J = 12, 5 Hz)
		4.60 (dd, J = 12, 1.5 Hz)

[a] Assignments were aided by spin decoupling.

21-hydroxysteroids[2] and 26-hydroxy steroids,[8] of which the latter values were quite different. At 500 MHz the ^1H NMR spectrum (Table I) of **1** showed three isolated signals for the methine protons on oxygen-bearing carbons of the aglycone. A narrow signal ($W_{1/2}$ = 7 Hz) at δ 4.72 upfield shifted to δ 4.10 in the spectrum of the desulfated derivative **1a**, was assigned to 3β-H. These data along with ^{13}C NMR frequencies of C-2, C-3, and C-4 in the spectrum of **1a**, which are shifted by +1.7, −8.8, and +2.1 ppm, respectively, relative to **1**, established the location of the sulfate group at C-3.

The alternative 3β-OSO_3^--5β-stanol structure could be eliminated mainly upon the basis of the chemical shift of C-19 at 15.3 ppm. In steroids with a *cis*-A/B ring fusion the 19-methyl carbon is significantly downfield (e.g., in 5β-cholestan-3β-ol, C at 23.9 ppm[7]). The remaining two downfield methine signals were seen at δ 3.55 (1 H) as dd with J = 11.0 and 4.1 Hz, characteristic of an axial proton coupled with two other protons (1β- or 12β-O), and at δ 3.72 (1 H) as an apparent quartet with J = 3 Hz, characteristic of an equatorial proton coupled with three other protons (6β- or 11β-O). The upfield shift of the 18-methyl carbon (9.7 ppm) strongly indicated that one hydroxyl substituent was located at the 12β-position[7,9] and accordingly the remaining one was located at the 6β-position. Acetylation of **1** gave a pentaacetate (**1b**), whose ^1H NMR still contained the essentially unshifted dd of H-12 at δ 3.58 and downfield multiplets at δ ca. 5.04 and 4.13 for 6-H and 21-H_2, respectively (cf. esterification shifts[10]). This pro-

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vided evidence for the location of xylose at C-12 in **1**. ^{13}C NMR data (Table I) when compared with those of 12β-hydroxy steroids,[9] taking into account the glycosidation shifts,[11] confirmed the location of the β-xylopyranosyl residue at C-12. Thus, the structure of longicaudoside-A has been determined as 12β-O-β-xylopyranosyl-5α-cholestane-3α,6β,12β,21-tetrol 3-sulfate.

Longicaudoside-B (**2**) is related to **1** by being the corresponding 12β-O-β-glucopyranoside.

Hydrolysis of the major substance **2** with HCl under different conditions, with a view to obtaining the free aglycone, only gave intractable material. When **2** was treated with 50% aqueous acetic acid at 60 °C for 12 h, followed by chromatography on silica gel, there was isolated in small amount a tetraacetate (**3**) [4 $CH_3C{=}O$ ranging from δ 2.04 to 2.05], whose ^1H NMR spectrum was in agreement with the 5α-cholestane-3α,6β,12β,21-tetrol 3,6,12,21-tetraacetate structure (**3**).

The physiological function of these steroidal glycosides may be of interest.

Experimental Section

Instrumental. ^1H and ^{13}C NMR spectra were recorded on a Bruker WM-250 or WM-500 spectrometer. Chemical shifts are reported relative to Me_4Si. The DEPT experiments[13] were made by using polarization transfer pulse of 90° and 135°, respectively, obtaining in the first case only CH groups and in the other case positive signals for CH and CH_3 and negative ones for CH_2 groups. Polarization transfer delays were adjusted to an average CH coupling of 135 Hz. FAB mass spectra were recorded on a Kratos MS 50 mass spectrometer equipped with Kratos FAB source. The spectra were obtained by dissolving the samples in a glycerol matrix and placing them on a copper probe tip prior to bombardment with Ar atom of energy 2–6 kV. EI mass spectra were recorded on an AEI MS-30 spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. DCCC separations were performed on a DCC-A apparatus manufactured by Tokyo Rikakikai Co. equipped with 300 tubes. HPLC separation were performed on a Waters Model 6000A pump equipped with a U6K injector and differential rifractometer Model 401 detector. GLC analysis were performed with a Carlo Erba Fractovap 2900 capillary column.

