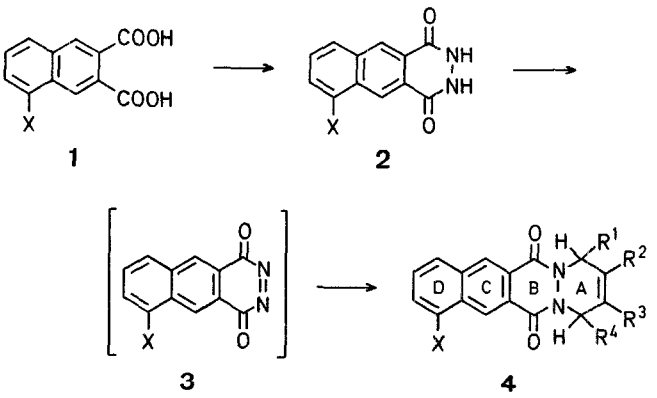
Diazapolycyclic Compounds; XXV. Improved Synthesis of 6-Substituted 2,3-Dihydrobenzo[*g*]phthalazine-1,4-dione Derivatives

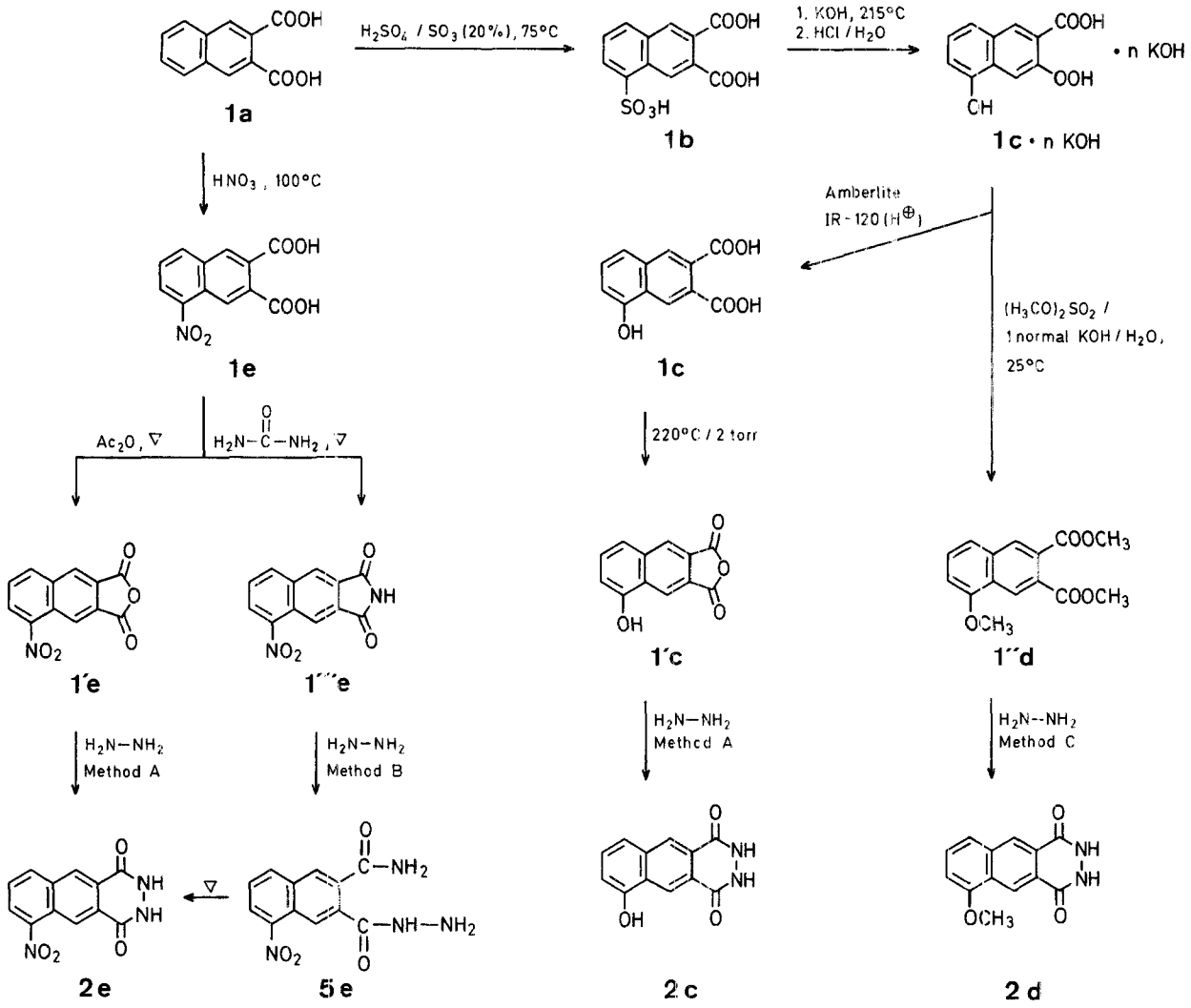
L. Campayo, B. Jimenez, T. Manzano, P. Navarro*

