NEW PHTHALAZINE- AND PYRIDAZINO[4,5-g]PHTHALAZINE DERIVATIVES

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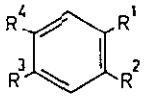
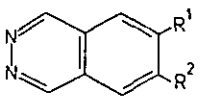
Abstract--Some new phthalazine- and pyridazino[4,5-g]phthalazine derivatives have been prepared through diethyl phthalazine-6,7-dicarboxylate (5), obtained by regioselective reduction of the tetraester (1) with sodium aluminium hydride at -50°C, and treatment of the intermediate diformyl derivative (2) with hydrazine. The tautomeric behaviour of both 1,4-dihydroxypyridazino[4,5-g]phthalazine (13) and the N-methyl derivative (14) were also investigated by comparison of their spectroscopic properties with those of the model compounds (15) and (16).

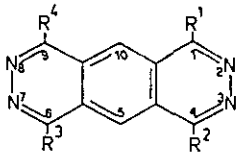
After the first researches at the beginning of the thirties,[1] the interest in the chemistry of pyridazino[4,5-g]phthalazine ring system increased in the subsequent years especially with regards to some peculiar features such as chemiluminescence[2] and to the possibility of obtaining new heat-resistant polymeric materials.[3,4] However, although the parent compound (9) as well as the corresponding 1,4,6,9-tetrahydroxy-, 1,6-, and 1,9-dihydroxy derivatives (10), (11), and (12) have been reported in the literature,[5,6] 1,4-dihydroxypyridazino[4,5-g]phthalazine (13) remained, to our knowledge, yet unknown. Whereas the former compounds were obtained from benzene derivatives, suitably 6,7-disubstituted phthalazines appeared more attractive as starting materials for the synthesis of the latter.

Several attempts to prepare compound (5) by selective reduction of the tetraester (1) with lithium aluminium hydride ($LiAlH_4$) in anhydrous tetrahydrofuran (THF) at different temperatures, followed by treatment with hydrazine, were unsuccessful. Conversely, when the reduction of (1) was carried out with sodium aluminium hydride ($NaAlH_4$) in the same solvent at -50°C, diethyl 1,2-diformyl-4,5-benzenedicarboxylate (2) was obtained as the main product. Its ^{1}H-NMR spectrum (Table 1), characterized by a singlet at δ 8.25 for two equivalent aromatic ring protons, ruled out the isomeric structure (3), whereas the alternative regioisomer (4) was discarded since the crude product of the above reaction afforded predominantly (t.l.c. and ^{1}H-NMR) diethyl phthalazine-6,7-dicarboxylate (5) by treatment with hydrazine. Reduction of (5) with $LiAlH_4$ and $AlCl_3$ at 60°C gave the corresponding 6,7-dihydroxymethyl derivative (6); on the contrary, when the same compound was treated with $NaAlH_4$ at

-65°C and the reduction products allowed to react with hydrazine, pyridazino[4,5-g]phthalazine (9) was obtained in 38% yield.



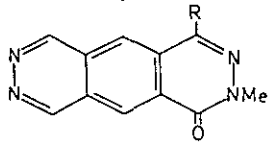




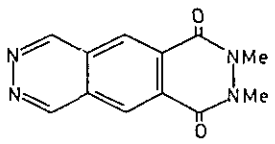
1 $R^1=R^2=R^3=R^4=CO_2Et$
2 $R^1=R^2=CHO, R^3=R^4=CO_2Et$
3 $R^1=R^4=CHO, R^2=R^3=CO_2Et$
4 $R^1=R^3=CHO, R^2=R^4=CO_2Et$

5 $R^1=R^2=CO_2Et$
6 $R^1=R^2=CH_2OH$
7 $R^1=R^2=CO_2H$
8 $R^1-R^2=CO-O-CO$

9 $R^1=R^2=R^3=R^4=H$
10 $R^1=R^2=R^3=R^4=OH$
11 $R^1=R^3=OH, R^2=R^4=H$
12 $R^1=R^4=OH, R^2=R^3=Ph$
13 $R^1=R^2=OH, R^3=R^4=H$