Extraction and Isolation. The fresh animals (0.7 kg) were collected in the bay of Naples in June 1984 and extracted with MeOH (4 L) twice. The MeOH extracted was filtered through Whatman No. 1 paper and concentrated to a water residue. The residue was diluted with H_2O (500 mL) and extracted with ethyl acetate (3 × 300 mL) and then with 1-butanol (3 × 500 mL). The combined 1-butanol layers were evaporated to give 3.7 g of yellow material. This material was chromatographed on Sephadex LH-20 (3 × 60 cm; MeOH; two runs; 8-mL fractions were collected) to yield 600 mg (fractions 20–35) of organic solid containing **1** and **2**.

Purification was continued by droplet counter current chromatography (DCCC, with 7:13:8 $CHCl_3$/MeOH/H_2O in which the stationary phase consisted of the lower phase; ascending mode; flow 12 mL/h; 3-mL fractions were collected) to yield a mixture of the glycosides **1** and **2** (44 mg) in the fractions 14–16 and **1** (22 mg) in the fractions 17–25. Both fractions were submitted to HPLC on a C_{18} μ-Bondapack column (30 cm × 7.8 mm i.d.) with MeOH/H_2O (1:1) to yield pure **1** (14 mg) and **2** (28 mg).

Longicaudoside-A (1): HPLC retention time 9.0 min; $[\alpha]_D$ ±0° (*c* 1.0, MeOH); FAB-MS, *m/z* 709 (M + K), 693 (M + Na), 671 (M + H), 591, 589, 573, 555, 543, 496, 441 [where M is the molecular weight of the sodium salt].

Longicaudoside-B (2): HPLC retention time 7.8 min; $[\alpha]_D$ + 3.8° (*c* 1.0, MeOH); FAB-MS, *m/z* 723 (M + Na), 701 (M + H), 679, 603, 499, 481 [where M is the molecular weight of the sodium salt]; ^1H and ^{13}C NMR of **1** and **2** in CD_3OD are in Table I, while ^1H NMR of **1** and **2** in pyridine-d_5 are in Table II.

Solvolysis of 1 and 2 Giving 1a and 2a. A solution of longicaudoside-A (**1**, 6 mg) in dioxane (0.2 mL) and pyridine (0.2 mL) was heated in a stoppered reaction vial at 120 °C for 4 h. After the solution had cooled, water (2 mL) was added, and the solution was extracted with 1-butanol (3 × 1 mL). The combined extracts were washed with water and evaporated under reduced pressure to give the desulfated **1a** (5 mg): R_f (TLC, SiO_2; eluent, 12:3:5 *n*-BuOH/AcOH/H_2O) 0.66 (**1**, R_f 0.36); FAB-MS, *m/z* 591 (M + Na), 569 (M + H), 419 (M + H − 132 − H_2O), 401 (M + H − 132 − 2H_2O), 383 (M + H − 132 − 3 H_2O); ^1H NMR (CD_3OD), all signals virtually identical with those of **1** (Table I) except the signal for 3-H, which was observed shifted upfield to δ 4.10 (br s, $W_{1/2}$ = 7 Hz); ^{13}C NMR (CD_3OD) δ 35.3 (C-1), 29.7 (C-2), 67.5 (C-3), 34.2 (C-4), 43.3 (C-5), 72.8 (C-6), 40.6 (C-7), 30.7 (C-8), 54.8 (C-9), 37.4 (C-10), 15.1 (C-19) [the remaining signals were within ±0.1 ppm with those of **1**].

