The Influence of $A^{1,3}$ Steric Interactions on the Conformational Features of Benzo[*g*]pyridazino[1,2-*b*]phthalazine-6,13-dione Derivatives

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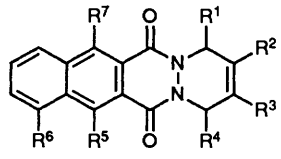
Diazatetracyclic compounds related to the anthracyclinone system have been synthesized *via* [4 + 2] cycloadditions of benzo[*g*]phthalazine-1,4-dione with the appropriate dienes. The geometry of the ring A moiety in methyl-substituted adducts **2a–g** has been studied by X-ray diffraction and NMR spectroscopic methods. The conformational properties of ring A are controlled by the carbonyl groups on ring B through $A^{1,3}$ steric interactions. Substitution at C-1 and/or C-4 freezes the conformational equilibrium to give terminal tetrahydropyridazine rings with the substituents axially oriented or exhibiting a boat-like geometry. Similar results have been found in the C-2–C-3 double-bond isomerization products **5a–d**, which are formed from the respective adducts only in the absence of substituents vicinal to the nitrogen atoms.

Benzo[*g*]pyridazino[1,2-*b*]phthalazine-6,13-dione derivatives **1** are structurally related to anthracycline aglycones of the daunomicinone type,[1] compounds known as highly active anticancer agents. They also contain the pharmacologically valuable pyridazinedione ring.[2]

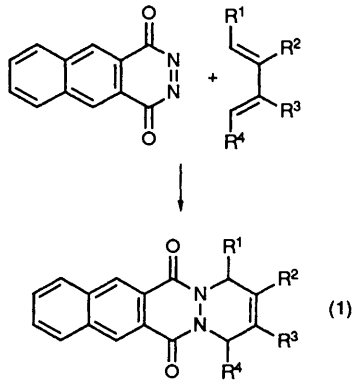


1

The diazatetracyclic backbone can be prepared *via* the [4 + 2] cycloaddition of benzo[*g*]phthalazine-1,4-dione with buta-1,3-diene derivatives.[3] A variety of dienes have been used in this reaction in order to prepare substrates substituted at diverse positions of the terminal tetrahydropyridazine ring for biological screening.[4] On the other hand, the geometry adopted by ring A in the anthracyclinone models decisively affects their pharmacological properties, because it provides proper interactions with DNA bases, performing the important anchoring function.[5] In compounds **1**, it is reasonable to expect the shape of ring A to be affected by the presence of the amidic carbonyl groups on ring B.[6] Therefore, a comparison of the shape of the tetrahydropyridazine ring in the series of mono- and di-methyl-substituted adducts **2a–g** is the main object of this study.

The reaction of benzo[*g*]phthalazine-1,4-dione (generated *in situ* by the oxidation of benzo[*g*]phthalic hydrazide with lead tetraacetate[3]) with 2-methylbuta-1,3-diene, penta-1,3-diene, 3-methylpenta-1,3-diene, (*E*)-2-methylpenta-1,3-diene, 2-ethylbuta-1,3-diene, 2,3-dimethylbuta-1,3-diene and (*E,E*)-hexa-2,4-diene leads to the cycloaddition products **2a–g** in yields ranging from 45 to 75%.

The most significative X-ray diffraction data for 1-methyl- **2b**, 1,3-dimethyl-**2d**, 2,3-dimethyl- **2f**, and *cis*-1,4-dimethyl- **2g** substituted adducts are shown in Table 1.[7] Predominant sp^2 character is found for the bridgehead nitrogen atoms. However, distortion parameters indicate important deformations from sp^2 hybridization,[8] especially when compared with those of the carbonyl carbons [X(N) 24.2° and 25.5°, X(C) 0.9° and 0.0° in **2f**; X(N) 27.8° and 30.6°, X(C) −5.7° and −0.6° in **2b**]. In fact,



(1)

