Effect of an 8-Hydroxymethyl Substituent on the Base-Catalyzed Ring Opening of 7,8-Epoxyiridoid Glucosides

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Base-catalyzed ring opening of 7,8-epoxyiridoids has been found to be dependent on the substitution pattern at C-8. Epoxyiridoids **5**, **6**, and **10** (CH_3-8) react in barium or sodium hydroxide solutions through a normal S_N2 process, yielding the expected 7α,8β-diols while for iridoids **3** and **4** (CH_2OH-8) the stereochemistry of the final diol function is reversed (7β,8α). This abnormal S_N2 process is explained by a preliminary "epoxide migration" from carbons 7,8 to 8,10 followed by normal oxirane cleavage. Participation of the CH_2OH-8 substituent in the cleavage reaction is proved by the behavior of the hexa-*O*-methyl derivative of **3** which gives the normal 7α,8β-diol. Four new nonnatural iridoid glucosides (**9**, **11**, **14**, **16**) are also described and spectroscopically (^1H and ^{13}C NMR) characterized.

In previous papers we reported on the structure and stereochemistry of two highly oxygenated iridoid glucosides, cynanchoside (**1**)[1] and 5,7-dideoxycynanchoside (**2**)[2], which were isolated from *Macfadyena cynanchoides* (Bignoniaceae) in addition to the known macfadyenoside (**3**)[3] (Chart I).

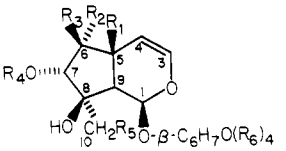
In the course of that research, chemical evidence for structure **2** was obtained by reductive cleavage of the epoxide ring of the hexaacetyl derivative of catalpol (**4**)[4] with $LiAlH_4$ in THF. As expected in a normal S_N2 process, the attack of the hydride ion occurred at the less highly substituted carbon atom (C-7) of the epoxide ring with retention of the configuration of the C-8 center and formation of 5,7-dideoxycynanchoside(**2**).

Previously two 7,8-epoxyiridoids, antirrhinoside (**5**)[5] and galiridoside (**6**),[6] were reported to react with hot barium hydroxide solutions to yield, respectively, 7α-hydroxyharpagide (**7**) and deepoxydihydroxygaliridoside (**8**).[7] In both cases the 7α,8β-diols obtained corresponded to the "normal diol"[8] expected from nucleophilic attack in the "normal" S_N2 process described above. By analogy we tried, therefore, to demonstrate the correct stereochemistry of **1**, only in part inferrable from analysis of ^{13}C NMR data, by transforming **3** into **1** through epoxide ring cleavage under the same basic conditions.

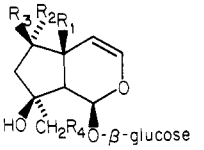
Surprisingly, the reaction whether carried out in hot barium hydroxide or 2 N sodium hydroxide solutions always gave as the only product the "abnormal diol" **9** (isocynanchoside) with the hydroxyl groups at C-7 and C-8 oriented in a configuration (7β,8α) opposite that expected.

To clarify this discrepancy, we repeated the reaction under both conditions on suitable epoxyiridoid models, procumbide (**10**) and catalpol (**4**), which differ, as do **5** and **3**, in having a CH_3 or a CH_2OH group at C-8 and in the configuration at C-6.

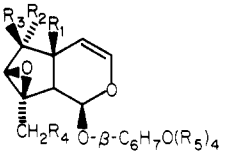
Chart I



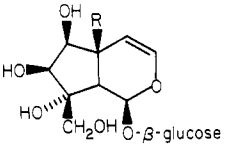
	R_1	R_2	R_3	R_4	R_5	R_6
1	OH	H	OH	H	OH	OH
7	OH	H	OH	H	H	OH
8	OH	H	H	H	H	OH
11	OH	OH	H	H	H	OH
13	H	H	OH	H	OH	OH
18	OH	H	OMe	H	OMe	OMe
19	OH	H	OMe	Me	OMe	OMe



