HIGHLY SUBSTRATE SELECTIVE NUCLEOPHILIC AMINATION OF NITRO-SUBSTITUTED 4-(2-HYDROXYETHYLAMINO)PHTHALAZIN-1(2*H*)-ONES

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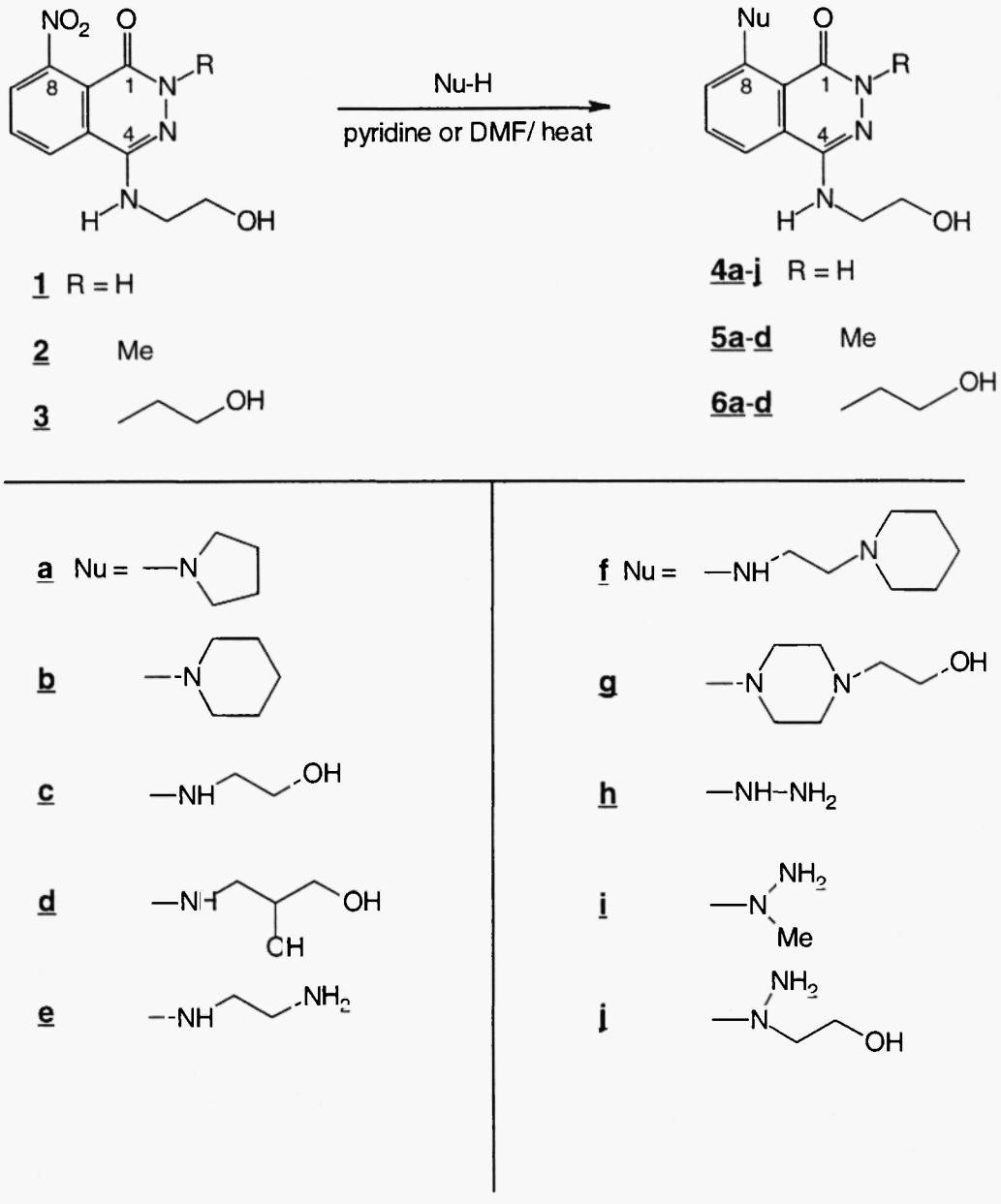
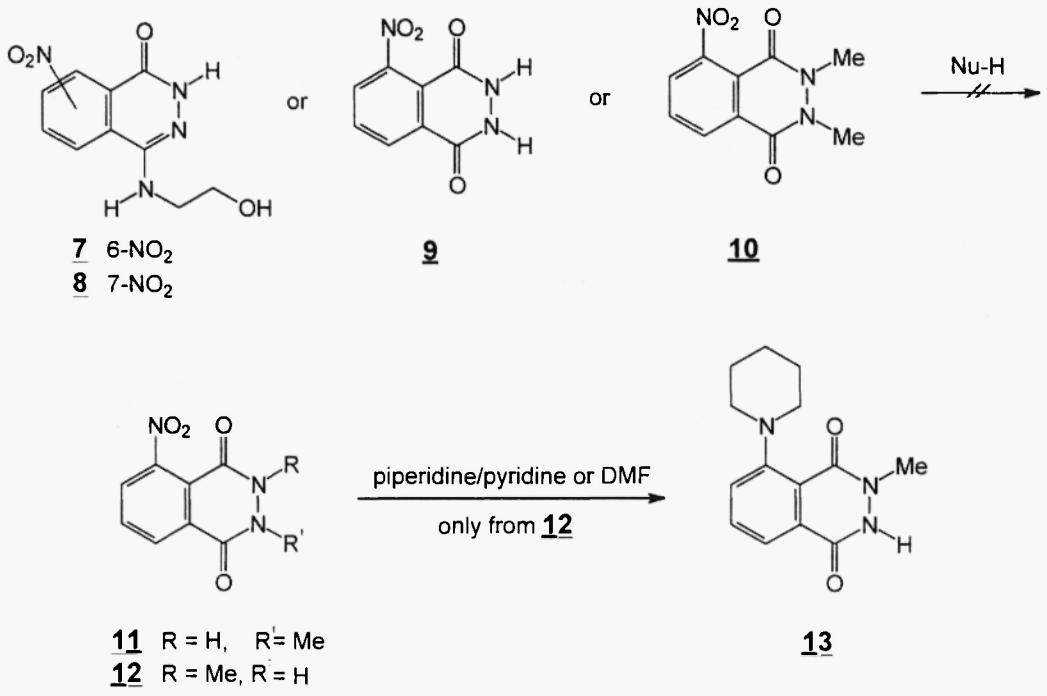
ABSTRACT: An unexpected selectivity was observed in the aromatic displacement reaction of 4-(2-hydroxyethylamino)phthalazinones **1**-**3** and **7**, **8** differently substituted with the leaving nitro group on the condensed benzene ring. On treatment with a series of amine and hydrazine nucleophiles, the 8-nitro isomers **1**-**3** were readily transformed into the corresponding aromatic amine (**4**-**6**), while the substrates carrying the nitro group at position 6 or 7 (**7** and **8**) remained unchanged on prolonged treatment with any of the reagents used. Application of pyridine or DMF as a solvent proved to be indispensable to successful conversions even of the 8-nitro derivatives **1**-**3**.