2

a; $R^1 = R^3 = R^4 = H$, $R^2 = Me$
b; $R^1 = Me$, $R^2 = R^3 = R^4 = H$
c; $R^1 = R^2 = Me$, $R^3 = R^4 = H$
d; $R^1 = R^3 = Me$, $R^2 = R^4 = H$
e; $R^1 = R^3 = R^4 = H$, $R^2 = Et$
f; $R^1 = R^4 = H$, $R^2 = R^3 = Me$
g; $R^1 = R^4 = Me$, $R^2 = R^3 = H$

Shuterland and co-workers have shown that considerable deformation towards a pyramidal configuration is permissible for the amidic nitrogens of diacyltetrahydropyridazines with little increase in strain energy.[9]

The geometry of ring A is strongly affected by the site of substitution. The lack of substituents vicinal to nitrogen allows a typical C-2–C-3 half-chair conformation in compound **2f**, favoured by the possibility of deformation from the trigonal stereochemistry of the nitrogen atoms. In the C-1-substituted adducts **2b** and **2d** the methyl group adopts a quasi-axial orientation in order to minimize its steric interaction with the neighbouring carbonyl group. This leads to a distorted half-chair wherein the C-1 methyl moves away from ring B. It can be seen that the dihedral angle between the planes N-14–C-2–C-1 and N-1–C-2 and the centroid of C-2–C-3–N-5–N-14 is a mere 23° for **2b**. A higher distortion from pure half-chair is found in compound **2d**, which exhibits a flattening of the ring in the neighbourhood of C-4. This is probably a way to minimize the steric interactions of the two C-4 hydrogens with the C-3 methyl group and the neighbouring carbonyl group (see Fig. 1).

Unexpectedly, the *cis*-1,4-dimethyl-substituted adduct **2g** displays, for ring A, a slightly flattened boat conformation in

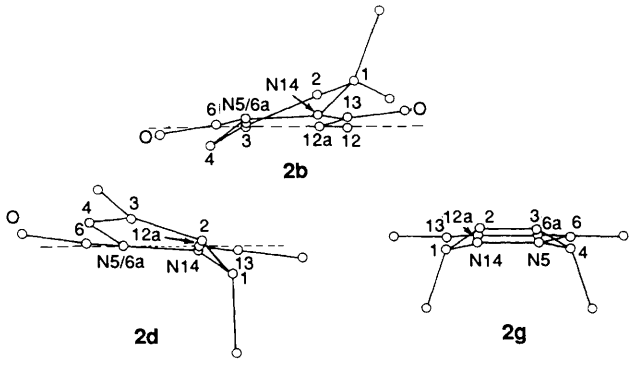
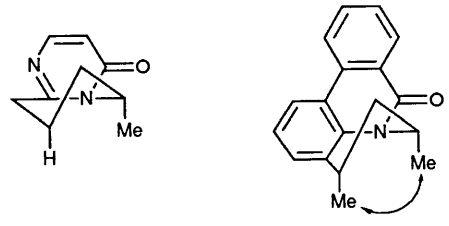


Fig. 1 Frontal view of ring A along the overall molecular plane for compounds **2b**, **2d** and **2g**

C-2–C-3 and C-5–N-14 [N-14–C-1–C-2–C-3, −25.7°; C-2–C-1–N-14–N-5, 25.0°], with the methyl groups *peri*-orientated. This is indicative of the decisive role played by the $A^{1,3}$ strain (methyl/carbonyl) in defining the shape of ring A. The boat conformation is achieved in spite of the unfavourable steric hindrance originating between the C-1 and C-4 substituents.