In a similar manner, longicaudoside-B (**2**) was desulfated to give **2a**: R_f (TLC, SiO_2; eluent, 12:3:5 *n*-BuOH/AcOH/H_2O) 0.67 (**2**, R_f 0.38); FAB-MS, *m/z* 621 (M + Na), 599 (M + H), 419 (M + H − 162 − H_2O), 401 (M + H − 162 − 2 H_2O), 383 (M + H − 162 − 3 H_2O); ^1H NMR (CD_3OD) all signals virtually identical with those of **2** except signal for 3-H, which was observed shifted upfield to δ 4.10 (br, s, $W_{1/2}$ = 7 Hz); ^{13}C NMR (CD_3OD) δ 35.3 (C-1), 29.8 (C-2), 67.6 (C-3), 34.2 (C-4), 43.4 (C-5), 72.8 (C-6), 40.6 (C-7), 30.7 (C-8), 54.8 (C-9), 37.4 (C-10) [the remaining signals were within ±0.1 ppm with those of **2**].

Methanolysis of 1 and 2: Sugar Analysis. A solution of longicaudoside-A (**1**, 0.5 mg) in anhydrous 2 M HCl–MeOH (0.1 mL) was heated at 80 °C in a stoppered reaction vial for 10 h. After being cooled the reaction mixture was neutralized with Ag_2CO_3 and centrifuged and the supernatant evaporated to dryness. The residue was dissolved in TRISIL Z (0.05 mL; *N*-(trimethylsilyl)imidazole in pyridine, Pierce Chemical Co.) left at room temperature for 15 min and analyzed by GLC (25-m SE-30 capillary column; 146 °C). GLC peaks coeluted with those of silylated methyl xyloside.

In a similar manner longicaudoside-B (**2**) was methanolyzed and glucose identified by GLC.

Acetylation of 1 to 1b and Subsequent Solvolysis to 1c. A mixture of **1** (4 mg) and excess of acetic anhydride (0.5 mL) and pyridine (0.5 mL) was kept at room temperature overnight. After removal of the excess reagents in vacuo, the residue was purified by passing through a Pasteur pipet filled with a slurry of silica gel in $CHCl_3$/MeOH (85:15) to give **1b**: FAB-MS, *m/z* 903 (M + Na), 881 (M + H); ^1H NMR (CD_3OD) δ 0.74 (3 H, s, 18-H_3), 0.94 (6 H d, *J* = 7 Hz, 26- and 27-H_3), 1.07 (3 H, s, 19-H_3), 2.03, 2.04, 2.05, 2.07 (15 H, each s, CH_3CO), 3.46 (1 H, dd, *J* = 11.5, 11.0 Hz, 5′-H_a), 3.58 (1 H, dd, *J* = 11.5, 5.0 Hz, 12-H), 4.04 (1 H dd, *J* = 11.5, 6.5 Hz, 5′-H_e), 4.13 (2 H, m, 21-H_2), 4.69 (1 H, br s, 3-H), 4.72 (1 H d, *J* = 7.5 Hz, 1′-H), 4.80–5.0 (3 H, br signal, 6-, 2′-, and 4′-H), 5.29 (1 H dd, *J* = 8.0, 8.0 Hz 3′-H).

1b was desulfated as described above to give, after purification of the reaction mixture by passing it through a Pasteur pipet filled with a slurry of silica gel in $CHCl_3$, **1c**: FAB-MS, *m/z* 817 (M + K), 801 (M + Na), 779 (M + H), 719, 443, 425, 383, 365; ^1H NMR ($CDCl_3$) δ 0.69 (3 H, s, 18-H_3), 0.89 (6 H, d, *J* = 7 Hz, 26- and 27-H_3), 0.97 (3 H s, 19-H_3), 2.02–2.04 (15 H, each s, CH_3CO), 3.28 (1 H, dd, *J* = 11.5, 10 Hz, 5′-H_a), 3.47 (1 H, dd, *J* = 11.0, 4.5 Hz, 12-H), 4.07 (1 H, dd, *J* = 11.5 and 6.0 Hz, 5′-H_e), 4.06 (2 H, m, 21-H_2), 4.15 (1 H, br s, 3-H), 4.50 (1 H, d, *J* = 7.5 Hz, 1′-H), 4.90 (1 H, br s, 6-H), 4.91 (1 H dd, *J* = 9.0, 7.5 Hz, 2′-H), 4.99 (1 H, ddd, *J* = 10.0, 9.0, 6.0 Hz, 4′-H), 5.20 (1 H dd, *J* = 9.0, 9.0 Hz, 3′-H).