Instituto des Química Médica, C.S.I.C. Juan de la Cierva 3, Madrid 28006, Spain

In order to evaluate the biological activity of the polycyclic 4a, 12a-diaza compounds **4** (X = H) we have already prepared a wide variety of derivatives obtained from 2,3-dihydrobenzo[*g*]phthalazine-1,4-dione **2** (X = H)[1-4]. In search for compounds possessing cytostatic activity[5], the introduction of substituents into the aromatic moiety of **2** has been attempted[6]. We now report the synthesis of new derivatives of **4** substituted at C-8 in the terminal aromatic ring D (X = NO_2, NH_2, OCH_3) obtained from **2** (X = NO_2, OCH_3). We have previously carried out a study on the synthesis of 6-nitro and 6-hydroxy derivatives of **2** using naphthalene-2,3-dicarboxylic acid as starting material[7] (Scheme **A**).



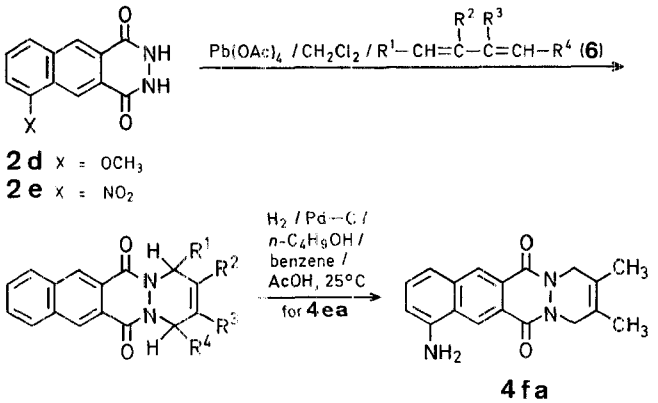
Scheme **A**



Scheme **B**

The 6-nitro hydrazide **2e** (X = NO_2) has previously been obtained in fair yield using either acetic acid[8] or ethanol[1] as the solvent. We have now found that with diethylene glycol solvent it is possible to improve the yield from 20% up to 90%. Thus, the reactions of anhydride **1'e** (prepared according to Scheme **B**) with an equivalent amount of hydrazine hydrate (1 h, reflux) in solvents of increasing boiling points (ethanol, butanol, diethylene glycol) afforded **2e** in 20, 33, and 90% yields, respectively. In a different approach to product **2e**, imide **1'''e** (prepared according to Scheme **B**) is converted into ring-cleavage product **5e** by reaction with hydrazine and product **5e** is cyclized by heating in diethylene glycol to afford **2e** in 70% yield. From these results it can be concluded that a sufficiently high temperature facilitates the ring closure reactions leading to compounds **2**.

6-Amino derivatives of **2** (X = NH_2, NH–Ac) have previously been reported. The low yields obtained in the synthesis of these compounds and their forseeable behavior in the oxidation step[9] **2** → **3** led us to discard them as starting materials for the synthesis of 8-amino-2,3-dimethyl-6,13-dioxo - 1,4,6,13 - tetrahydrobenzo[*g*]pyridazino[1,2 - *b*]phthalazine (**4fa**). Instead, we prepared compound **4fa** by catalytic hydrogenation of the corresponding 8-nitro compound **4ea** (Scheme **C**) using palladium-on-carbon in a mixture of butanol, benzene, and acetic acid as solvent.



