HETEROCYCLES, Vol. 63, No. 6, 2004, pp. 1299 - 1310
Received, 18th February, 2004, Accepted, 9th April, 2004, Published online, 9th April, 2004

FUNCTIONALIZATION OF THE RING A IN SOME BENZO[*g*]PYRIDAZINO[1,2-*b*]PHTHALAZINE-6,13-DIONE DERIVATIVES RELATED TO ANTHRACYCLINONES

Rafael Jiménez, Ana M. Sanz, Fernando Gómez-Contreras,* M. Carmen Cano, María J. R. Yunta, Mercedes Pardo, and Lucrecia Campayo

Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense. 28040-Madrid (Spain). E-mail: fercon@quim.ucm.es.

Dedicated with warmest wishes to Professor Jose Luis Soto as a tribute to a life devoted to Organic Chemistry

Abstract- A synthesis of benzo[*g*]pyridazino[1,2-*b*]phthalazine-6,13-dione derivatives (**2**) and (**3**)**,** respectively related to the feudomicinone B and daunomicinone skeletons, has been accomplished by [4+2] cycloaddition of benzo[*g*]phthalazine-1,4-dione with the adequate 1,3-diene. Functionalization of ring A with hydroxy substituents has been performed by reaction with *N*-bromosuccinimide in acid aqueous medium, sodium hydroxide, or hydrobromic acid *via* the corresponding epoxide, and the stereochemical features of electrophilic additions involved are commented in terms of steric and stereoelectronic factors. Easy isomerization of the C2-C3 double bond allows the introduction of hydroxy groups at the C1 or C4 positions, paving a way to further formation of the glycosides derivatives related to natural anthracyclines.

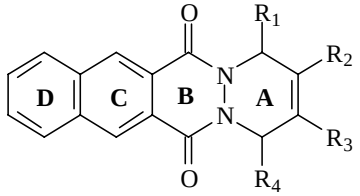
Anthracyclines represent an important class of antitumour agents.[1] Numerous synthetic analogues have been prepared in order to find the related compounds showing better therapeutic efficacy together with fewer side effects.[2] One way of achieving this goal is the introduction of heteroatoms into the carbocyclic backbones of aglycons, as has been shown in the derivatives containing γ-pyrone and γ–thiopyrone moieties.[3]

Our group is interested in the preparation of anthracycline analogues lacking the redox properties found in the natural models, so that we have developed a simple procedure for the synthesis of the benzo[*g*]pyridazino[1,2-*b*]phthalazine-6,13-dione system (**1**), by taking advantage of the dienophilic activity of benzo[*g*]phthalazine-1,4-dione.[4] This system can be considered very close to

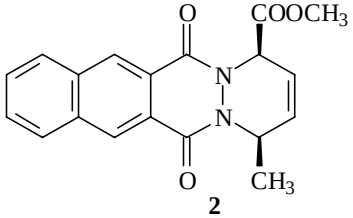
anthracycline chromophores, since it exhibits: a) an aromatic moiety with the planarity area required for intercalation, b) a terminal flexible ring able to assume a half chair or a twisted boat conformation related to those found in natural anthracyclines, and on the other hand it presents a smaller redox potential owing to the modifications at ring B.[5]

Since only simple dienes can be used in this procedure, further functionalization of the ring A is required in order to assure a proper interaction with DNA bases and provides an adequate group for anchoring the aminosugar. In preceding papers[6] we have reported on the preparation of a series of mono- and dimethyl substituted diazatetracyclic adducts of the type (**1**), and the steric course of electrophilic additions to C2-C3 double bond has been studied in depth.

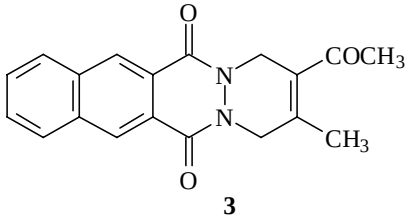
Now, we deal here with the synthesis of new adducts containing the 1-methoxycarbonyl (**2**) or 2-acetyl (**3**) functionalizations typical, respectively, of feudomicinone B and daunomicinone series, and also on their transformations with the aim of introducing adequate electronegative substituents in strategic positions of the ring A.