Hydrolysis with Acetic Acid of 2 to 3. Longicaudoside-B (**2**, 4 mg) was hydrolyzed by being treated with 50% aqueous AcOH (1 mL) at 60 °C overnight. The solution was then evaporated to dryness and the residue was chromatographed on silica gel in $CHCl_3$ to give **3** (1 mg): EI-MS, *m/z* (relative intensity) 502 (M − AcOH − $CH_2{=}C{=}O$, 48), 487 (94), 484 (M − 2 AcOH,

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51), 424 (M - 3 AcOH, 46), 364 (M - 4 AcOH, 56), 313 (48), 253 (100); ^{1}H NMR ($CDCl_3$) δ 0.85 (3 H, s, 18-H_3), 0.88 (6 H, d, J = 7 Hz, 26- and 27-H_3), 1.00 (3 H, s, 19-H_3), 2.04-2.05 (12 H, CH_3CO), 3.83 (1 H dd, J = 11.0, 7.0 Hz, 21-H), 3.97 (1 H dd, J = 11.0, 4.5 Hz, 21-H), 4.64 (1 H dd, J = 11.0, 5.0 Hz, 12-H), 4.90 (1 H, br s, $W_{1/2}$ = 11.0 Hz, 6α-H), 5.07 (1 H, br s, $W_{1/2}$ = 7 Hz, 3β-H).

Acknowledgment. This study was supported by M.P.I. (Roma). We thank the supply Department of Zoological Station (Napoli) for collection of the animals. Mass spectra were provided by the "Servizio di Spettrometria di massa" of the CNR and the Università di Napoli. The assistance of the staff is gratefully acknowledged.

Registry No. 1, 99494-32-3; **1a**, 99458-05-6; **1b**, 99458-07-8; **1c**, 99458-08-9; **2**, 99458-04-5; **2a**, 99458-06-7; **3**, 99475-53-3.

A General, Selective, and Convenient Procedure of Homolytic Formylation of Heteroaromatic Bases

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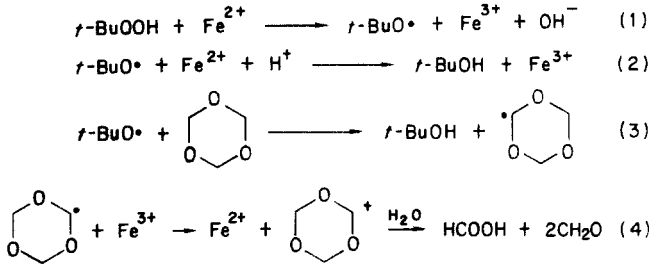
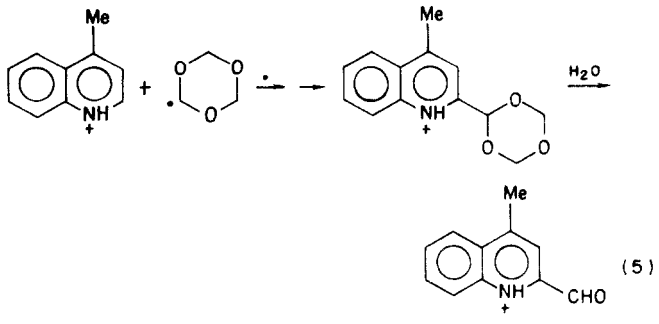
Received July 2, 1985

The substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals reproduces the numerous aspects of the aromatic Friedel-Crafts alkylation and acylation, formylation included, but with opposite reactivity and selectivity.[1]