4	X	R^1	R^2	R^3	R^4
da	OCH_3	H	CH_3	CH_3	H
db	OCH_3	C_6H_5	H	H	C_6H_5
ea	NO_2	H	CH_3	CH_3	H
ec	NO_2	H	CH_3	H	H
ed	NO_2	H	H	CH_3	H

Scheme **C**

Naphthalene-2,3-dicarboxylic acid (**1a**) and the nitro compounds **1e**, **1'e**, and **1'''e** were prepared according to Ref.[7,8]. The sulfo derivative **1b** and the hydroxy derivative **1c** were prepared according to Ref.[10]; however, the product obtained

Table 1. Naphthalene-2,3-dicarboxylic Acid Derivatives **1**, **1'**, **1''**, and **1'''** prepared

Product	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a]	I.R.[b] ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6/TMS$_{int}$)[c] δ [ppm]
1b	80	183–184°	$C_{12}H_8O_7S \cdot 3H_2O$ (350.3)	(KBr) 3650–2800 (OH); 1720 (CO); 1210, 1035, 705 (SO)	9.38 (s, 1H); 8.50 (s, 1H); 8.45–8.15 (m, 2H); 8.00–7.62 (m, 1H); 8.45 (bs, 6H)[d]; 8.40–7.55 (bm, 3H)[d]
1c	77	284–286°	$C_{12}H_8O_5$ (232.2)	(KBr) 3460, 3250–2500 (OH); 1675 (CO); 1290 (C—O); 1105, 930	8.71 (s, 1H); 8.33 (s, 1H); 7.80–7.60 (m, 2H); 7.40–7.00 (m, 1H); 10.75 (br. s, 1H)[d]; 7.90–6.90 (br. m, 2H)[d]
1'c	56		$C_{12}H_6O_4 \cdot 0.5H_2O$ (223.2)	(KBr) 3400 (OH); 1830, 1740 (CO); 1290, 1270 (C—O); 1135, 910	8.72 (s, 1H); 8.64 (s, 1H); 7.77–7.57 (m, 2H); 7.28–7.10 (m, 1H); 11.15 (s, 1H)[d]
1''d	75	85–87°	$C_{15}H_{14}O_5 \cdot 0.5H_2O$ (283.3)[f]	(KBr) 2940, 2870 (OCH_3); 1720 (CO); 1290–1270 (C—O—C); 1035	[e]8.84 (s, 1H); 8.30 (s, 1H); 7.70–7.55 (m, 2H); 7.15–6.90 (m, 1H); 4.05 (s, 3H); 4.01 (s, 6H)
1e	90	238° (AcOH)	$C_{12}H_7NO_6$ (261.2)	(Nujol) 3300–2200 (OH); 1690 (CO); 1525 (NO_2); 910	8.93 (s, 1H); 8.73 (s, 1H); 8.85–8.55 (m, 2H); 8.01 (m, 1H); 8.60–7.50 (br. m, 2H)[d]
1'e	87	206–208° (toluene)	$C_{12}H_5NO_5$ (243.2)	(Nujol) 1840, 1780 (CO); 1525 (NO_2); 1175, 910	9.24 (s, 1H); 9.18 (s, 1H); 9.00–8.60 (m, 2H); 8.40–7.90 (m, 1H)
1'''e	70	290° (ethanol/H_2O)	$C_{12}H_6N_2O_4$ (242.2)	(Nujol) 3290 (NH); 1775, 1720 (CO); 1535 (NO_2); 1175, 930	8.78 (s, 1H); 8.77 (s, 1H); 8.90–8.50 (m, 2H); 8.20–7.80 (m, 1H); 12.10–11.80 (m, 1H)[d]

[a] The microanalyses were in satisfactory agreement with the calculated values: C ±0.33, H ±0.26, N ±0.30.
[b] Perkin-Elmer 257 spectrophotometer.
[c] Varian EM-390 spectrometer.
[d] Signal disappears on addition of D_2O.
[e] In $CDCl_3$.
[f] M.S. (70 eV): m/e = 274 (M^+, 86%); Hitachi Perkin-Elmer RMV-6MG.