1



2

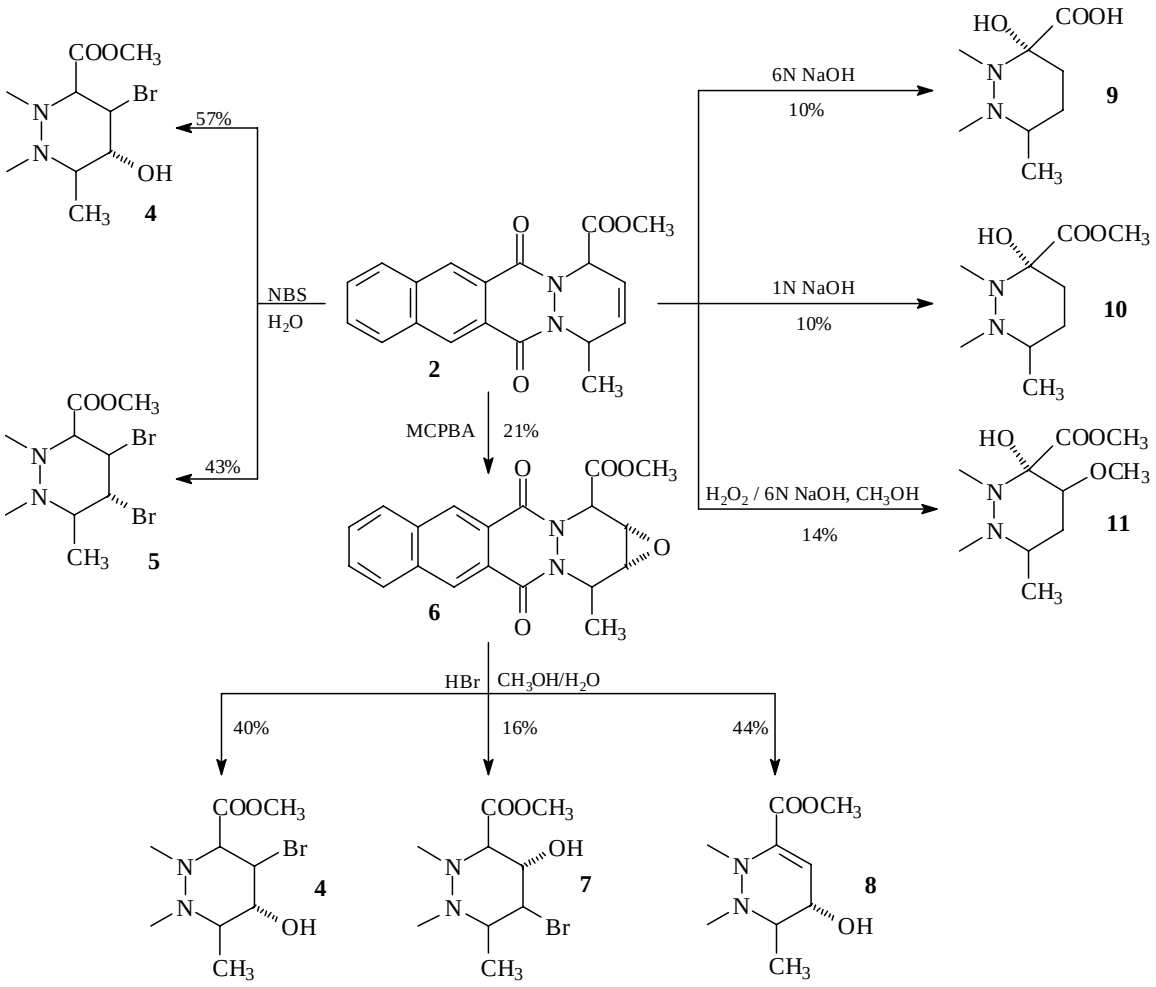


3

Compounds (**2**), (1*R**,4*R**)-1-methoxycarbonyl-4-methyl-1,4-dihydrobenzo[*g*]pyridazino[1,2-*b*]-phthalazine-6,13-dione[7] and (**3**), 2-acetyl-3-methyl-1,4-dihydrobenzo[*g*]pyridazino[1,2-*b*]phthal-azine-6,13-dione, have been prepared in high yields by the cycloaddition of benzo[*g*]phthalazine-1,4-dione with methyl *trans, trans*-2,4-hexadienoate and 4-methyl-3-methylene-4-penten-2-one,[8] respectively. The diazaquinone was formed *in situ* by low-temperature oxidation of benzo[*g*]phthalic hydrazide with lead tetraacetate according to the procedure previously established by us.[9]

The adduct (**2**) was functionalized with hydroxy substituents by reaction with *N*-bromosuccinimide in acidic aqueous medium, sodium hydroxide, or hydrobromic acid *via* the corresponding epoxide. Thus, the reaction with *N*-bromosuccinimide/water/H^+ afforded the (1*S**,2*R**,3*R**,4*R**)-2-bromo-3-

hydroxy-1-methoxycarbonyl-4-methyl (**4**) and (1*S**,2*R**,3*R**,4*R**)-2,3-dibromo-1-methoxy-carbonyl-4-methyl (**5**) derivatives in 57:43 relative yields (Scheme 1). As could be expected on the basis of electronic considerations, the hydroxy group is attached to the carbon atom more distant from the ester.