	R_1	R_2	R_3	R_4
2	H	H	OH	OH
14	OH	H	OH	OH
15	OH	H	OH	H
16	OH	OH	H	H



	R_1	R_2	R_3	R_4	R_5
3	OH	H	OH	OH	OH
4	H	H	OH	OH	OH
5	OH	H	OH	H	OH
6	OH	H	H	H	OH
10	OH	OH	H	H	OH
17	OH	H	OMe	OMe	OMe



9, R = OH
12, R = H

(1) C. Bonini, E. Davini, C. Iavarone, and C. Trogolo, *Phytochemistry*, **20**, 1587 (1981).
(2) C. Adriani, C. Iavarone, and C. Trogolo, *Phytochemistry*, **21**, 231 (1982).
(3) A. Bianco, M. Guiso, C. Iavarone, and C. Trogolo, *Gazz. Chim. Ital.* **104**, 731 (1974).
(4) (a) J. M. Bobbitt, D. W. Spiggle, S. Mahboob, H. Schmid, and W. von Philipsborn, *J. Org. Chem.*, **31**, 500 (1966). (b) J. M. Bobbitt, D. E. Kiely, A. Y.-w. Lam, and E. I. Snyder, *J. Org. Chem.*, **32**, 1459 (1967).
(5) M. L. Scarpati, M. Guiso, and P. Esposito, *Gazz. Chim. Ital.*, **98**, 177 (1968).
(6) O. Sticher, *Helv. Chim. Acta*, **53**, 2010 (1970).
(7) This compound was later named daunoside by the same author (see ref 12 b).
(8) In accordance with general practice, products resulting from compliance with "normal S_N2 nucleophilic attack" to the 7,8-epoxide function will be termed "normal" while those from reactions violating it will be termed "abnormal" (see ref 15 a).

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In agreement with the results obtained from **3** and **5**, procumbide (**10**)[9] (α-OH at C-6, α-CH_3 at C-8) gave the "normal diol" (7α-OH,8β-OH) **11** (6α-hydroxydaunoside) while catalpol (**4**) (β-OH at C-6, α-CH_2OH at C-8) yielded the "abnormal diol" (7β-OH,8α-OH) **12** identical with the known 10-decinnamoylglobularinin.[10]

The structures and stereochemistries of the new 7,8-diols were inferred by comparing their ^{13}C NMR data (Table I) with those of useful models, applying the known "C-8 epimeric pairs rule".[11] For establishing the stereochemistry of the diol **12** we used ^{13}C spectra of both possible 7,8-diols, 10-decinnamoylglobularimin (**13**,[10] "normal diol") and 10-decinnamoylglobularinin (**12**,[10] "abnormal diol") while in the case of the cleavage product of **3** ^{13}C data of only the "normal diol", cynanchoside (**1**),[1] were available.

Use of the "trans diol rule"[13] provided a further criterion for verifying the relative stereochemistry at C-6 and C-7.

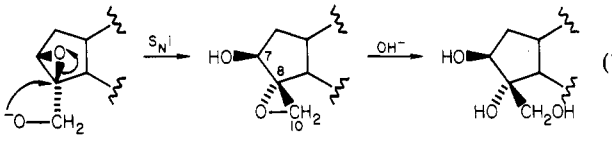
Participation of the hydroxyl on C-6 in the 7,8-epoxide ring cleavage may be ruled out as **6** (6-deoxyantirrhinoside), **5**, and **10** (6-epiantirrhinoside) were opened to the "normal diol". On the other hand, the results seem to indicate that base-catalyzed cleavage of the epoxide ring depends on the presence or absence of a hydroxyl group on C-10 symmetrically disposed to the hydroxyl on C-6.

This anomalous behavior prompted us to acquire more details on the reactivity of 7,8-epoxyiridoids.

As already observed for the $LiAlH_4$ reduction of catalpol hexaacetate,[2,4b] reduction of acetyl derivatives of **3**, **5**, and **10** proceeded by normal S_N2 process to give invariably the "normal" opened products 7-deoxycynanchoside (**14**), harpagide (**15**), and 6-epiharpagide (**16**).

The formation of the "normal" product in the reaction of $LiAlH_4$ with two pairs of differently C-8-substituted epoxyiridoids (**5**-**10** with CH_3-8 and **3** and **4** with CH_2OH-8) ruled out the possibility that the anomalies observed in the base-catalyzed ring opening of epoxyiridoids with a CH_2OH-8 could be ascribed to the α orientation of the epoxide ring, opposite the one currently accepted.

To rationalize the anomalous results obtained in the basic cleavage of **3** and **4**, we postulated the mechanistic hypothesis shown in eq 1.