INTRODUCTION

Nucleophilic substitution of nitro group attached to aromatic ring is a well documented reaction having wide synthetic utility (1-3). This type of conversion is highly promoted by the presence of strong electron-withdrawing groups capable of stabilizing the anionic intermediate. Numerous reports have presented the efficiency of a properly positioned cyano-, carboxy-, carboxyalkyl- and related groups (1), or an other nitro substituent (2) in promoting such displacement reactions. Nevertheless, there are only a few examples in which the activation can be attributed to a heterocycle with electron acceptor character condensed to the aromatic ring carrying the nitro leaving group (3). In this contribution we report on an unexpected substrate specific nitro displacement wich can easily be effected by a series of amine and hydrazine nucleophiles on 8-nitro-4-(2-hydroxyethylamino)phthalazin-1(2*H*)-ones **1**-**3** (Scheme 1), but does not take place on the isomerous nitro compounds **7** and **8** (Scheme 2). On the other hand, from a pharmaceutical point of view it is worth emphasizing that the convenient introduction of basic side chains into the benzene ring of a 4-aminophthalazinone derivative may open a straightforward and economical way to a wide variety of novel compounds with potential biological activity, because the preparation of precursors **1**-**3** and numerous related compounds can be based on the readily available 3-nitrophthalic anhydride (cf. Experimental). The outstanding biological activity of structurally related compounds has also been reported (4).