14 R = OH
15 R = OMe



16

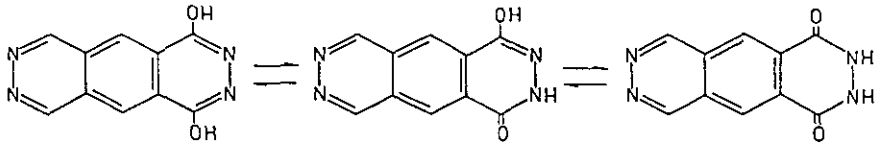
Since the most unreacted starting material could be easily recovered, this method represented a possible alternative route to the synthesis of (9) from 1,2,4,5-tetraformylbenzene,[5] available from the corresponding tetramethyl derivative by a four-steps procedure.[7]

The ester (5) reacted with hydrazine hydrate in boiling methanol to give a red-orange solid which afforded 1,4-dihydroxypyridazino[4,5-g]phthalazine (13) in 80.2% yield by heating at 220-230°C under vacuum (15-20 mm Hg); the same compound (13) was also obtained in very good yield (84.1%) by refluxing phthalazine-6,7-dicarboxylic acid anhydride (8) with anhydrous hydrazine in glacial acetic acid. Compound (8) was synthesized by dehydration (refluxing acetic anhydride, 2 h) of the corresponding acid (7), prepared by alkaline hydrolysis ($Ba(OH)_2$, H_2O; 80-90°C, 1 h) of (5). According to the behaviour of pyrazine- and pyridazinedicarboxylic anhydrides under electron impact,[8,9] the mass spectrum of (8) exhibited, beside peaks at m/e 200 (M) and 156 ($M-CO_2$), a signal at m/e 128 ($M-CO_2$ and CO) probably due to a species having the composition of 6,7-didehydrophthalazine molecular ion. Compound (13), for which three tautomeric forms (13a-c) could be considered, reacted with an excess of diazomethane (methanol-ether; 24 h) to give 1-methoxy-3-methyl-3*H*-pyridazino[4,5-g]phthalazin-4-one (15) as the largely predominant product which was separated from a very small amount of the N,N'-dimethyl derivative (16) by preparative layer chromatography (chloroform-methanol 25:1 v/v); on the other hand (16) was obtained in 78.5% yield from the anhydride (8) and N,N'-dimethylhydrazine in refluxing glacial acetic acid.

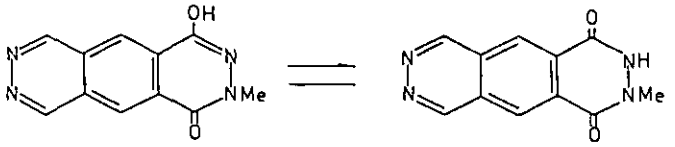
Methylation under the same conditions of 3-methyl-2*H*,3*H*-pyridazino[4,5-g]phthalazine-1,4-dione (14), prepared from (8) and N-methylhydrazine in 83% yield, gave similar results.

The ^1H-NMR values (Table 1) and the I.r. frequencies (see below and the Experimental Section) strongly supported the assigned structures of all new products, for which satisfactory microanalyt-

ical data were obtained.



13a 13b 13c



14a 14b

As regards the tautomeric behaviour of (13) and (14), we tried to throw some light upon this problem by comparison of their spectroscopic properties with those of the model compounds (15) and (16). The I.r. spectra of the former compounds showed a strong band at 1670 and 1650 cm^{-1}, respectively, for an amidic CO group, strictly comparable to that of the N,O-dimethyl derivative (15) (1650 cm^{-1}); this finding ruled out the dihydroxy structure (13a), whereas the dioxo forms (13c) and (14b) were discarded on the basis of the spectrum of the N,N'-dimethyl derivative (16) where the CO group gave rise to a characteristic double band at lower frequencies (1620 and 1640 cm^{-1}).