Scheme 1

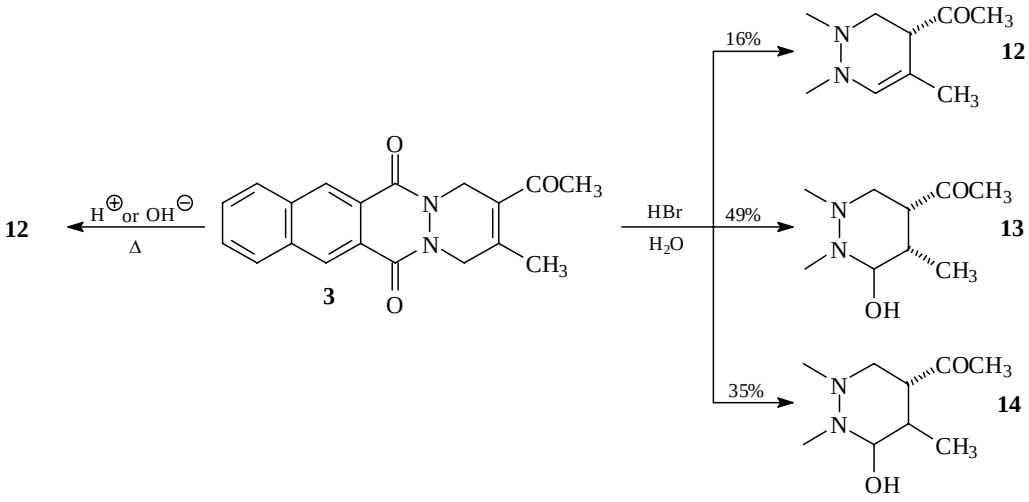
Oxidation of **2** with *m*-chloroperbenzoic acid yielded exclusively the sterically most favored *trans*-epoxide (**6**), which reacted with hydrobromic acid to give the isomeric bromohydrins, (1*R**,2*S**,3*S**,4*R**)-3-bromo-2-hydroxy-1-methoxycarbonyl-4-methyl and (1*S**,2*R**,3*R**,4*R**)-2-bromo-3-hydroxy-1-methoxycarbonyl-4-methyl derivatives (**7** and **4),** together with the dehydro-halogenated compound (**8**)**,** in 16:40:44 relative yields. Sterically favoured nucleophilic attack at C2 prevails in the opening of the epoxide (**6**).

With the aim of forming glycosides containing aminosugar moieties, the introduction of hydroxy groups at the C1 or C4 positions of ring A is essential. It could be achieved by the reaction of **2** with aqueous sodium hydroxide giving the (1*S**,4*R**)-1-carboxy-1-hydroxy-4-methyl and (1*S**,4*R**)-1-

hydroxy-1-methoxycarbonyl-4-methyl derivatives (**9** and **10**). The proton at C1 is acidic enough for allowing isomerization of the double bond and subsequent regioselective addition of water.

Eventually, treatment of **2** with sodium hydroxide/hydrogen peroxide in methanol afforded the (1*S**,2*S**,4*R**)-1-hydroxy-2-methoxy-1-methoxycarbonyl-4-methyl derivative (**11**) *via* isomerization, epoxidation, and regioselective addition of methanol.[10]

On the other hand, the daunomicinone related adduct (**3**) reacted with aqueous hydrobromic acid giving the double bond isomerization product (**12**) and the (2*R**,3*S**,4*R**)-2-acetyl-4-hydroxy-3-methyl[7] and (2*R**,3*R**,4*R**)-2-acetyl-4-hydroxy-3-methyl[7] derivatives (**13** and **14**) in 16:49:35 relative yields. The two hydroxy derivatives (**13**) and (**14**) were formed from **12** by regiospecific addition of water. (Scheme 2)



Scheme 2

Isomerization is favored in this case because the intermediate carbocation is stabilised by the methyl group.[11] In fact, the isomerization of **3** can be achieved by the treatments both in acidic or basic medium, so that the reactions with concentrated sulfuric acid or aqueous sodium hydroxide lead in good yields to the formation of the same product (**12**). The predominance of **13** over **14** could be due to the easier introduction of the hydroxy group by the opposite side to the methyl group.

The easy isomerization of **3** allows the OH functionalization at C4 and gives a way to the preparation of C4 substituted glycosides with potential biological activity. It should be noted that the substituents at C2 and C4 adopt a *trans* disposition, as it happens in the ring A of biologically active daunomicinone derivatives.[12]

In Table 1 are summarised the whole yields obtained for both the starting adducts and their derivatives, and also the mass and IR spectra, and elemental analysis data used for identification.

The molecular ion values measured in the mass spectra matched well with those corresponding to the proposed structures.