NO2
O
R
8
1
N
4
N
H
N
OH
Nu-H
pyridine or DMF/ heat
Nu
1 R = H
2 Me
3
OH
4a-j R = H
5a-d Me
6a-d
OH
a Nu =
b
c
NH
OH
d
NH
OH
CH
e
NH
NH2
f Nu =
NH
N
g
N
N
OH
h
NH–NH2
i
NH2
N
Me
j
NH2
N
OH

Scheme 1



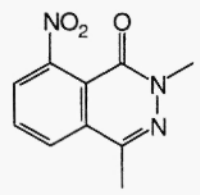
Scheme 2

RESULTS AND DISCUSSION

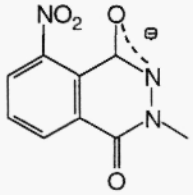
Reactions of **3** yielding the amino derivatives (**4a-i**, **5a-d** and **6a-d**) were carried out in boiling pyridine in the presence of the appropriate amine reagent. These conversions could also be effected in refluxing DMF, and were completed within 2-5 hours. In the absence of pyridine or DMF the unchanged nitro compound **1-3** could only be recovered from any of the refluxing amine component. These findings are in keeping with earlier experiences (5) demonstrating the accelerating effect of DMF in analogous reactions. Obviously, similar catalytic activity can be attributed to pyridine. The nucleophilicity of the reagent is also a very important factor in this type of conversion. This view is supported by the following observations: i) methylhydrazine and hydroxyethylhydrazine react with the alkylated nitrogen producing **4i,j**; ii) not any reaction took place with aniline and even with morpholine (pK_b = 5.3) and thiomorpholine (pK_b = 5.0). On the other hand, steric factors seem to have also significant role in these reactions, because on prolonged treatment with hexamethylene imine or *iso*-propylamine even substrates **1-3** were recovered quantitatively from the reaction mixtures.

Interestingly, a striking substrate selectivity could be observed in the amination reaction. Neither of the two other investigated nitro isomers **7** and **8** (Scheme 2) reacted with any of the amine components under the conditions successfully applied to the conversion of **1-3**: after boiling for 50 hours unchanged **7** and **8** were recovered almost quantitatively from the reaction mixtures. It means that reactivity of **1-3** containing the leaving nitro group in *ortho* position relative to the activating carbonyl group is larger by powers of magnitude than that of **7** carrying the nitro

substituent in *para* position relative to the carbonyl group. (For the sake of simplicity, terms *ortho* and *para* are used here for these bicyclic compounds.) It must be emphasized that no analogous reactions exhibiting such an extreme *ortho/para* selectivity have been reported so far. In order to collect more information about the cause of this strange substrate selectivity, 8-nitrophthalic hydrazide (**9**) and its methylated analogues **10**-**12** were tried out as models (Scheme 2). On treatment with piperidine in pyridine or DMF, compounds **9**-**11** proved to be completely resistant to any substitution, while **12** readily underwent amination to give piperidino derivative **13**. These experiments suggest that successful displacement of the nitro group even from position 8 (as numbered in **9**, **10** and **12**) or position 5 (as numbered in **11**) requires the possibility of development of the tautomer from **I** (Figure) containing carbonyl group adjacement to the nitro group and an endocyclic C=N bond in the pyridazine ring. Such tautomer seems to be favoured for the reactive aminophthalazinones **1**-**3** and monomethylhydrazide **12**, while can obviously be excluded for dimethylhydrazide **10** and the isomerous monomethylhydrazide **11**. This view gains support from the fact that analogous tautomeric form has been determined by comparative spectroscopic methods for phthalic hydrazide (6). In principle, tautomeric form **I** can not be excluded for hydrazide **9**, but under the applied basic conditions this model and **11**, both of them are of enhanced acidity, probably undergo deprotonation to give anions of type **A** (Figure), which are resistant to amination. In accordance with this assumption, **9** and **11** were isolated as piperidine salts from the reaction mixtures. Nevertheless, taking all the discussed experimental findings and assumptions into consideration, it must be stated that any explanation of the observed substrate selectivity would inevitably be highly speculative at this stage, so further work on this system is clearly necessary before the difficulty in the mechanistic interpretation can be resolved.



I
for **1**-**3** and **12**



A
for **9** and **11**

Figure

EXPERIMENTAL

Melting points (uncorrected) were measured with a Boetius apparatus. The IR spectra were recorded in KBr pellets with a Zeiss specord 75 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded in DMSO-d_6 (internal reference: TMS) at 500.13 and 125.77 MHz by a BRUKER DRX-500 instrument. The NMR data of each compound described in this paper are provided as supplementary material.