from the reaction of acid **1b** with potassium hydroxide in the melt and work-up involving acidification with hydrochloric acid is 5-hydroxynaphthalene-2,3-dicarboxylic acid containing ~8 mol equiv of KOH (**1c** · n KOH) as evidenced by element analysis and I.R. and ^{1}H-N.M.R. spectra. The free acid **1c** is obtained by treating **1c** · n KOH with Amberlite® IR-120 (H^+). The anhydride **1'c** is obtained by thermal dehydration of **1c** whereas dimethyl 5-methoxynaphthalene-2,3-dicarboxylate (**1''d**) is prepared by reaction of **1c** · n KOH with dimethyl sulfate.

5-Hydroxynaphthalene-2,3-dicarboxylic Acid (1c) or Dimethyl 5-Methoxynaphthalene-2,3-dicarboxylate (1''d):

Compound **1c** *containing Potassium Hydroxide* (**1c** · n KOH): A mixture of 5-sulfonaphthalene-2,3-dicarboxylic acid (**1b**; 10 g, 0.03 mol) and powdered potassium hydroxide (13.2 g, 0.23 mol) is heated at 215°C (melt) for 120 min, and then allowed to cool to 25°C. The product is dissolved in ice/water (40 ml) and potassium hydrogen sulfate (formed in the reaction) is filtered off. The filtrate is acidified to pH 1 with conc. hydrochloric acid and the resultant precipitate isolated by suction; yield of **1c** · n KOH: 19 g; m.p. > 350°C.

5-Hydroxynaphthalene-2,3-dicarboxylic Acid (**1c**): Product **1c** · n KOH (19 g) is dissolved in hot water (200 ml) and the solution allowed to cool. The clear solution thus obtained is treated with Amberlite® IR-120 (H^+) (50 g). The product **1c** precipitates and is isolated by suction filtration yield: 5.90 g (77%; based on **1b**); m.p. 286°C (Ref.[10], m.p. 284).

Dimethyl 5-Methoxynaphthalene-2,3-dicarboxylate (**1''d**): Dimethyl sulfate (9.46 g, 0.07 mol) is added to a stirred solution of product **1c** · n KOH (2.86 g) in 1 normal potassium hydroxide solution (50 ml) yield: 0.91 g (75%); m.p. 87°C.

6-Substituted 1,4-Dioxo-1,2,3,4-tetrahydrobenzo[*g*]phthalazines (2c, d, e); General and Typical Procedures:

Method A, from Anhydrides **1'c** and **1'e**: The anhydride (**1'c** or **1'e**; 0.01 mol) is dissolved in hot diethyleneglycol (20 ml), this solution is allowed to cool, and 98% hydrazine hydrate (0.51 g, 0.01 mol) is added with stirring. The stirred mixture is heated to reflux for 1 h, the product **2** precipitating from the hot solution as it is formed. The solid product is isolated by suction, washed with water and ethanol, dried under vacuum, and recrystallized from ethanol (**2c**) or dimethylformamide (**2e**); yield of **2c**: 58%; yield of **2e**: 90%.

When in the above procedure ethanol or butanol is used as solvent in place of diethylene glycol, product **2e** is obtained in only 20 or 33% yield, respectively.

Method B, from Imide **1'''e**: A solution of 6-nitronaphthalene-2,3-dicarboxylic acid imide (**1'''e**; 2.422 g, 0.01 mol) and 98% hydrazine hydrate (0.51 g, 0.01 mol) in ethanol (20 ml) is heated to reflux for 1 h. The resultant precipitate (intermediate **5e**, as identified by I.R. and ^{1}H-N.M.R. spectrometry) is isolated by suction and dissolved in diethylene glycol (15 ml). This solution is refluxed for 1 h, the precipitated product **2e** isolated by suction, and recrystallized from dimethylformamide; yield: 70%.