Table 1. Analytical, IR, and MS Spectral Data of Compounds (**2**, **3**) and Derivatives

Compd	Yield [a]	MS (m/e, %)	IR (KBr, cm^{-1})					Analytical Data		
			OH	*COR* [b]	*C=O*	*C=C*		*C %*	*H %*	*N %*
2	68	336 (47, M^+)	-	1750	1640	1620	Calcd	67.90	4.80	8.30
($C_{19}H_{16}N_2O_4$)							Found	67.42	5.18	7.96
3	77	320 (100, M^+)	-	1700	1640	1620	Calcd	71.25	5.00	8.75
($C_{19}H_{16}N_2O_3$)							Found	71.17	5.20	9.00
4	16	434 (47, MH^+)	3600	1740	1640	-	Calcd	52.65	3.92	6.46
($C_{19}H_{17}N_2O_5Br$)							Found	51.43	4.17	6.05
5	12	496 (4, M^+)	-	1750	1660	-	Calcd	45.96	3.22	5.64
($C_{19}H_{16}N_2O_4Br_2$)							Found	46.10	3.51	5.85
6	21	352 (72, M^+)	-	1750	1640	-	Calcd	64.77	4.54	7.95
($C_{19}H_{16}N_2O_5$)							Found	65.09	4.68	8.22
7	4	433 (47, M^+)	3600	1750	1640	-	Calcd	52.65	3.92	6.46
($C_{19}H_{17}N_2O_5Br$)							Found	52.59	4.03	6.55
8	11	352 (84, M^+)	3600	1735	1650	1620	Calcd	64.77	4.54	7.95
($C_{19}H_{16}N_2O_5$)							Found	64.33	4.58	7.48
9	10	292 (30, M^+-48)	3400	1720	1690	-	Calcd	63.52	4.74	8.23
($C_{18}H_{16}N_2O_5$)							Found	63.30	4.67	7.90
10	10	354 (4, M^+)	3500	1730	1690	-	Calcd	64.40	5.12	7.91
($C_{19}H_{18}N_2O_5$)							Found	64.30	5.45	7.77
11	14	384 (2, M^+)	3600	1730	1690	-	Calcd	62.49	5.24	7.29
($C_{20}H_{20}N_2O_6$)							Found	62.50	5.46	7.37
12	5	320 (27, M^+)	-	1700	1640	1620	Calcd	71.25	5.00	8.75
($C_{19}H_{16}N_2O_3$)							Found	71.36	4.98	8.95
13	14	338 (36, M^+)	3600	1700	1650	-	Calcd	67.44	5.36	8.24
($C_{19}H_{18}N_2O_4$)							Found [c]	67.28	4.97	8.14
14	10	338 (36, M^+)	3600	1700	1650	-	Calcd	67.44	5.36	8.24
($C_{19}H_{18}N_2O_4$)							Found [c]	67.28	4.97	8.14

a) Whole yields taking into account the very high percentage of unreacted adduct recovered.

b) R = CH_3 in **3**, **12**, **13**, **14**; R = OCH_3 in **2**, **4**, **5**, **6**, **7**, **8**, **10**, **11**; R = OH in **9**.

c) Found for a sample of the mixture of isomers (**13**) and (**14**).

Stereo- and regiochemical features in the ring A have been elucidated mainly on the basis of ^{1}H-NMR spectral data (Table 2). In contrast with the nitrogen inversion usually found in less

substituted analogues,[9] the three- and tetrasubstituted compounds isolated have been shown to be conformationally homogeneous.

The chemical shifts and coupling constants of ring A protons obtained from the ^{1}H NMR spectra have been used for assigning the position and orientation of the ring substituents. As in previous series, the nature of substituents can be accurately deduced from the chemical shifts of hydrogens[6] attached to the same carbon atoms. The J_{H1-H2} coupling constants show the stereochemical relationship between the C1 group and the C2 substituent and the high J_{He-Ha} values found are indicative of chair deformations due to steric hindrance. At last, the stereochemistry of the methyl group at C4 in derivatives of **2** is confirmed by the J_{Me-H4} values, which increase when the methyl group is axially oriented.[13]

Table 2. ^{1}H NMR Chemical Shifts (δ scale, $CDCl_3$) and Coupling Constants (Hz) for the Terminal Tetrahydropyridazine Ring of Compounds (**2**, **3**) and Derivatives.[7]