Similar features have been found in pyrido[1,2-*a*]pyrimidine systems **3**, which also exhibit the C-6 Me group anchored in an axial orientation.[10] Furthermore, Nagarajan *et al.* have reported that the two methyl groups present in the pyrido[3,2,1-*de*]phenanthridin-8-one **4** are axially orientated, so that the *syn*-1,3-methyl/methyl hindrance is not a decisive factor in determining ring conformation.[11] The $A^{1,3}$ equatorial methyl/carbonyl strain has been evaluated as 7.7 kcal mol^{-1}.[11,*]



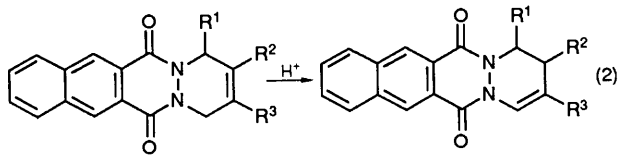
3 **4**

^{1}H NMR data (Table 2) are also indicative of a different behaviour in solution depending on the presence or absence of substituents vicinal to nitrogen in compounds **2**. The ^{1}H NMR spectra of compounds **2a**, **2e** and **2f** show equivalent signals for the methylene protons both at C-1 and at C-4. This fact suggests a rapid conformational motion for ring A that should take place *via* nitrogen inversion,[4] as has been shown to occur in polycyclic tetrahydropyridazines with energy barriers too high for ring inversion.[12]

On the other hand, substitution at C-1 in compounds **2b**, **2c** and **2d** results in a stable, fixed conformation for ring A, as can be inferred from the large chemical shifts found for the protons on C-4, the characteristic values found for J_{gem} (14.0, 16.0 and 17.5 Hz), and the appearance of allylic and homoallylic couplings for only one of the two methylenic hydrogens involved. The quasi-equatorial position of 1-H is shown by its downfield shift (δ 5.4–5.5), due to the anisotropic effect of the adjacent carbonyl group,[13] and by the fact that $J_{1\text{-H,4e-H}} > J_{1\text{-H,4a-H}}$ in accordance with the arguments proposed by Cameron *et al.* for related compounds.[14] Anchoring of the C-1 substituent into the quasi-axial position is a consequence of the allylic strain arising between the Me and C=O groups, which freezes the equilibrium and makes the ring conformationally stable.

In the ^{1}H NMR spectrum of the *cis*-1,4-dimethyl-substituted adduct **2g**, both methyls are shifted downfield with respect to the C-4-unsubstituted compounds (Δδ 0.2–0.3 ppm), and the same effect is noted in the ^{13}C spectrum (Δδ 3–4 ppm), whereas the methinic protons are also consistently unshielded. These data are in agreement with the boat-like geometry found in the solid state for adduct **2g**.

In a previous paper[15] we reported that heating of adducts **2a** and **2f** with conc. sulphuric acid affords the C-2–C-3 double-bond isomerization products **5a** and **5b** in nearly quantitative yields [equation (2)]. Isomerization gives rise to an area of planarity C-3–C-4–N–C=O in the ring A moiety, and intermediate conformations between half-chair and 1,2-diplanar are formed for **5a** and **5b**. The C-2 Me group is quasi-axial in compound **5b**.[15] We have now tried this reaction for compounds **2b–e** and **2g**, and it has been found that isomerization takes place only in the 2-ethyl and 1,3-dimethyl-substituted adducts to give, respectively, compounds **5c** and **5d**.

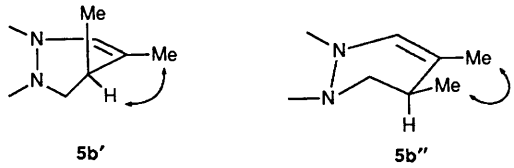


(2)

2 **5**

a; $R^1 = R^2 = H$, $R^3 = Me$
b; $R^1 = H$, $R^2 = R^3 = Me$
c; $R^1 = R^2 = H$, $R^3 = Et$
d; $R^1 = R^3 = Me$, $R^2 = H$

From the ^{1}H NMR data (Table 2) it can be deduced that ring A of the C-2-substituted isomerization products reproduces, at room temperature, the fast interconversion found in the corresponding adducts. However, the presence of a second methyl freezes the conformational equilibrium. The C-1 substituent is axially orientated in **5d** ($J(H^1,H^{2a})$ 6.2 Hz, $J(H',H^{2e})$ 1.8 Hz) as expected on the basis of the steric interaction with the C=O group arising from a coplanar equatorial orientation. With respect to the C-2 Me group of **5b**, it is well known that $A^{1,2}$ interactions favour the conformer with the C-6 substituent axially orientated in 1,6-disubstituted cyclohexenes.[16] In our case, **5b′** is favoured over conformer **5b″**, in which the Me–C-2–C-3–Me angle should be less than 60°. Furthermore, conformer **5b′** does not present any destabilizing *syn*-1,3-diaxial interactions.