Furthermore, since in the same spectra were also present two broad structural bands at 2700-2000 and 1900-1700 cm^{-1} (NH^{+}) and a band at 1610-1600 cm^{-1} (CO^{-}), we reached the conclusion that the compounds under investigation exist in the solid state in the mixed hydroxy-oxo forms (13b) and (14a), respectively, as dipolar ions; such zwitterionic structures were probably favoured by the presence in the tricyclic ring system of a second fully heteroaromatic pyridazine moiety containing two basic nitrogen atoms. Whereas the ^{1}H-NMR spectrum of the symmetrical N,N'-dimethyl derivative (16) in DMSO-d_6 (Table 1) displayed a singlet at δ 9.02 for the aromatic ring protons at the position 5 and 10, the resonances of the same protons appeared well separated ($\Delta\delta$ = 0.29 ppm) in the spectrum of the N,O-isomer (15); the remarkable difference of the chemical shift of 5- and 10-H protons for compound (14) ($\Delta\delta$ = 0.46 ppm) led us to argue that it exists predominantly in solution too in the form (14a). The behaviour of this compound did not change in methanol solution since its U.v. pattern in this solvent was almost identical, apart some small differences in the relative intensities of the absorption maxima (Experimental Section), to that of N,O-model compound (15).

As for the ^{1}H-NMR spectrum of the dihydroxy derivative (13) in DMSO-d_6, only a singlet was detectable at δ 8.96 for the 5- and 10-H ring protons and, unfortunately, this result did not allow an unambiguous decision since also the asymmetrical structure (13b) could now fit the spectral data if a rapid proton exchange between oxygen and nitrogen atoms was present in this solvent.

Table 1. ^{1}H-NMR data (ppm from tetramethylsilane, J in Hz)

Compound	Solvent	δ/J	Assignment
2	$CDCl_3$	1.40t ^{7}	2xMe
		4.40q	2xOCH_2
		8.25s	3- and 6-H
		10.50s	2xCHO
5	$CDCl_3$	1.44t ^{7}	2xMe
		4.49q	2xOCH_2
		8.46s	5- and 8-H
		9.68s	1- and 4-H
6	DMSO-d_6	4.75d[a] ^{5}	2xCH_2
		5.55t[b]	2xOH
		8.15s	5- and 8-H
		9.65s	1- and 4-H
9	CF_3CO_2H	10.07s	5- and 10-H
		10.64s	1-,4-,6-,and 9-H
13	DMSO-d_6	8.96s	5- and 10-H
		9.98s	6- and 9-H
14	DMSO-d_6	3.60s	N-Me
		8.66s[c]	10-H
		9.12s[c]	5-H
		10.10s	6- and 9-H
15	DMSO-d_6	3.67s	N-Me
		4.04s	O-Me
		8.81s[c]	10-H
		9.10s[c]	5-H
		9.98s	6- and 9-H
16	DMSO-d_6	3.69s	2xN-Me
		9.02s	5- and 10-H
		9.98s	6- and 9-H

[a]Signal collapses to a singlet on deuteriation. [b]Signal disappears on deuteriation. [c]These signals appear slightly broadened probably due to long range couplings.

EXPERIMENTAL SECTION

Unless otherwise stated, I.r. spectra were measured for potassium bromide discs with a Perkin-Elmer 283 spectrometer and U.v. spectra for solutions in methanol on a Cary 14 spectrophotometer. ^{1}H-NMR spectra were recorded with a Perkin-Elmer R32 instrument and mass spectra were taken with a Perkin-Elmer 270 spectrometer. Silica-gel plates (Merck F_{254}) and silica-gel 60 (Merck; 230-400 mesh) were used for analytical and preparative t.l.c., and for column chromatography, respectively.

General Procedure for Reduction of Compounds (1) and (5)

A solution of the ester in THF was added dropwise under nitrogen to a stirred suspension of the reducing agent in the same solvent and stirring was continued for several hours. The reaction mixture was then hydrolysed very slowly with aqueous acetic acid (50%) in THF and filtered through a sin-

tered glass funnel. For the synthesis of (5) and (9) the filtrate was allowed to react with an excess of hydrazine in methanol at -60°C under nitrogen for 1 h and set aside overnight.