Compd	δ_{H1}	δ_{H2}	δ_{H3}	δ_{H4}	δ_{COR}	δ_{CH3}	J_{H1H2}	J_{H2H3}	J_{H3H4}	J_{HaHe}	J_{CH3H4}
2	5.45 (d)	6.30 (dd)	6.09 (dd)	5.61 (m)	3.85 (s)	1.52 (d)	4.2	9.2	3.9	-	6.6
3	4.83 (m)	-	-	4.63 (m)	2.43 (s)	2.20 (s)	-	-	-	-	-
4	5.25 (d)	4.58 (dd)	4.33 (dd)	5.55 (m)	3.90 (s)	1.60 (d)	6.3	10.4	5.4	-	6.4
5	5.30 (d)	4.72 (dd)	4.51 (dd)	5.71 (m)	3.95 (s)	1.62 (d)	6.4	11.9	5.2	-	6.6
6	5.84 (d)	3.54 (t)	3.93 (m)	5.73 (m)	3.90 (s)	1.54 (d)	2.2	3.5	2.4	-	6.8
7	5.60 (d)	4.78 (dd)	4.32 (dd)	5.34 (m)	3.80 (s)	1.53 (d)	3.9	10.1	4.6	-	7.0
8	-	6.27 (d)	4.35 (d)	5.50 (m)	3.90 (s)	1.29 (d)	-	6.2	0.9	-	7.1
9	-	2.26 (ddd) 2.55 (dd)	1.57 (m) 1.88 (dd)	4.85 (m)	-	1.18 (d)	-	11.9 5.9 3.3	2.0	19.7 13.1	6.3
10	-	2.36 (ddd) 2.80 (dd)	1.85 (m) 2.02 (dd)	5.12 (m)	3.83 (s)	1.35 (d)	-	12.7 7.8 4.1	3.9	19.5 13.7	6.8
11	-	4.69 (dd)	1.97 (ddd) 2.31 (ddd)	5.08 (m)	3.84 (s)	1.39 (d)	-	13.0 7.1	5.1 2.2	13.1	6.6
12	3.75 (dd) 5.40 (dd)	3.33 (m)	-	7.60 (s)	2.32 (s)	1.95 (s)	4.4 2.3	-	-	-	-
13	4.38 (dd) 4.49 (dd)	2.60 (m)	2.48 (m)	5.48 (s)	2.05 (s)	1.23 (d)	8.8	2.9	-	-	-
14	4.06 (dd) 4.22 (d)	2.83 (ddd)	2.22 (m)	5.59 (d)	2.10 (s)	1.30 (d)	6.1 3.2	11.0	4.4	-	-

a) TMS as internal standard

b) R = CH_3 in **3**, **12**, **13**, **14**; R = OCH_3 in **2**, **4**, **5**, **6**, **7**, **8**, **10**, **11**; R = OH in **9**

For more accurate confirmation of the stereochemical relationships proposed above, we have calculated the torsion angles between the protons at C2, C3, and C4 by means of the Altona relation-ship[14] from the experimental coupling constants. Results obtained (Table 3) are indicative of a distortion from the 'pure' chair form, and agree with theoretical calculations obtained by molecular modelling, so that they provide a solid support for the stereochemistry assigned to derivatives (**4**-**14**). These calculations were carried out using the AMBER[15] method implemented in Hyper Chem 6.0 package,[16] modified by the inclusion of appropriate parameters.[17] The equilibrium bond length and angle values came from experimental values on reasonable reference compounds. In all cases, full geometry optimizations with Polak-Ribiere algorithm were carried out with no restraints, and the dielectric constant was assumed to be distance independent of the organic solvent.[18]

Table 3 Torsion Angles (º) Calculated for the Tetrahydropyridazine Terminal Ring of Some Derivatives of **2** and **3**.

Compd	Φ_{H1-H2}		Φ_{H2-H3a}		Φ_{H2-H3e}		Φ_{H3-H4}	
	Altona	Amber	Altona	Amber	Altona	Amber	Altona	Amber
4	322.4	308.2	180.0*	182.2	-	-	225.6	211.1
5	323.7	301.9	180.0*	168.1	-	-	229.7	230.4
7	121.9	142.7	180.0*	183.6	-	-	46.0	60.2
9	-	-	208.1 278.1	177.9 296.1	46.5 305.5	56.1 297.9	287.5 86.9	297.0 57.0
10	-	-	204.3 301.6	177.1 296.1	43.1 305.1	56.1 297.9	54.9 273.1	58.5 298.3
11	-	-	180.0*	181.6	29.4	63.5	256.1 313.5	213.0 330.9
12	299.6 228.5	233.5 42.0	-	-	-	-	-	-
13	255.0 51.2	307.9 190.3	205.2	191.5	-	-	316.3	304.4
14	212.4 273.0	191.7 309.7	-	-	59.5	64.4	86.2	68.4

***J values out of limits in Altona equation.

EXPERIMENTAL

Mp are uncorrected, and were determined in open capillary tubes with a Gallenkamp apparatus. IR spectra were recorded in KBr pellets on a Perkin-Elmer 257 spectrophotometer. NMR spectra were obtained with a Varian XL-300 spectrophotometer for solutions in $CDCl_3$ or DMSO-d_6 with Me_4Si as internal reference. Assignments were made on the basis of decoupling experiments and comparison with the spectra of related structures. Direct inlet MS were measured on a Hitachi Perkin-Elmer RMV-GM6 spectrometer. All the chromatographic separations were carried out by using 20x20 cm preparative TLC plates coated with a 2 mm layer of silica gel $60PF_{254}$ Merck.