(1)

The reaction implies initial formation of the anion from the hydroxyl group at C-10, adjacent to the epoxide ring. This nucleophile attacks the C-8 carbon from the α side of the molecule, so realizing an intramolecular nucleophilic displacement (S_Ni) with formation of an isomeric 8,10-

Table I. ^{13}C NMR Data of Compounds 1-19[a]

compd	solv	ref	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
1	D_2O	1	91.69	140.55	109.28	64.95	82.53	78.90	76.27	56.16	62.11	98.86	73.35	76.27[b]	70.60	77.05[b]	61.63
2	D_2O	2	93.28	140.14	105.28	40.82	76.56	44.15	82.14	50.38	67.00	98.93	73.54	76.56[b]	70.50	76.98[b]	61.63
3	D_2O	21	95.13	142.78	107.13	74.05	77.06	63.27	66.51	50.12	60.56	99.31	73.46	76.38[b]	70.42	77.06[b]	61.62
4	D_2O		95.53	141.40	103.94	38.10	78.42	62.83	66.61	42.58	60.94	99.34	73.63	76.47[b]	70.34	76.99[b]	61.55
5	D_2O	21	94.94	142.90	107.06	74.25	76.78	66.23	64.96	52.07	17.00	99.24	73.45	76.39[b]	70.43	77.07[b]	61.55
6	CD_3OD	12	95.30	141.72	109.57	76.57	44.42	64.20	67.28	54.45	17.60	99.63	74.78	78.46[b]	71.82	77.85[b]	63.00
7	D_2O	21	92.01	139.96	109.48	64.17	82.64	78.92	74.91	56.36	16.69	98.74	73.36	76.28[b]	70.61	77.06[b]	61.63
8	CD_3OD	12	92.31	139.30	111.46	65.64	46.55	78.21[b]	80.45	58.78	15.91	99.31	74.58	78.06[b]	71.80	77.61[b]	62.86
9	D_2O		93.79	142.91	106.48	68.78	79.03	77.77	81.17	51.11	66.34	99.06	73.36	76.21[b]	70.45	76.99[b]	61.55
10	D_2O		95.61	144.18	103.72	79.60	77.64	65.73	67.04	52.18	17.10	99.14	73.55	76.56[b]	70.42	77.06[b]	61.62
11	D_2O		92.79	141.42	105.19	71.49	78.25	78.25	79.70	56.56	18.28	98.92	73.35	77.05[b]	70.52	76.21[b]	61.53
12	CD_3OD[c]	12	95.16	141.61	105.27	37.16	78.34[b]	79.34[b]	81.03	43.70	66.37	99.20	74.61	77.99[b]	70.39	78.34[b]	62.42
12	D_2O		94.83	140.54	105.78	36.53	77.75	79.50	81.95	43.18	66.13	99.15	73.47	76.47[b]	70.33	76.97[b]	61.44
13	CD_3OD	12	93.34	140.39	106.54	37.32	83.14	86.42	80.33	48.04	64.29	99.55	74.61	77.94[b]	71.54	77.71[b]	62.70
14	D_2O		92.90	142.68	106.82	72.57	77.04	41.57	80.47	56.85	66.49	99.31	73.35	77.10[b]	70.51	76.26[b]	61.51
15	D_2O	21	93.56	141.99	107.25	71.89	77.06	46.22	77.75	57.83	24.73	99.04	73.27	76.19[b]	70.45	77.06[b]	61.54
16	D_2O		93.48	142.68	102.74	73.08	76.66	45.44	74.82	57.92	25.69	99.04	73.27	77.05[b]	70.43	76.21[b]	61.53
17	$CDCl_3$		92.68	143.06	106.75	79.28	86.03	60.84	63.67	46.10	70.80	98.33	83.40	86.42	79.28	75.09	71.45
17[d]	$(CD_3)_2CO$		92.62			79.79	85.46	60.30	64.46	47.37	72.51[b]	99.21	84.47	87.06	80.18	75.83	72.17[b]
18	$CDCl_3$		91.79	142.46	107.41	72.28	90.81	81.93	76.56	52.53	71.28[b]	98.42	83.39	86.79	79.29	75.00	73.13[b]
18[d]	$(CD_3)_2CO$		92.25			72.08	90.84	82.22	76.12	54.00	72.08[b]		84.45	87.36	80.19	75.74	73.30[b]
19	$CDCl_3$		91.29	142.38	108.22	71.27	89.25	88.16	76.17	53.91	71.27	98.43	83.88	86.90	79.39	75.00	71.27
19[d]	$(CD_3)_2CO$		92.11			71.84	90.26	89.70	76.64	54.46	72.11[b]		84.66	87.37	80.23	75.75	72.28[b]

[a] Chemical shifts are given in parts per million. [b] Values with same superscript in the horizontal columns are interchangeable. [c] A few drops of Me_2SO-d_6 were added to increase the solubility. [d] In order to maximize digital resolution to distinguish the C-5 and C-8 signals the spectra were permitted to "fold", care being taken to minimize or avoid actual superimposition of folded and nonfolded resonances.