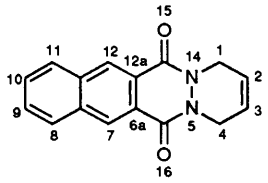


5b′ **5b″**

Attempts to isomerize compounds **2b**, **2c** and **2g** were unsuccessful, and the starting adducts were recovered unchanged. The use of more forcing reactions conditions afforded only ring A-opened products. It has been pointed out for related diazapolycyclic compounds that isomerization occurs when an intermediate tertiary carbon can be formed,[17] but this reasoning does not account for the lack of reactivity shown by compound **2c**. From arguments expounded above, we think now that steric factors must be determinant, since isomerization of adduct **2b**, **2c**, or **2g** should lead to a sterically

* 1 cal = 4.184 J.

Table 1 X-Ray diffraction data: geometrical parameters with standard deviations for A and B rings in the cycloaddition products



Torsion angles (°)	Compound 2b	2d	2f	2g
C-1–C-2–C-3–C-4	1.4(5)	0.2(4)	1.4(4)	0.0(3)
C-2–C-3–C-4–N-5	11.5(4)	−5.8(3)	11.5(4)	25.7(4)
C-3–C-4–N-5–N-14	−39.4(3)	−14.4(3)	−31.5(3)	−25.0(3)
C-4–N-5–N-14–C-1	56.1(3)	39.8(2)	38.8(3)	0.0(3)
N-5–N-14–C-1–C-2	−40.4(3)	−42.9(2)	−24.9(3)	25.0(3)
N-14–C-1–C-2–C-3	12.1(4)	23.5(3)	4.7(4)	−25.7(4)
N-5–N-14–C-13–C-12a	−0.9(4)	3.3(3)	8.1(3)	4.3(4)
N-14–C-13–C-12a–C-6a	−1.9(4)	−5.8(3)	−1.6(4)	−4.1(4)
C-4–N-5–C-6–O-16	−24.2(4)		−17.6(3)	−23.3(3)
C-1–N-14–C-13–O-15	−23.0(4)		−17.1(3)	23.3(4)
Bond angles (°)				
C-1–N-14–N-5	115.0(2)	116.5(2)	117.6(2)	120.1(2)
C-1–N-14–C-13	117.0(2)	118.0(2)	115.3(2)	117.3(2)
C-13–N-14–N-5	122.4(2)	122.4(2)	122.7(2)	122.6(2)
C-4–N-5–C-6	116.0(2)	116.0(2)	115.9(2)	117.2(2)

Table 2 ^{1}H NMR data for the terminal tetrahydropyridazine ring in adducts and isomerization products

Compound	δ_{H^1}	δ_{R^1}	δ_{R^2}	δ_{R^3}	$\delta_{R^4}/\delta_{H^2}$	δ_{H^4}
2a	4.50 (br s)		1.95 (br s)	5.80 (m)	4160 (m)	
2b	1.35 (d)	5.49 (m)	6.09 (m)	6.09 (m)	4.30 (dm)	5.08 (dm)
2c	1.35 (d)	5.40 (m)	1.85 (dd)	5.65 (m)	4.40 (m)	4.84 (m)
2d	1.25 (d)	5.50 (m)	5.72 (m)	1.82 (br s)	4.15 (d)	4.89 (d)
2e	4.49 (br s)		1.22 (t)	6.11 (m)	4.49 (br s)	
			1.90 (q)			
2f	4.55 (s)		1.85 (s)		4.55 (s)	
2g	1.57 (d)	5.40 (dq)	6.05 (dd)		1.57 (d)	5.40 (o)
5a	4.45 (t)		2.40 (tm)	1.95 (dd)	2.40 (tm)	7.55 (m)
5b	4.50 (dd)	4.10 (dd)	1.20 (d)	1.90 (d)	2.55 (m)	7.48 (o)
5c	4.40 (t)		2.43 (t)	1.15 (t), 2.24 (q)	2.43 (t)	7.46 (s)
5d	1.32 (d)	5.63 (m)	2.75 (dm)	1.93 (t)	2.03 (dd)	7.50 (o)