Benzo[*g*]phthalic hydrazide was obtained from α,α,α',α'-tetrabromo-*o*-xylene and maleic anhydride according to Cava *et al*.[19] Methyl *trans, trans*-2,4-hexadienoate was prepared by direct esterification of *trans, trans*-2,4-hexadienoic acid. 4-Methyl-3-methylene-4-penten-2-one was prepared by the reaction of mesityl oxide with paraformaldehyde in DBN according to the procedure described by Lantzsch.[8]

*Synthesis of the diazatetracyclic adducts (**2**) and (**3**)*

(1R,4R*)-1-methoxycarbonyl-4-methyl-1,4-dihydrobenzo[g]pyridazino[1,2-b]phtalazine-6,13-dione* (**2**):

Glacial acetic acid (2 mL) and methyl *trans, trans*-2,4-hexadienoate (1.76 g, 14 mmol) were slowly added to a stirred dichloromethane (200 mL) suspension of benzo[*g*]phthalic hydrazide (3.60 g, 17 mmol) cooled at 0 ºC. After that, small portions of lead tetraacetate (7.51 g, 17 mmol) were added during a period of 60 min. A vivid orange coloration due to formation of the diazaquinone was intermitently observed. The mixture was stirred for 24 h at rt. The white precipitate formed was filtered off, and the filtrate washed successively with 5% aqueous sodium bicarbonate and water. The organic layer was evaporated to dryness under reduced pressure. The residue was crystallized from ethanol to give a yellow solid identified as **2** (3.17 g, 68%), mp = 198-199 ºC.

2-Acetyl-3-methyl-1,2-dihydrobenzo[g]pyridazino[1,2-b]phthalazine-6,13-dione (**3**):

This compound was prepared as described for compound (**2**), from benzo[*g*]phthalic hydrazide (1.51 g, 7.1 mmol), 4-methyl-3-methylene-4-penten-2-one (0.61 g, 5.5 mmol) and lead tetraacetate (3.54 g, 8 mmol). After usual work up, the residue was crystallized from ethanol to give a yellow solid identified as **3** (1.35 g, 77%), mp = 216-218 ºC

*Reaction of **2** with aqueous NBS*

Equimolecular amounts of **2** (504 mg, 1.5 mmol) and *N*-bromosuccinimide (267 mg, 1.5 mmol) were suspended in 30 mL of water, two drops of H_2SO_4 were added, and the whole was stirred for 24 h at 50-60ºC. After addition of ice, the solid was filtered and submitted to preparative TLC on silica gel using chloroform as eluent, to give 105 mg (16 %) of (1*S**,2*R**,3*R**,4*R**)-2-bromo-3-hydroxy-1-methoxycarbonyl-4-methyl- (**4)** (R_f = 0.13, mp = 212-214º C); and 91 mg (12 %) of (1*S**,2*R**,3*R**,4*R**)-2,3-dibromo-1-methoxycarbonyl-4-methyl-1,2,3,4-tetrahydrobenzo[*g*]pyridazino[1,2-*b*]phthalazine-6,13-dione (**5**) (R_f = 0.48, mp = 78-80º C).

*Epoxidation of **2***

To a cooled (0º C) chloroform (20 mL) solution of **2** (504 mg, 1.5 mmol), 0.28 g (1.6 mmol) of *m*-chloroperbenzoic acid (85 %) were slowly added. The mixture was refluxed for 56 h, and stirring was maintained at rt during 12 h more. The solution was sucessively washed with 5% aqueous sodium bicarbonate and water. The organic layer was dryed over anhydrous magnesium sulfate and evaporated *in vacuo* to give a solid which was crystallized from ethanol affording 110 mg (21 %) of (1*R**,2*S**,3*R**,4*R**)-2,3-epoxi-1-methoxycarbonyl-4-methyl-1,2,3,4-tetrahydrobenzo[*g*]pyridazino-[1,2-*b*]phthalazine-6,13-dione (**6**) (mp = 194-196º C).

*Ring opening of **6** with HBr*

A solution of 1 g (2.8 mmol) of the epoxide (**6**) and 20 mL of 48% aqueous hydrobromic acid in 20 mL methanol was heated at 50ºC for 24 h. Stirring was maintained at rt for 24 h more. The mixture was filtered and the precipitate chromatographed on silica gel using chloroform as eluent to give 117 mg (16 %) of **4** (R_f = 0.13, mp = 212-214º C); 41 mg (4 %) of (1*R**,2*S**,3*S**,4*R**)-3-bromo-2-hydroxy-1-methoxycarbonyl-4-methyl-1,2,3,4-tetrahydrobenzo[*g*]pyridazino[1,2-*b*]phthalazine-6,13-dione (**7**) (R_f = 0.09), and 110 mg (11 %) of (3*S**,4*R**)-3-hydroxy-1-methoxycarbonyl-4-methyl-3,4-dihydrobenzo[*g*]pyridazino[1,2-*b*]phthalazine-6,13-dione (**8**) (R_f = 0.04, mp = 230-232º C).