Method C, from Ester **1''d**: A stirred solution of dimethyl 5-methoxynaphthalene-2,3-dicarboxylate (**1''d**; 2.83 g, 0.03 mol) is heated at reflux temperature, 98% hydrazine hydrate (2.1 g, 0.04 mol) is added dropwise, and heating and stirring is continued for 8 h. The precipitated *6-methoxy-1,4-dioxo-1,2,3,4-tetrahydrobenzo*[g]*phthalazine* (**2d**) is isolated by suction and recrystallized from acetone/water; yield: 68%.

8-Methoxy- and 8-Nitro-6,13-dioxo-1,4,6,13-tetrahydrobenzo[*g*]pyridazino[1,2-*b*]phthalazines (4); General Procedure:

To a vigorously stirred mixture of the 1,4-dioxo-1,2,3,4-tetrahydrobenzo[*g*]phthalazine **2d** or **2e** (0.01 mol), the diene **6a, b, c** (0.01 mol), dichloromethane (175 ml), and acetic acid (5 drops), lead(IV) acetate (4.434 g, 0.01 mol) is added in small portions at 10–15°C. Stirring is continued for 24–72 h, the solid material then removed by suction, and washed with dichloromethane. The filtrate is shaken with 5% sodium hydrogen carbonate solution (25 ml) and with water (100 ml). The organic phase is dried with magnesium sulfate and roto-evaporated. The residual product is purified as follows: products **4da**, **4db**, and the isomer mixture **4ec** and **4ed** are column-chromatographed on silica gel using benzene/ethyl acetate (3/1) for **4da**, chloroform/ethyl acetate/benzene (1/1/2) for **4db**, and ethanol/chloroform (1/4) for **4ec** + **4ed**; product **4ea** is recrystallized from acetic acid.

Table 2. 1,4-Dioxo-1,2,3,4-tetrahydrobenzo[*g*]phthalazines (**2**) and 6,13-Dioxo-1,4,6,13-tetrahydrobenzo[*g*]pyridazino[1,2-*b*]phthalazines (**4**) prepared

Product	Method	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a]	M.S.[h] m/e of M^+ (%)	I.R.[b] ν[cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6/TMS$_{int}$)[c] δ [ppm]
2c	A	60	>340°	$C_{12}H_8N_2O_3 \cdot 0.5DEG$[f]	228 (100)	(Nujol) 3.600–2.600 (OH, NH); 1650 (CO); 1620, 1565, 1275 (C—O); 820, 750	9.17 (s, 1H); 8.82 (s, 1H); 8.00–7.50 (m, 2H); 7.40–7.10 (m, 1H); 12.00–10.50 (br. m, 3H)[d]; 3.55 (m, DEG[i])
2d	C	68	>340°	$C_{13}H_{10}N_2O_3$ (242.2)	242 (100)	(KBr) 3350–2400 (NH); 1660 (CO); 1625, 1565, 1270 (C—O); 820, 700	8.93 (s, 1H); 8.65 (s, 1H); 7.90–7.55 (m, 2H); 7.30–7.10 (m, 1H); 4.08 (s, 3H); 11.65–10.35 (m, 2H)[d]
2e	A B	90 70	>350°	$C_{12}H_7N_3O_4$ (257.2)	257 (100)	(KBr) 3400–2800 (NH); 1670 (CO); 1630, 1530 (NO_2); 1330, 825	(compound not soluble in the usual N.M.R. solvents)
4da		41	254–256° (ethyl acetate)	$C_{19}H_{18}N_2O_3$ (322.4)	322 (91)	(KBr) 2950, 2870, 1645, 1635 (CO); 1355, 1270, 805, 755	9.36 (s, 1H); 8.90 (s, 1H); 7.87–7.63 (m, 2H); 7.67–7.10 (m, 1H); 5.03–4.77 (m, 4H); 4.13 (s, 3H); 1.98 (s, 6H)[e]
4db		44	239–241° (benzene/hexane)	$C_{29}H_{22}N_2O_3$ (446.5)	446 (57)	(KBr) 3070, 2960, 1645, 1620 (CO); 1385, 1335, 1270, 1070, 800	9.33 (s, 1H); 8.78 (s, 1H); 7.65–7.50 (m, 2H); 7.20 (s, 10H); 7.04–6.86 (m, 1H); 6.60–6.46 (m, 2H); 6.41–6.28 (m, 2H); 4.04 (s, 3H)
4ea		40	275–276° (AcOH)	$C_{18}H_{15}N_3O_4$ (337.3)	337 (90)	(KBr) 1650, 1630 (CO); 1530 (NO_2); 1385, 1350, 1210, 765	9.80 (s, 1H); 9.20 (s, 1H); 8.80–8.50 (m, 2H); 8.10–7.80 (m, 1H); 5.00–4.80 (m, 4H); 2.00 (s, 6H)[g]
4ec + **4ed**		10	246–248° (ethyl acetate)	$C_{17}H_{13}N_3O_4$ (323.3)	323 (100)	(KBr) 1650, 1630 (CO); 1530 (NO_2); 1385, 1350, 1210, 765	9.55 (s, 1H); 8.97 (s, 1H); 8.55–8.30 (m, 2H); 7.87–7.67 (m, 1H); 5.87–5.68 (m, 1H); 4.73–4.47 (m, 4H); 1.93 (s, 3H)[e]
4fa		21	263–264° (ethanol)	$C_{18}H_{17}N_3O_2$ (307.3)	307 (84)	(Nujol) 3350, 3250 (NH_2); 1655, 1640 (CO); 1610, 1360, 750	9.00 (s, 1H); 8.58 (s, 1H); 7.48–7.30 (m, 2H); 6.92–6.80 (m, 1H); 6.33–6.18 (m, 2H)[d]; 4.48–4.24 (m, 4H); 1.75 (s, 6H)