(9) The transformation 10 → 11 occurred under both basic conditions with very poor yields, in agreement with the reported instability in Ba(OH)$_2$ of iridoids having a trans 5β,6α-diol system (H. Rimpler and B. Schäfer, *Z. Naturforsch., C: Biosci.*, **34C**, 311 (1979)). The reaction proceeded with more satisfactory yields in strong anionic-exchange resin (see ref 4a).

(10) R. K. Chaudhuri, O. Sticher, and T. Winkler, *Tetrahedron Lett.* 3149 (1979).

(11) This rule, widely used in ^{13}C spectral analysis of iridoids, permits one to assign unambiguously the configuration of geminal substituents at C-8 using the chemical shift values of C-9 as a diagnostic probe (see ref 1 and 12).

(12) (a) C. Adriani, C. Bonini, C. Iavarone, and C. Trogolo, *Lloydia*, **44**, 739 (1981); (b) R. K. Chaudhuri, F. Ü. Afifi-Yazar, O. Sticher, and T. Winkler, *Tetrahedron*. **36**, 2317 (1980); (c) S. Damtoft, S. R. Jensen, and B. J. Nielsen, *Phytochemistry*, **20**, 2717 (1981).

(13) This rule establishes that in *vic*-dihydroxyiridoids the signals from carbons in a *trans*-1,2-diol arrangement appear at lower field than those of the corresponding cis isomer (see ref 12b).

epoxide ring.[14] The new oxirane function then undergoes normal S_N2 attack of OH^- on the less substituted C-10 carbon to yield the final 7β,8α-diol.

This phenomenon, referred to as "epoxide migration" of 3-hydroxy 1,2-epoxides under basic conditions, is well documented[15] in the carbohydrate and inositol series[15c] and in simple α,β-epoxy alcohols[16] while the present instance seems to be the first report of this effect in cyclopentanoid epoxides.[17]

To achieve a chemical proof of the proposed mechanism we prepared **17** from **3** with CH_3I/Ag_2O in dry DMF at room temperature. Protection of the CH_2OH group at C-8 was expected to block the postulated "epoxide migration" and therefore to shift the course of the reaction back toward formation of the "normal" 7,8-diol.

For solubility reasons, cleavage of **17** was carried out in 2 N sodium hydroxide solution containing small amounts of methanol and afforded two products the hexa-*O*-methyl derivative **18** (the 7,8-diol expected by OH^- attack) and the hepta-*O*-methyl derivative **19** (the 7-*O*-methyl ether of **18**, formed by MeO^- attack). Structures were established by analysis of ^{13}C NMR spectra: in particular the "C-8 epimeric pairs rule"[11] confirmed the presence in both compounds of a free β-orientated OH group at C-8 that is the normal trend of the S_N2 process.

These results confirm the peculiar role exerted by the hydroxymethyl group attached to C-8 in the base-catalyzed cleavage of epoxyiridoids like **3** and **4** and corroborate the mechanistic pathway proposed for explaining the anomalies observed.

Experimental Section

Silica gel SIF_{254} (C. Erba) and cellulose (Merck) plates were used for TLC. Spray reagents were as follows: 2 N H_2SO_4, heating at 120 °C (silica gel plates); vanillin (vanillin, 1 g; concentrated HCl, 2 mL; methanol, 100 mL), heating at 100 °C (cellulose plates). ^1H NMR spectra were registered with Perkin-Elmer R32 (90 MHz) and Varian EM 360–A (60 MHz) instruments, with Me_4Si as an internal standard for the spectra run in $CDCl_3$ and the HDO signal (δ 4.70 from Me_4Si) for those in D_2O. ^{13}C NMR spectra, determined at 20 MHz on a Varian CFT-20 Fourier transform computer, were referred to the carbon signal of dioxane (67.4 ppm) and computer converted to δ values from Me_4Si.