Preparation of 6-,7- and 8-nitro derivatives of 4-(2-hydroxyethylamino)phthalazin-1(2*H*)-one (1-3): Starting from the corresponding nitrophthalic anhydride, 2-aminoethanol and the appropriate hydrazine **1**, **2**, **3**, **7** and **8** were

prepared by proceeding on the well documented synthetic route described for 4-(2-hydroxyethylamino)phthalazin-1(2*H*)-ones (7) and their 6,7-dimethoxy derivatives (8). In this way 3-nitrophthalic anhydride was exclusively converted into **1**, **2** and **3** (no formation of the 5-nitro derivative could be detected), but 4-nitrophthalic anhydride gave an approximately 1:1 mixture of **7** and **8**. Manifold recrystallization from water yielded **7** in pure form, while **8** was isolated by a series of recrystallization from ethanol. Differentiation between **7** and **8** was made by DNOE measurements, in the course of which irradiation of the triplet due to the NH-group of the hydroxyethylamino chain resulted an increase in the intensity of the H-5 signal (*d* of 1.9 Hz for **7** and *d* of 8.9 Hz for **8**).

4-(2-Hydroxyethylamino)-8-nitrophthalazin-1(2*H*)-one (1): Yield 58% (counted for 3-nitrophthalic anhydride); Mp 291-293°C (water); IR (cm^{-1}) $\nu_{OH,NH}$ 3360 and 3200-2600, amide-I 1642, ν_{NO_2} 1525 and 1370; Anal. Calcd for $C_{10}H_{10}N_4O_4$ (250.21) C, 48.00; H, 4.03; N, 22.39; Found C, 48.03; H, 4.11; N, 22.35.

4-(2-Hydroxyethylamino)-2-methyl-8-nitrophthalazin-1(2*H*)-one (2): Yield 78%; Mp 183-185° (DMF); IR (cm^{-1}) $\nu_{OH,NH}$ 3320 and 3300-2600, amide-I 1628, ν_{NO_2} 1535 and 1365; Anal. Calcd for $C_{11}H_{12}N_4O_4$ (264.24) C, 50.00; H, 4.58; N, 21.20; Found C, 50.08; H, 4.56; N, 21.30.

2-(2-Hydroxyethylamino)-4-(2-hydroxyethylamino)-8-nitrophthalazin-1(2*H*)-one (3): Yield 53%; Mp 180-183°C (water); IR (cm^{-1}) $\nu_{OH,NH}$ 3445 and 3200-2600, amide-I 1630, ν_{NO_2} 1535 and 1370; Anal. Calcd for $C_{12}H_{14}N_4O_5$ (294.27) C, 48.98; H, 4.80; N, 19.04; Found C, 48.92; H, 4.77; N, 19.12.

4-(2-Hydroxyethylamino)-6-nitrophthalazin-1(2*H*)-one (7): Yield 14% (counted for 4-nitrophthalic anhydride); Mp 265-266°C (water); IR (cm^{-1}) $\nu_{OH,\ NH}$ 3400-2700, amide-I 1646, ν_{NO_2} 1553 and 1349; Anal. Calcd for $C_{10}H_{10}N_4O_4$ (250.21) C, 48.00; H, 4.03; N, 22.39; Found C, 48.04; H, 3.99; N, 22.32.

4-(2-Hydroxyethylamino)-7-nitrophthalazin-1(2*H*)-one (8): Yield 11% (counted for 4-nitrophtalic anhydride); Mp 268-270°C (EtOH); IR (cm^{-1}) $\nu_{OH,\ NH}$ 3597 and 2700-2400, amide-I 1663, ν_{NO_2} 1553 and 1348, Anal. Calcd for $C_{10}H_{10}N_4O_4$ (250.21) C, 48.00; H, 4.03; N, 22.39; Found C, 47.97; H, 4.08; N, 22.42.

General procedure for preparation of 4a-j; 5a-d; 6a-d and 13:

Compound **3** (5.0 g, 0.02 mol) and the corresponding amine components (0.04 mol) were dissolved in pyridine or DMF (20 cm^3), and the mixture was refluxed for 5 hours. After evaporation to dryness in vacuo, the solid residue was suspended in water, filtered off, washed with water and dried. Recrystallization from the solvent presented in the parenthesis after the melting points afforded the products in 80-95% yield.