[a–e] See Table 1.
[g] In F_3C–COOH.
[h] Hitachi Perkin-Elmer RMV-6MG.
[i] Diethylene glycol.

8-Amino-2,3-dimethyl-6,13-dioxo-1,4,6,13-tetrahydrobenzo[*g*]-pyridazino[1,2-*b*]phthalazine (4fa):
A solution of the 8-nitro compound **4ea** (0.675 g, 2 mmol) in butanol/benzene/acetic acid (10/5/1; 175 ml) is hydrogenated on 10% palladium-on-carbon (60 mg) at ~ 5 at for 17 h at room temperature. The solid material formed (containing the catalyst) is diluted with butanol/benzene/acetic acid (10/5/1; 100 ml), the solution heated, and the catalyst filtered off. The filtrate is concentrated to a volume of ~ 10 ml. The yellow product which gradually precipitates is isolated by suction and recrystallized from ethanol; yield: 0.13 g (21%); m.p. 263–264°C.

Received: April 9, 1984

* Address for correspondence.

[1] B. Lopez, M. Lora-Tamayo, P. Navarro, J.L. Soto, *Heterocycles* **2**, 649 (1974).
[2] F. Gómez-Contreras, M. Lora-Tamayo, P. Navarro, *Tetrahedron* **33**, 2109 (1977).
[3] F. Gómez-Contreras, M.Lora-Tamayo, P. Navarro, M. Pardo, *Tetrahedron* **34**, 3499 (1978).
[4] M.C. Cano, F. Gómez-Contreras, A.M. Sanz, *J. Heterocyclic Chem.* **17**, 1265 (1980).
[5] Personal Communication of P. Navarro in a seminar held on 5th, April 1983 in the Institute of Biorganic Chemistry, Poznan, Poland.
[6] M. Lora-Tamayo et al., *An. Quim.*, **79C**, 138 (1983).
[7] L. Friedman, *Org. Synth. Coll. Vol.* V, 810 (1973); *J. Org. Chem.* **30**, 1453 (1965).
[8] H.D.K. Drew, R.F. Garwood, *J. Chem. Soc.* **1939**, 836.
[9] Y. Omote, T. Miyake, N. Sugiyama, *Bull. Chem. Soc. Jpn.* **40**, 2446 (1967).
[10] S. Imahori, K. Ken, F. Shi, T.Chiyodaku, *Jap. Patent* 86454 (1976); *C.A.* **85** 192450 (1976).