Isolation of Iridoids. The naturally occurring iridoid glucosides were isolated according to known procedures from the following plants: cynanchoside (**1**),[1] 5,7-dideoxycynanchoside (**2**),[2] and macfadyenoside (**3**)[3] from *Macfadyena cynanchoides*; antirrhinoside (**5**)[5] from *Antirrhinum tortuosum*; procumbide (**10**) and harpagide (**15**) from *Harpagophytum procumbens*.[18] Catalpol (**4**) from *Globularia alypum*[19] was kindly supplied by Prof. G. Di Maio, Institute of Organic Chemistry, University of Rome.

General Cleavage Procedure of 7,8-Epoxyiridoids with Barium Hydroxide. Iridoid glucoside (200 mg) was dissolved in 5 mL of a saturated solution of $Ba(OH)_2$ and heated at 70 °C for 5 h. After neutralization with CO_2, decolorizing charcoal was added until a vanillin test was negative, and the suspension was deposited on a gooch funnel. The salts were removed by elution with water, and the organic fraction was extracted with methanol, which was concentrated in vacuo to give a crude residue.

Isocynanchoside (9) from Macfadyenoside (3). The residue (70 mg) was chromatographed on silica gel (7 g); elution with acetone/water (9:1) afforded **9** (50 mg) as an amorphous compound: ^1H NMR (D_2O) δ 2.65 (1 H, brs, H-9), 3.60–3.95 (1 H, H-7), 3.88 (2 H, brs, 2H-10), 4.16 (1 H, d, $J_{6,7}$ = 4.5 Hz, H-6), 5.18 (1 H, d, $J_{3,4}$ = 6 Hz, H-4), 5.70 (1 H, s, H-1), 6.50 (1 H, d, $J_{3,4}$ = 6 Hz, H-3). Anal. Calcd for $C_{15}H_{24}O_{12}$: C, 45.45; H, 6.10. Found: C, 45.37; H, 6.17.

10-Decinnamoylglobularinin (12) from Catalpol (4). The residue (100 mg) was chromatographed on silica gel (10 g); elution with methylene chloride/ethanol/water (30:20:1) afforded **12** (60 mg). ^1H NMR data are in agreement with those reported in ref 10.

7α-Hydroxyharpagide (7) from Antirrhinoside (5). The residue (80 mg) was chromatographed on silica gel (8 g); elution with *n*-butyl alcohol/methanol/water (14:1:4) afforded **7** (60 mg). ^1H NMR data are in agreement with those reported in ref 1.

Cleavage of the Oxirane Ring of Procumbide (10).[9] Compound **10** (300 mg) dissolved in 5 mL of water was added to an aqueous suspension of strong anionic exchange resin (Merck Type III). The suspension was heated at 70 °C for 48 h with stirring. After filtration the aqueous suspension was concentrated in vacuo and the residue chromatographed on silica gel (20 g). Elution with chloroform/methanol (7:3) afforded unreacted **10** (80 mg) and **11**: 32 mg); ^1H NMR (D_2O) δ 1.24 (3 H, s, CH_3-10), 2.40 (1 H, brs, H-9), 3.94 (1 H, d, $J_{6,7}$ = 6 Hz, H-7), 4.14 (1 H, d, $J_{6,7}$ = 6 Hz, H-6), 5.22 (1 H, d, $J_{3,4}$ = 6 Hz, H-4), 5.70 (1 H, s, H-1), 6.40 (1 H, d, $J_{3,4}$ = 6 Hz, H-3). Anal. Calcd for $C_{15}H_{24}O_{11}$: C, 47.37; H, 6.36. Found: C, 47.28; H, 6.40.

General Cleavage Procedure of 7,8-Epoxyiridoids with Sodium Hydroxide. A study of the effects of reaction time and temperature and the base concentration on this reaction was carried out. The procedure described for the conversion of **3** into **9** refers to the optimal conditions found. Similar procedures were followed for the conversion of **4** and **5** into **12** and **7**, respectively. Final yields were comparable with those reported for **9**.

Isocynanchoside (9) from Macfadyenoside (3). Compound **3** (300 mg) was dissolved in 5 mL of 2 N NaOH and heated at 80 °C for 1 h. The solution was neutralized with 2 N HCl, and decolorizing charcoal was added until the vanillin test was negative. The suspension was deposited on a gooch funnel and eluted first with water to remove the salts and afterward with methanol. The residue was chromatographed on silica gel (20 g) in chloroform/methanol (7:3) and afforded unreacted **3** (120 mg) and **9** (50 mg).