4-(2-Hydroxyethylamino)-8-pyrrolidinophthaiazin-1(2*H*)-one (4a): Mp 204-206°C (EtOH); IR (cm^{-1}) $\nu_{OH,\ NH}$ 3270 and 3100-2600, amide-I 1617; Anal. Calcd for $C_{14}H_{18}N_4O_2$ (274.32) C, 61.30; H, 6.61; N, 20.42; Found C, 61.23; H, 6.70; N, 20.33.

4-(2-Hydroxyethylamino)-8-piperidinophthalazin-1(2*H*)-one (4b): Mp 229-231°C (EtOH); IR (cm^{-1}) $\nu_{OH,NH}$ 3450 and 3100-2400, amide-I 1640; Anal. Calcd for $C_{15}H_{20}N_4O_2$ (288.35) C, 62.48; H, 6.99; N, 19.43; Found C, 62.59; H, 7.04; N, 19.37.

4,8-Bis(2-hydroxyethylamino)phthalazin-1(2*H*)-one (4c): Mp 208-209°C (EtOH); IR (cm^{-1}) $\nu_{OH,\ NH}$ 3340 and 3200-2400, amide-I 1640; Anal. Calcd for $C_{12}H_{16}N_4O_3$ (264.29) C, 54.54; H, 6.10; N, 21.20; Found C, 54.65; H, 6.12; N, 21.11.

4-(2-Hydroxyethylamino)-8-(2,3-dihydroxypropylamino)phthalazin-1(2*H*)-one (4d): Mp 198-201°C (EtOH); IR (cm^{-1}) $\nu_{OH,\ NH}$ 3230 and 3400-2400, amide-I 1645; Anal. Calcd for $C_{13}H_{18}N_4O_4$ (294.31) C, 53.05; H, 6.16; N, 19.04; Found C, 53.18; H, 6.21; N, 18.92.

8-(2-Aminoethylamino)-4-(2-hydroxyethylamino)phthalazin-1(2*H*)-one (4e): Mp 175-176°C; IR (cm^{-1}) $\nu_{OH,NH,}$ 3340, 3275 and 3100-2400, amide-I 1627; Anal. Calcd for $C_{12}H_{17}N_5O_2$ (263.30) C, 54.74; H, 6.51; N, 26.60; Found C, 54.71; H, 6.63; N, 26.52.

4-(2-Hydroxyethylamino)-8-(2-piperidinoethylamino)phthalazin-1(2*H*)-one (4f): Mp 173-175°C (EtOH); IR (cm^{-1}) $\nu_{OH,\ NH}$ 3263 and 3150-2400, amide-I 1640; Anal. Calcd for $C_{17}H_{25}N_5O_2$ (331.41) C, 61.61; H, 7.60; N, 21.13; Found C, 61.60; H, 7.71; N, 21.10.

4-(2-Hydroxyethylamino)-8-[4-(2-hydroxyethylamino)piperazin-1-yl]phthalazin-1(2*H*)-one (4g): Mp 207-210°C (EtOH); IR (cm^{-1}) $\nu_{OH,\ NH}$ 3245 and 3300-2400, amide-I 1630; Anal. Calcd for $C_{16}H_{23}N_5O_3$ (333.38) C, 57.64; H, 6.95; N, 21.00; Found C, 57.55; H, 6.93; N, 21.06.

8-Hydrazino-4-(2-hydroxyethylamino)phthalazin-1(2*H*)-one (4h): Mp 234-237°C; IR (cm^{-1}) $\nu_{OH,NH}$ 3600-2400, amide-I 1630; Anal. Calcd for $C_{10}H_{13}N_5O_2$ (235.25) C, 51.06; H, 5.57; N, 29.77; Found C, 50.98; H, 5.69; N, 29.83.

4-(2-Hydroxyethylamino)-8-(methylhydrazin-1-yl)phthalazin-1(2*H*)-one (4i): Mp 191-193°C; IR (cm^{-1}) $\nu_{OH,NH}$ 3375, 3248, 3150 and 3100-2400, amide-I 1647; Anal. Calcd for $C_{11}H_{15}N_5O_2$ (249.27) C, 53.00; H, 6.07; N, 28.10; Found C, 53.04; H, 6.15; N, 28.16.

4-(2-Hydroxyethylamino)-8-[(2-hydroxyethyl)hydrazin-1-yl]phthalazin-1(2*H*)-one (4j): Mp 193-196°C (EtOH); IR (cm^{-1}) $\nu_{OH,\ NH}$ 3230 and 3300-2400, amide-I 1640; Anal. Calcd for $C_{12}H_{17}N_5O_3$ (279.3) C, 51.60; H, 6.14; N, 25.08; Found C, 51.60; H, 6.11; N, 25.13.