The formylation by trioxane has till now given poor results;[1] the main reason is that the reaction has been carried out at room temperature, which requires almost stoichiometric amounts of Fe(II) salt. The relatively high concentration of Fe(III) salt formed according to eq 1 and 2 determines the fast oxidation[2] of the trioxanyl radical generated by hydrogen abstraction from trioxane (eq 3 and 4). The competition of the reactions 2 and 4 leads to poor



yields of attack of the trioxanyl radical to the protonated heteroaromatic base (eq 5). We have developed a new



(1) Minisci, F. *Top. Curr. Chem.* **1976**, *62*, 1. Vismara, E. *Chim. Ind. (Milan)* **1983**, *65*, 34. Gardini, G. P. *Tetrahedron Lett.* **1972**, 4113.
(2) Citterio, A.; Gentile, A.; Minisci, F.; Serravalle, M.; Ventura, S. *J. Chem. Soc., Chem. Commun.* **1983**, 916.

Table I. Formylation of Heteroaromatic Bases

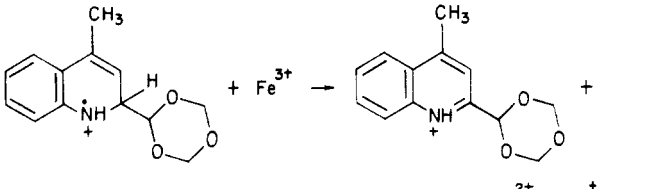
heteroaromatic base (mmol)	*t*-BuOOH, mmol	position of formylation	conversion, %	yield,[a] %
quinoline (16)	32	2 (58%) 4 (42%)	81	92
4-methylquinoline (14)	17	2	65	95
4-methylquinoline (14)	33	2	89	94
2-methylquinoline (14)	32	4	65	94
isoquinoline (14)	30	1	83	92
quinoxaline (14)	28	2	38	94
benzothiazole (14)	30	2	37	90

[a] GLC, based on converted heteroaromatic compound.

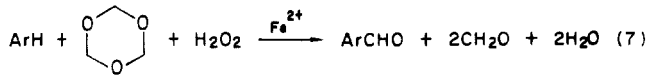
procedure[3] by combining the thermal effect and the redox catalysis which allows use of small amounts of Fe(II) salt (1%) to minimize therefore the competitive reactions 2 and 4 and to obtain much higher yields.

Moreover the new procedure is much simpler because the small amount of catalyst does not interfere during the isolation of the reaction products, whereas with stoichiometric iron salt considerable amount of Fe(III) hydroxide precipitates during the separation of the reaction products (sometimes complexing the heterocyclic compounds) and heavily affects the overall process.

The reaction is very selective and only the positions α and γ of the heterocyclic ring are substituted. The results are reported in Table I; the conversions can be further increased by increasing the amount of *t*-BuOOH. No reaction takes place in the absence of iron salt at the temperature used in the table, and only traces of substitution products are formed at room temperature in the presence of the catalytic amounts of employed Fe(II) salt, thus clearly indicating that the combination of the thermal effect and the redox catalysis is necessary for the success of the reaction. The Fe(II) salt consumed in eq 1 is regenerated in the oxidation of the heteroaromatic radical adduct (eq 6).



Hydrogen peroxide can be used instead of *t*-BuOOH; the stoichiometry is shown by the eq 7. The difference between *t*-BuOOH and aqueous H_2O_2 is that *t*-BuOOH leads to 97-98% of trioxanyl derivatives and only to 2-3% of the aldehyde generated by hydrolysis. The trioxanyl



derivative can be useful, as a masked aldehyde, for further transformations, and the hydrolysis can be accomplished at the right step. H_2O_2 always leads to mixtures of comparable amounts of trioxanyl derivatives and aldehyde due to the presence of more water; it is convenient in this case to transform all the reaction products to the aldehyde by complete hydrolysis.

1,3-Dioxolane can also be utilized by a similar procedure for the synthesis of heteroaromatic aldehydes, but the

(3) Minisci, F.; Giordano, C.; Vismara, E.; Levi, S.; Tortelli, V. Ital. Pat. 23798 A/84, 1984.

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