General Cleavage Procedure of 7,8-Epoxyiridoids with Lithium Aluminium Hydride. Preparation of Iridoid Acetates. Iridoid glucoside (100 mg) was dissolved in dry pyridine (0.5 mL) and treated with acetic anhydride (1 mL) for 1 h at room temperature. After addition of methanol, the solution was evaporated in vacuo. The residue was chromatographed on silica gel (10 g) in ethyl ether/benzene (7:3) and afforded the iridoid acetate (95 mg).

$LiAlH_4$ Reduction of the Oxirane Ring. To iridoid acetate (100 mg) in 10 mL of dry THF was added $LiAlH_4$ (25 mg). The suspension was heated to reflux temperature. After the mixture cooled, methanol was added and the solution concentrated in vacuo after addition of water, the solution was neutralized with 6 N HCl, and decolorizing charcoal was added until the vanillin test was negative. The suspension was deposited on a gooch funnel, and salts were removed with water. Successive elution with methanol gave the organic fraction which was concentrated in vacuo and afforded a residue.

7-Deoxycynanchoside (14) from Hexa-*O*-acetylmacfadyenoside. The residue (60 mg) was chromatographed on silica gel (6 g) in chloroform/methanol (7:3) and afforded **14**: 38 mg; ^1H NMR (D_2O) δ 1.80 and 2.10 (2 H, o, J_{AB} = 15 Hz, J_{AX} = 4.5 Hz, J_{BX} = 3 Hz, 2H-7), 2.64 (1 H, brs, H-9), 3.52 (2 H, AB, J_{AB} = 14 Hz, 2H-10), 3.80 (1 H, q, $J_{6,7}$ = 4.5 Hz, $J_{6,7}$ = 3 Hz, H-6), 5.03 (1 H, d, $J_{3,4}$ = 6 Hz, H-4), 5.88 (1 H, s, H-1), 6.34 (1 H, d, $J_{3,4}$ = 6 Hz, H-3). Anal. Calcd for $C_{15}H_{24}O_{11}$:C, 47.37; H, 6.36. Found: C, 47.25; H, 6.39.

5,7-Dideoxycynanchoside (2) from Hexa-*O*-acetylcatalpol. See ref 2.

(14) An attempt to detect the formation of the postulated 8,10-epoxy intermediate, made by registering a set of ^1H NMR spectra of **4** in 2 N sodium deuterioxide solution in deuterium oxide while increasing the temperature from 25 to 80 °C, was unsuccessful.

(15) (a) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959); (b) J. G. Buchanan, H. Z. Sable in "Selective Organic Transformations", B. S. Thyagarajan, Ed., Wiley-Interscience, New York, 1972, Vol. 2, p 1; (c) S. J. Angyal and P. T. Gilham, *J. Chem. Soc.*, 3691 (1957).

(16) G. B. Payne, *J. Chem. Soc.* **27**, 3819 (1962).

(17) (a) J. A. Franks, Jr., B. Tolbert, R. Stein, and H. Z. Sable, *J. Org. Chem.*, **30**, 1440 (1965); (b) A. Hasegawa and H. Z. Sable, *J. Org. Chem.*, **31**, 4161 (1966).

(18) A. Bianco, P. Esposito, M. Guiso, and M. L. Scarpati, *Gazz. Chim. Ital.*, **101**, 764 (1971).

(19) G. Di Maio and L. Panizzi, *Ric. Sci.*, **36**, 845 (1966).

Harpagide (15) from Penta-*O*-acetylantirrhinoside.[20] The residue (70 mg) after chromatography on silica gel (6 g) in *n*-butyl alcohol/methanol/water (14:1:4) afforded **15**: 50 mg; ^{1}H NMR and ^{13}C NMR spectra superimposable on those of natural harpagide.