Diethyl 1,2-diformyl-4,5-benzenedicarboxylate (2)

The ester (1)[10] (4 g) was reacted with $NaAlH_4$ (1.17 g) in THF (50 ml) at -50°C for 6 h to give a semi-solid residue (2.1 g) containing the diformyl derivative (2) as the main product [(60-65%; ^{1}H-NMR and GLC (3% OV 17 on 100-120 mesh Gas-Chrom Q)]. Preparative layer chromatography (chloroform-acetone 10:1 v/v) followed by sublimation at 130°C and 0.05 mm Hg afforded (2) as a waxy white solid; I.r. 1725 and 1700 cm^{-1}.

Diethyl phthalazine-6,7-dicarboxylate (5)

Reduction of (1) (4 g) with $NaAlH_4$ carried out as above, followed by treatment with hydrazine (95%; 2.6 ml) afforded compound (5) which was purified by column chromatography (chloroform) and vacuum sublimation (1 g; y 33.3%); mp 81-82°C (from ligroin); I.r. 3040, 2990, 1745, 1725, and 1045 cm^{-1}; U.v. max (log ε): 222 (4.75), 306 (3.31), and 317 nm (3.31).

6,7-Dihydroxymethylphthalazine (6)

Treatment of compound (5) (1 g) with $LiAlH_4$ (0.34 g) and $AlCl_3$ (0.3 g) in THF (100 ml) at 60°C for 24 h, gave compound (6) (0.4 g; y 57.7%); mp 254-256°C (from ethanol); I.r. 3300, 3050, 2880, 2720, and 1430 cm^{-1}.

Pyridazino[4,5-g]phthalazine (9)

Reduction of (5) (0.8 g) with $NaAlH_4$ (0.5 g) in THF (50 ml) at -65°C for 6 h, followed by reaction with hydrazine (95%; 1.3 ml) yielded a solid which was washed with THF (3 x 10 ml) and water (3 x 10 ml) to give compound (9) (0.2 g; y 38%) as a yellow-brown product, mp > 350°C (from DMSO); I.r. 3060, 3030, 3000, 1585, 1510, 1155, 945, and 895 cm^{-1}; U.v. (DMSO) max (log ε): 305 (3.71), 317 (3.77), 331 (3.76), and 338sh nm (3.65); M.S.: m/e (relative intensity): 182 (M^+, 100).
The original filtrate and the tetrahydrofuran washings were combined and evaporated to dryness; the starting material (5) (0.4 g) was recovered from the residue by extraction with ether (3 x 20 ml).

Phthalazine-6,7-dicarboxylic acid (7)

Compound (7) (y 84.8%) had mp > 330°C (after purification by dissolution in aqueous NaOH and reprecipitation with conc. HCl); I.r. 3060, 3040, 3000-2100vbr, 2100-1770vbr, 1695, and 1275 cm^{-1}.

Phthalazine-6,7-dicarboxylic acid anhydride (8)

The anhydride (8) (y 78%) gradually darkened above 200°C and decomposed at about 260°C (after sublimation at 120°C and 0.02 mm Hg); I.r. 1860, 1785, and 1700 cm^{-1}.

1,4-Dihydroxypyridazino[4,5-g]phthalazine (13)

Compound (13) had mp > 350°C (from DMSO); U.v. max (log ε): 232 (4.49), 263 (3.72), 291sh (3.65), and 333 nm (3.69).

3-Methyl-2*H*,3*H*-pyridazino[4,5-g]phthalazine-1,4-dione (14)

The methyl derivative (14) (y 83%) had mp > 300°C (from DMSO); U.v. max (log ε): 234 (4.70), 263 (3.61), 274 (3.63), 291 (3.53), and 340 nm (3.68).

1-Methoxy-3-methyl-3*H*-pyridazino[4,5-g]phthalazin-4-one (15)

Compound (15) (y 70.8%) had mp 249-251°C (from methanol); U.v. max (log ε): 234 (4.49), 264 (3.70), 274 (3.74), 291 (3.64), and 338 nm (3.81).

2,3-Dimethyl-2*H*,3*H*-pyridazino[4,5-g]phthalazine-1,4-dione (16)

The derivative (16) had mp > 320°C (from DMSO); U.v. max (log ε): 232 (4.69), 238 (4.67), 270 (3.59), and 334 nm (3.62).

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