Compound	$J(H^2,R^2)$/ $J(H^1,R^3)$	$J(H^1,R^1)$	$J(H^2,H^4)$/ $J(H^4,R^4)$	$J(R^3,H^4)$	$J(H^2,R^2)$/ $J(R^3,R^4)$	Other
2b	0.6	6.0	16.0	2.5	2.5	$J(H^1,R^4)$ 1.8
2c	1.3	6.2	14.0	1.8	2.0	$J(H^2,R^4)$ 1.4
2d	0.9	6.7	17.5			$J(H^1,R^2)$ 4.2
2g	3.2	6.5	6.5	3.2		
5a	5.7		1.5	1.6		$J(H^2,R^3)$ 1.2
5b	4.2	13.5	1.3	1.2	7.1	$J(R^1,R^2)$ 4.5
						$J(H^2,R^3)$ 1.1
5c	5.8					J(Et) 7.5
5d	1.8	7.5	1.4	0.8	14.8	$J(H^1,H^2)$

disfavoured situation of coplanarity between the C-1 substituent and the neighbouring carbonyl group.

Experimental

M.p.s 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 Varian FT-80, Brücker WP80 and Varian XL-300 spectrophotometers for solutions in $CDCl_3$ with Me_4Si as internal reference. Assignments were made by appropriate decoupling experiments and comparison of the spectra of related structures. Direct-inlet mass spectrum was measured on a Hitachi Perkin-Elmer RMV-GM6 spectrometer. X-Ray diffraction studies were carried out in the X-ray Department of the Instituto de Química-Física Rocasolano of the CSIC, Madrid. The structures were obtained on a four-circle Philips PW1100 diffractometer by using the TRADIR program, and crystallographic results are being published in full elsewhere by Drs. F. H. Cano and C. Foces-Foces. Co-ordinates are available on request from Dr. C. Foces-Foces, Departamento de Rayos X, Instituto de Química-Física Rocasolano, CSIC, Madrid, Spain. Microanalyses were performed on a Perkin-Elmer 240 microanalyser. Chromatographic separations were carried out by using 20 × 20 cm preparative TLC plates coated with a 2 mm layer of silica gel $60PF_{254}$ Merck. Yields are given

in mg of isolated product showing one spot on an analytical chromatoplate and no trace of impurities detectable in the NMR spectrum.

All the dienes used in the cycloaddition reactions were commercial, except 3-methylpenta-1,3-diene and 2-ethylbuta-1,3-diene, which were respectively obtained as the main and the secondary products in the dehydration of 3-methylpentane-2,4-diol with hydrobromic acid in the presence of aniline hydrobromide.[18]

Adducts **2a**, **2b** and **2f** were prepared *via* cycloaddition of benzo[*g*]phthalazine-1,4-dione with the required diene, and isomerization products **5a** and **5b** by the respective heating of compounds **2a** and **2f** with conc. sulphuric acid, all according to procedures previously described.[1,15,19,20] Benzo[*g*]phthalic hydrazide was obtained from 2,3-dimethylnaphthalene following the procedure of Drew and Garwood.[21]