6-Epiharpagide (16) from Penta-*O*-acetylprocumbide. The residue (80 mg) after chromatography on silica gel (7 g) in chloroform/methanol (4:1) afforded **16**: 55 mg; ^{1}H NMR (D_2O) δ 1.21 (1 H, s, CH_3-10), 1.69 (2 H, o, J_{AB} = 14 Hz, J_{AX} = 7 Hz, J_{BX} = 12 Hz, 2H-7), 2.33 (1 H, brs, H-9), 4.26 (1 H, q, $J_{6,7}$ = 7 Hz, $J_{6,7}$ = 12 Hz, H-6), 5.06 (1 H, d, $J_{3,4}$ = 6 Hz, H-4), 5.64 (1 H, brs, H-1), 6.42 (1 H, d, $J_{3,4}$ = 6 Hz, H-3). Anal. Calcd for $C_{15}H_{24}O_{10}$: C, 49.45; H, 6.64. Found: C, 48.97; H, 6.92.

Preparation of Hexa-*O*-methylmacfadyenoside (17). CH_3I (1 mL) and Ag_2O (1.2 g, freshly prepared) were added to **3** (250 mg) dissolved in dry DMF (10 mL) with stirring at room temperature and in the dark. After 24 h, CH_3I (0.5 mL) and Ag_2O (0.6 g) were added and stirring continued for 12 h. The suspension was filtered on a gooch funnel and the salts were washed with chloroform. A white precipitate was filtered off and washed repeatedly with chloroform. The combined solutions were concentrated in vacuo. The residue was chromatographed on silica gel (25 g), and elution with chloroform/methanol (24:1) afforded pure hexa-*O*-methylmacfadyenoside (**17**): 188 mg; ^{1}H NMR ($CDCl_3$) δ 2.86 (1 H, d, $J_{1,9}$ = 5 Hz, H-9), 3.2–3.6 (18 H, 6 OCH_3), 3.61 (2 H, s, 2H-10), 3.4–3.8 (1 H, H-7), 3.94 (1 H, m, H-6, partly masked), 4.65 (1 H, d, $J_{1',2'}$ = 7 Hz, H-1'), 4.98 (1 H, d, $J_{3,4}$ = 6 Hz, H-4), 5.50 (1 H, d, $J_{1,9}$ = 5 Hz, H-1), 6.48 (1 H, d, $J_{3,4}$ = 6 Hz, H-3).

Reaction of 17 with Sodium Hydroxide. Compound **17** (450 mg) was dissolved in methanol (1 mL). NaOH (2 N, 10 mL) was added, and the solution was heated for 10 h at 80 °C. After cooling, the solution was neutralized with 2 N HCl and extracted twice with chloroform. The combined organic solutions were evaporated in vacuo, and the residue was chromatographed on silica gel (40 g). Elution with chloroform/methanol (24:1) afforded hepta-*O*-methylcynanchoside (**19**, 170 mg) and hexa-*O*-methylcynanchoside (**18**, 200 mg): ^{1}H NMR of **19** ($CDCl_3$) δ 2.60 (1 H, dd, $J_{1,9}$ = 1.5 Hz, $J_{4,9}$ = 1 Hz, H-9), 3.1–3.7 (23 H, 7 OCH_3 and 2H-10 signals), 3.80 (1 H, d, $J_{6,7}$ = 7 Hz, H-7), 4.56 (1 H, d, $J_{6,7}$ = 7 Hz, H-6), 5.06 (1 H, dd, $J_{3,4}$ = 6.5 Hz, $J_{4,9}$ = 1 Hz, H-4), 5.67 (1 H, d, $J_{1,9}$ = 1.5 Hz, H-1), 6.38 (1 H, d, $J_{3,4}$ = 6.5 Hz, H-9); ^{1}H NMR of **18** ($CDCl_3$) δ 2.54 (1 H, d, $J_{1,9}$ = 3.5 Hz, H-9), 3.5–4.2 (21 H, H-7, 2H-10 and 6 OCH_3 signals), 4.50 (1 H, d, $J_{6,7}$ = 7 Hz, H-6), 5.04 (1 H, d, $J_{3,4}$ = 6.5 Hz, H-4), 5.47 (1 H, d $J_{1,9}$ = 3.5 Hz, H-1), 6.30 (1 H, d, $J_{3,4}$ = 6.5 Hz, H-3).

Preparation of Hexa-*O*-methylcynanchoside (19) from Cynanchoside (1). Cynanchoside (1, 150 mg), methylated as described for **3** (0.6 mL of CH_3I and 720 mg of Ag_2O), afforded a crude residue which on chromatography on silica gel (8 g) and elution with chloroform/methanol (97:3) afforded pure **19** (60 mg).