*Hydroxilation of **2** in basic medium*

a) A suspension of **2** (200 mg, 0.60 mmol) in 0.13 mL (0.78 mmol) of aqueous 6N NaOH was stirred for 24 h. After addition of water the solution was neutralized with 20 % HCl and extracted with chloroform.The organic layer was dryed over anhydrous magnesium sulfate and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel by using chloroform/methanol

(85:15) as the eluent, affording 20 mg (10 %) of (1*S**,4*R**)-1-carboxy-1-hydroxy-4-methyl-1,2,3,4-tetrahydrobenzo[*g*]pyridazino[1,2-*b*] phthalazine-6,13-dione (**9**) (mp = 148-150º C).

b) A suspension of **2** (200 mg, 0.6 mmol) in 30 mL of methanol containing 0.10 mL (0.1 mmol) of aqueous 1N NaOH was stirred for 1 h. After the same work up than in part a), 17 mg (10 %) were obtained of (1*S**,4*R**)-1-hydroxy-1-methoxycarbonyl-4-methyl-1,2,3,4-tetrahydrobenzo[*g*] pyridazino[1,2-*b*]phthalazine-6,13-dione (**10**) (mp = 190-192º C).

c) To a suspension of **2** (504 mg, 1.5 mmol) in 30 mL of methanol containing 0.45 mL (0.04 mmol) of 30% H_2O_2 , 0.13 mL (0.78 mmol) of aqueous 6N NaOH were added, and the mixture was stirred for 48 h. After usual work up, the residue was chromatographed on silica gel using chloroform/methanol (95:5) as the eluent affording 78 mg (14 %) of (1*S**,2*S**,4*R**)-1-hydroxy-2-methoxy-1-methoxycarbonyl-4-methyl-1,2,3,4-tetrahydrobenzo[*g*]pyridazino[1,2-*b*]phthalazine-6,13-dione (**11**) (R_f = 0.69, mp = 146-148º C).

*Reaction of **3** with HBr*

A suspension of **3** (200 mg, 0.6 mmol) in 20 mL of 48% aqueous hydrobromic acid was stirred for 1 h at rt. The solution was extracted with chloroform and then treated with 5% aqueous sodium bicarbonate. The organic layer was dryed over anhydrous sodium sulfate and evaporated *in vacuo* to give a residue which was chromatographed on silica gel using chloroform as eluent to give 10 mg of 2-acetyl-3-methyl-1,2-dihydrobenzo[*g*]pyridazino[1,2-*b*]phthalazine-6,13-dione (**12**) (R_f = 0.76), 30 mg (14 %) of (2*R**,3*S**,4*R**)-2-acetyl-4-hydroxy-3-methyl-1,2,3,4-tetrahydrobenzo[*g*]pyridazino [1,2-*b*]phthalazine-6,13-dione[7] (**13**), and 22 mg (10 %) of (2*R**,3*R**,4*R**)-2-acetyl-4-hydroxy-3-methyl-1,2,3,4-tetrahydrobenzo[*g*]pyridazino[1,2-*b*] phthalazine-6,13-dione (**14**) (R_f = 0.28).

*Isomerization of **3***

a) *In acidic medium:* A solution of **3** (250 mg, 0.78 mmol) in sulfuric acid (d. 1.84 g/mL, 10 mL) was heated at 50ºC for 1 h, then the dark brown solution was poured onto ice-water and the mixture was filtered. The precipitate formed was chromatographed on silica gel with chloroform as eluent to give 200 mg of **12** (80% yield, mp = 184-186º C).

b) *In basic medium*: To a suspension of **3** (500 mg, 1.6 mmol) in 30 mL of methanol and 0.45 mL (0.04 mmol) of 30% H_2O_2, 0.13 mL (0.78 mmol) 6N NaOH were added and the mixture was stirred for 3 h. The organic layer was dryed over anhydrous magnesium sulfate and evaporated *in vacuo* to give a solid which was crystallised from ethanol to afford 120 mg (24 %) of **12**.

ACKNOWLEDGEMENTS

Support of this work by a grant from the D.G.I.C.Y.T. (Project SAF-0101) is gratefully acknowledged. We are also grateful to the contribution of the Centro de Resonancia Magnética Nuclear and the Centro de Microanálisis of the Univ. Complutense.

REFERENCES AND NOTES

1 a) T. R. Kelly, *Tetrahedron*, 1984, **40**, 4537; b) M. Braun, *ibid.*, **40**, 4585; c) M. J. Broadhurst, C. H. Hassall, and G. Thomas, *Chem. Ind. (London)*, 1985, 106; d) K. Krohn, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 790; e) K. Krohn, *Tetrahedron*, 1990, **46**, 291; f) F. Arcamore, P. Perego, S. Pilotti, G. Pratesi, R. Supino, and F. Zunino, *Pharmacol. Ther.*,1997, **76**, 117.