1,2-*Dimethyl*-1,4-*dihydrobenzo*[g]*pyridazino*[1,2-b]*phthalazine*-6,13-*dione* **2c** *and* 2-*Ethyl*-1,4-*dihydrobenzo*[g]*pyridazino*[1,2-b]*phthalazine*-6,13-*dione* **2e**.—To a stirred, cooled (−10 °C) dichloromethane suspension of benzo[*g*]phthalic hydrazide (2.3 g, 0.01 mol; in 60 cm^3) were added glacial acetic acid (2 cm^3) and 3-methylpenta-1,3-diene (0.8 g, 0.011 mol) containing 15% 2-ethylbuta-1,3-diene. Lead tetraacetate (6.0 g, 0.013 mol) was added during 60 min. A vivid orange colouration due to formation of the diazaquinone was intermittently observed. The mixture was stirred for 24 h. The white precipitate formed was filtered off, and the filtrate was washed successively with 5% aq. sodium hydrogen carbonate and water, and dried over magnesium sulphate. Solvent was removed by rotary evaporation and the residue was chromatographed (TLC) on silica gel with toluene–ethyl acetate (9:1) as developer. The more polar fraction (R_f 0.2) was crystallized from ethanol to give a yellow solid identified as *compound* **2c** (1.8 g, 57%), m.p. 143–145 °C (Found: C, 73.7; H, 5.3; N, 9.6. $C_{18}H_{16}N_2O_2$ requires C, 73.97; H, 5.48; N, 9.58%); ν_{max}(KBr)/cm^{-1} 1645 (C=O), 1620 (C=C), 1460, 1405, 1345, 1240, 1205 and 745; δ_C(300 MHz; $CDCl_3$) 17.23 (1-Me), 20.13 (2-Me), 45.29 (C-4), 53.48 (C-1), 114.82 (C-3), 124.51 (C-6a, -12a), 128.87 (C-7), 128.99 (C(12), 129.34 (C-8, -9, -10, -11), 134.46 (C-2), 134.98 (C-7a, -11a), 158.09 (C-6) and 159.21 (C-13).

From the less polar fraction (R_f 0.6) was obtained a compound (0.2 g) which was identified as *compound* **2e** (48%) (Found: C, 73.8; H, 5.25; N, 9.4%); ν_{max}(KBr)/cm^{-1} 3060 (C=C), 1650 (C=O), 1630 (C=C), 1455, 1380, 1215 and 765.

1,3-*Dimethyl*-1,4-*dihydrobenzo*[g]*pyridazino*[1,2-b]-*phthalazine*-6,13-*dione* **2d**.—This compound was prepared as described for compound **2c**, from benzo[*g*]phthalic hydrazide (7.6 g, 0.035 mol), (*E*)-2-methylpenta-1,3-diene (2.9 g, 0.035 mol) and lead tetraacetate (20.0 g, 0.044 mol). After usual work-up, the residue was crystallized from ethanol to give a yellow solid identified as compound **2d** (5.55 g, 57%), m.p. 182–186 °C (Found: C, 74.1; H, 5.7; N, 9.8%); ν_{max}(KBr)/cm^{-1} 3060 (C=C), 1645 (C=O), 1625 (C=C), 1460, 1405, 1345, 1240 and 760; δ_C(300 MHz; $CDCl_3$) 18.94 (1-Me), 19.93 (3-Me), 48.62 (C-1), 50.55 (C-4), 121.34 (C-2), 124.61 (C-6a, -12a), 125.04 (C-3), 127.58 (C-7), 127.77 (C-12), 129.01 (C-8), 129.25 (C-9), 129.45 (C-10), 130.45 (C-11), 135.09 (C-7a, -11a), 158.52 (C-6) and 159.77 (C-13).

cis-1,4-*Dimethyl*-1,4-*dihydrobenzo*[g]*pyridazino*[1,2-b]-*phthalazine*-6,13-*dione* **2g**.—This compound was prepared as described for compound **2c**, from benzo[*g*]phthalic hydrazide (6.7 g, 0.03 mol), (*E,E*)-hexa-2,4-diene (4.2 g, 0.05 mol), and lead tetraacetate (5.7 g, 0.085 mol). After usual work-up, the residue was crystallized from ethanol to give a yellow solid identified as compound **2g** (5.5 g, 60%), m.p. 199–201 °C (Found: C, 73.9; H, 5.7; N, 9.7%); ν_{max}(KBr)/cm^{-1} 1645 (C=O), 1625 (C=C), 1475, 1410, 1380, 1340, 1245, 1130, 920 and 750; δ_C(300 MHz; $CDCl_3$) 21.17 (1- and 4-Me), 50.12 (C-1, -4), 124.25 (C-2, -3), 126.09 (C-6a, -12a), 128.32 (C-7, -12), 128.41 (C-9, -10), 128.89 (C-8, -11), 134.43 (C-7a, -11a) and 156.41 (C-6, -13).