4-(2-Hydroxyethylamino)-2-methyl-8-pyrrolidinophthalazin-1(2*H*)-one (5a): Mp 133-135°C (water); IR (cm^{-1}) $\nu_{OH, NH}$3360 and 3150-2500, amide-I 1615; Anal. Calcd for $C_{15}H_{20}N_4O_2$ (288.35) C, 62.48; H, 7.00; N, 19.43; Found C, 62.44; H, 6.93; N, 19.51.

4-(2-Hydroxyethylamino)-2-methyl-8-piperidinophthalazin-1(2*H*)-one (5b): Mp 177-179°C (EtOH); IR (cm^{-1}) $\nu_{OH, NH}$ 3376 and 3000-2400, amide-I 1625; Anal. Calcd for $C_{16}H_{22}N_4O_2$ (302.38) C, 63.55; H, 7.33; N, 18.53; Found C, 63.47; H, 7.31; N, 18.59.

4,8-Bis(2-hydroxyethylamino)-2-methylphthalazin-1(2*H*)-one (5c): Mp 202-204°C (water); IR (cm^{-1}) $\nu_{OH, NH}$ 3355 and 3200-2400, amide-I 1628; Anal. Calcd for $C_{13}H_{18}N_4O_3$ (278.31) C, 56.10; H, 6.52; N, 20.13; Found C, 56.21; H, 6.56; N, 20.25.

4-(2-Hydroxyethylamino)-8-(2,3-dihydroxypropylamino)-2-methylphthalazin-1(2*H*)-one (5d): Mp 181-184°C (water); IR (cm^{-1}) $\nu_{OH, NH}$ 3345, 3202 and 3150-2500, amide-I 1625; Anal. Calcd for $C_{14}H_{20}N_4O_4$ (308.34) C, 54.54; H, 6.54; N, 18.17; Found C, 54.63; H, 6.57; N, 18.11.

2-(2-Hydroxyethyl)-4-(2-hydroxyethylamino)-8-pyrrolidinophthalazin-1(2*H*)-one (6a): Mp 179-182°C (EtOH); IR (cm^{-1}) $\nu_{OH, NH}$ 3227 and 3200-2600, amide-I 1645; Anal. Calcd for $C_{16}H_{22}N_4O_3$ (318.4) C, 60.36; H, 6.97; N, 17.60; Found C, 60.31; H, 6.92; N, 17.65.

2-(2-Hydroxyethyl)-4-(2-hydroxyethylamino)-8-piperidinophthalazin-1(2*H*)-one (6b): Mp 196-198°C (EtOH); IR (cm^{-1}) $\nu_{OH, NH}$ 3337, 3220 and 3100-2400, amide-I 1623; Anal. Calcd for $C_{17}H_{24}N_4O_3$ (332.40) C, 61.43; H, 7.28; N, 16.86; Found C, 61.38; H, 7.22; N, 16.73.

2-(2-Hydroxyethyl)-4,8-bis(2-hydroxyethylamino)phthalazin-1(2*H*)-one (6c): Mp 131-134°C (EtOH); IR (cm^{-1}) $\nu_{OH, NH}$ 3365, 3302 and 3200-2400, amide-I 1635; Anal. Calcd for $C_{14}H_{20}N_4O_4$ (308.34) C, 54.54; H, 6.54; N, 18.17; Found C, 54.62; H, 6.61; N, 18.07.

2-(2-Hydroxyethyl)-4-(2-hydroxyethylamino)-8-(2,3-dihydroxypropylamino)phthalazin-1(2*H*)-one (6d): Mp 142-145°C (EtOH); IR (cm^{-1}) $\nu_{OH, NH}$ 3390 and 3200-2400, amide-I 1628; Anal. Calcd for $C_{15}H_{22}N_4O_5$ (338.36) C, 53.25; H, 6.55; N, 16.56; Found C, 53.32; H, 6.52; N, 16.71.

2-Methyl-8-piperidinophthalazin-1,4(2*H*,3*H*)-dione (13): Mp: 222-224°C (EtOH); IR (cm^{-1}) ν_{NH} 3420, amide-I 1638 and 1602; Anal. Calcd for $C_{15}H_{22}N_4O_5$ (259.31) C, 64.85; H, 6.61; N, 16.20; Found C, 64.78; H, 6.59; N, 16.17.

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