2 a) For instance: K. Krohn, K. Tolkien, V. Lehne, H. W. Schmalle, and H. F. Grützmacher, *Liebigs Ann. Chem.*, 1985, 1311; b) T. Antonsson and P. Vogel, *Tetrahedron Lett.*, 1990, **31**, 89; c) B. Deguin, J. C. Florent, and C. Monneret, *J. Org. Chem.*, 1991, **56**, 405.

3 J. W. Lown and S. M. Sondhi, *J. Org. Chem.*, 1985, **50**, 1413.

4 F. Gómez Contreras and M. Lora-Tamayo, *Heterocycles*, 1979, **13**, 389.

5 a) F. Arcamone, Doxorubicin Anticancer Antibiotics in Medicinal Chemistry, Academic Press, New York, Vol. **17**, 1981; b) R. Mondelli, E. Ragg, G. Fronza, and A. Arcamone, *J. Chem. Soc., Perkin Trans. II*, **1987**, 15; c) E. Ragg, R. Mondelli, and S. Penco, *J. Chem. Soc., Perkin Trans. II*, **1988**, 1673; d) J. W. Lown and H. H. Chen, *Can. J. Chem.*, 1981, **59**, 3212; e) V. Malatesta, S. Penco, N. Sacchi, L. Valentini, A. Vigevani, and F. Arcamone, *Can. J. Chem.*, 1984, **62**, 2845; f) F. Matsuda, M. Kawasaki, M. Ohraki, K. Yamada, and S. Terashima, *Chem. Lett*., 1988, 653.

6 a) M. C. Cano, F. Gómez-Contreras, A. M. Sanz, and M. J. R.Yunta, *Tetrahedron*, 1993, **49,** 243; b) M. C. Cano, F. Gómez-Contreras, and M. J. R. Yunta, *An. Quim.*, 1995, **91**, 124; c) M. C. Cano, F. Gómez-Contreras, A. M. Sanz, and M. J. R.Yunta, *Can. J. Chem.*, 1997, **75**, 348.

7 Addition products have been arbitrariously numbered in some cases in order to allow comparison with the starting compounds and make easier the discussions on stereochemical features. For the same reasons, the centres of chirality first cited in the naming of a particular compound are not always represented by the descriptor *R**.

8 R. Lantzsch and D. Arlt, *Liebigs Ann. Chem.*, 1976, 1757.

9 F. Gómez-Contreras and P. Navarro, *J. Heterocycl. Chem.*, 1979, **16**, 1035.

10 J. Gorzyuski Smith, *Synthesis*, 629, 1984.

11 M. C. Cano, F. Gómez-Contreras, and P. Navarro, *An. Quim., Ser. C*, 1980, **76**, 147.

12 M. C. Cano, F. Gómez-Contreras, and M. Lora-Tamayo, *J. Chem. Soc., Perkin Trans. I*, 1991, 273.

13 This fact is due to the antiperiplanar arrangement that may addopt the hydrogen atoms of an axial methyl group with respect to the neighbouring bridgehead nitrogen, which reduces the J value. That arrangement is not possible when the alkyl substituent is equatorially oriented because of steric hindrance with the neighbouring carbonyl group at ring B.

14 C. A. G. Hassnoot, F. A. A. M. de Leeuw, and C. Altona, *Tetrahedron*, 1980, **36**, 2783.

15 W. D. Cornell, P. Cieplak, C. I. Bayly, K. M. Jr. Merz, and D. M. Ferguson, *J. Am. Chem. Soc.*, 1995, **117**, 5179.

16 Hyperchem 6.0 (Hipercube Inc).

17 a) T. Fox, T. S. Scanlan, and P. A. Kollman, *J. Am. Chem. Soc.*, 1997, **119**, 11571; b) P. D. Grootenhuis and P. A. Kollman, *J. Am. Chem. Soc.*, 1989, **111**, 2152; c) G. Moyna, G. Hernandez, H. J. Williams, R. J. Nachman, and A. I. Scott, *J. Chem. Inf. Comput. Sci.*, 1997, **37**, 951; d) C. D. J. Boden and G. Patenden, *J. Computer-Aided Mol. Des.*, 1999, **13**, 153; e) http:/ www.amber.ucsf.edu/amber; f) A. J. Hopfinger and R. A. Pearlstein, *J. Comput. Chem.*, 1984, **5**, 486.

18 J. Wang and P. A. Kollman, *J. Am. Chem. Soc.*, 1998, **120**, 11106.

19 M. P. Cava, A. A. Deana, and K. J. Muth, *J. Am. Chem. Soc.*, 1959, **81**, 6458.