3-*Ethyl*-1,2-*dihydrobenzo*[g]*pyridazino*[1,2-b]*phthalazine*-6,13-*dione* **5c**).—A solution of the crude mixture obtained from the reaction of benzo[*g*]phthalazine-1,4-dione with 3-methylpenta-1,3-diene (1.0 g, 0.003 mol) in sulphuric acid (*d* 1.84 g/cm^{-3}) (10 cm^3) was heated at 50 °C for 9 h, then the dark brown solution was poured onto ice–water (100 cm^3) and the mixture was filtered. The precipitate was chromatographed (TLC) on silica gel with toluene–ethanol (95:5) as developer. Two fractions were isolated; the more polar (R_f 0.40) was compound **2c**, whereas from the less polar (R_f 0.25) was isolated a solid identified as *compound* **5c** (80 mg, 23%), m.p. 140–142 °C (Found: C, 74.0; H, 5.3; N, 9.4%; ν_{max}(KBr)/cm^{-1} 1655 (C=O), 1625 (C=C), 1415, 1305, 1215, 1190 and 765; δ_C(300 MHz; $CDCl_3$) 25.36 (Me), 27.76 (3-CH_2), 40.82 (C-1, -2), 115.99 (C-4), 124.29 (C-6a, -12a), 124.49 (C-3), 128.97 (C-7, -12), 129.40 (C-8, -9, -10, -11), 134.87 (C-7a, -11a), 154.35 (C-6) and 156.89 (C-13); *m/z* 292 (M^+, 82%), 210 (29), 180 (17), 154 (15) and 126 (100).

1,3-*Dimethyl*1,2-*dihydrobenzo*[g]*pyridazino*[1,2-b]-*phthalazine*-6,13-*dione* **5d**.—This compound was prepared as described for compound **5c**, from compound (1.0 g, 0.003 mol) and sulphuric acid (10 cm^3). After the mixture had been heated for 24 h, usual work-up afforded a yellow solid identified as compound **5d** (0.7 g, 70%), m.p. 154–156 °C (Found: C, 73.6; H, 5.4; N, 9.5%); ν_{max}(KBr)/cm^{-1} 1655 (C=O), 1625 (C=C), 1460, 1415, 1365, 1250, 1215, 915 and 755; δ_C(300 MHz; $CDCl_3$) 17.95 (1-Me), 20.74 (3-Me), 32.80 (C-2), 45.84 (C-1), 115.38 (C-4), 115.81 (C-3), 124.60 (C-6a, -12a), 128.97 (C-7, -12), 129.37 (C-8, -9, -10, -11), 134.91 (C-7a, -11a), 150.02 (C-13) and 154.90 (C-6).

Attempted Isomerization of Compounds **2b** *and* **2g**.—A solution of compound **2b** or **2g** (1.0 g, 0.003 mol) in conc. sulphuric acid (*d* 1.84 g/cm^{-3}) (10 cm^3) was heated at 50 °C for 24 h and poured onto ice–water (100 g). The brown precipitate was isolated and identified as a mixture of unchanged adduct and a small amount of benzo[*g*]phthalic hydrazide.

Acknowledgements

Support of this work by a grant from the Comisión Asesora de Investigación Científica y Técnica de la Presidencia del Gobierno of Spain (Project PB86-0570) is gratefully acknowledged. The authors also thank Drs. F. Cano and C. Foces-Foces for determining and solving the crystal structure.

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Paper 0/03546G
Received 2nd *August* 1990
Accepted 10th *September* 1990