Registry No. **1**, 80666-56-4; **2**, 81892-75-3; **3**, 54835-65-3; **3** hexaacetate, 54621-31-7; **4**, 2415-24-9; **4** hexaacetate, 6910-20-9; **5**, 20770-65-4; **5** hexaacetate, 20770-66-5; **6**, 30688-55-2; **7**, 79549-53-4; **8**, 86372-54-5; **9**, 86362-15-4; **10**, 20486-27-5; **10** hexaacetate, 35993-19-2; **11**, 36476-17-2; **12**, 73366-31-1; **13**, 73366-30-0; **14**, 86309-49-1; **15**, 6926-08-5; **16**, 86362-16-5; **17**, 86309-50-4; **18**, 86309-52-6; **19**, 86309-51-5.

(20) In ref 5 the reduction was carried out with Li/NH_3.
(21) A. Bianco, P. Caciola, M. Guiso, C. Iavarone, and C. Trogolo, *Gazz. Chim. Ital.*, 111, 201 (1981).

Syntheses and Reactivity of *trans*-6-Azabicyclo[3.1.0]hexan-2-ol Derivatives and Indano[1,2-*b*]aziridine. Structural Analogues of Mitomycin C

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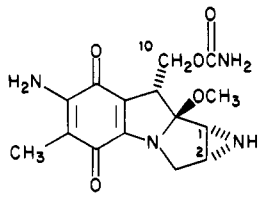
The synthesis and reactivity of three annelated aziridines (**4–6**) are described. *trans*-6-Azabicyclo[3.1.0]hexan-2-ol (**4**) and *cis*-2-methyl-*trans*-6-azabicyclo[3.1.0]hexan-2-ol (**5**) undergo regio- and stereospecific ring opening of the aziridine ring in aqueous HCl and $HClO_4$ acid solutions. In each case, reaction proceeds at carbon-5 to give the trans-ring-opened product. Correspondingly, treatment of indano[1,2-*b*]aziridine (**6**) with aqueous $HClO_4$ acid gave a 2.7:1 mixture of *cis*- and *trans*-2-amino-1-indanol (**39** and **40**, respectively). Comparison of these results with those previously reported for the acid-promoted hydrolysis of mitomycin C (**1**) suggests that hydrolysis in the latter case may proceed by initial loss of methanol to give the indoloquinone, followed by regiospecific ring opening of the aziridine ring by an S_N1-type process.

Mitomycin C (**1**) is a clinically useful antineoplastic



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antibiotic compound. Its mechanism of action at the molecular level both in vitro and in vivo is ill-defined.[2] Extensive studies have indicated that the biological event of primary importance induced by the mitomycins is probably the alkylation of DNA.[1] A series of mechanisms have been advanced that invoke the involvement of both the aziridine and the carbamate moieties.[3] The initial step is believed to be reduction of the quinone moiety to a semiquinone. This is suggested to be a necessary step for efficient, noncovalent binding of the drug with the substrate DNA. Subsequent reduction of the complexed semiquinone radical to the hydroquinone is followed by loss of methanol at C-9 and C-9a to give an indolohydroquinone ring system. This then fully activates the drug by unmasking electrophilic centers at carbon-1 of the aziridine ring and carbon-10 adjacent to the carbamate

(1) Alfred P. Sloan Foundation Fellow, 1977–1981. Camille and Henry Dreyfus Teacher-Scholar Grant Recipient, 1977–1982.
(2) (a) Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley: New York, 1979; Vol. 1, pp 221–276. (b) Crooke, S. T.; Bradner, W. T. *Cancer Treat. Rev.* **1976**, *3*, 121–140. (c) Comis, R. L.; Carter, S. K. *Cancer* **1974**, *34*, 1576–1586 and references therein.
(3) (a) Iyer, V. N.; Szybalski, W. *Science* **1964**, *145*, 55–58. (b) Szybalski, W.; Iyer, V. N. In "Antibiotics. Mechanism of Action"; Gottlieb, D., Shaw, P. D., Eds.; Springer: New York, 1967; Vol. 1, pp 211–245. (c) Patrick, J. B.; Williams, R. P.; Meyer, W. E.; Fulmor, W.; Cosulich, D. B.; Broschard, R. W. *J. Am. Chem. Soc.* **1964**, *86*, 1889–1990. (d) Moore, H. W. *Science* **1977**, *197*, 527–532.

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