

Adel Amer (2) and Hans Zimmer\*

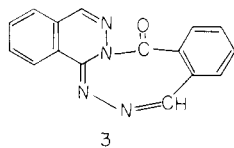
Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221

Received June 1, 1981

A reaction involving 1-hydrazinophthalazine (hydralazine, **1**) designed to give a condensed heterocyclic system in which an eight membered ring is fused to phthalazine was investigated. With phthalaldehydic acid (**2**) the expected system was obtained. However, it occurs as an easily convertible mixture of ring-chain tautomers. It was found that the course of the reaction depends on the solvent. Thus, 6,7-dihydro-7-hydroxy-12*H*-phthalazino[2,1-*b*][2,4]benzodiazocin-12-one (**5**) and 2-(2-formylbenzoyl)-1-hydrazono-1,2-dihydrophthalazine (**6**) were the products of the reaction of **1** with **2** in aqueous medium. Upon prolonged standing this mixture converts into 3-(2-carboxyphenyl)-*s*-triazolo[3,4-*a*]phthalazine (**8**). In contrast, the isomeric ring-chain tautomers 2-(1-aminophthalazino)-3-hydroxy-1-oxoisindole (**12**) and 1-[2-(2-formylbenzoyl)hydrazino]phthalazine (**13**) were formed when the reaction was run in ethanol as solvent.

*J. Heterocyclic Chem.*, 18, 1625 (1981).

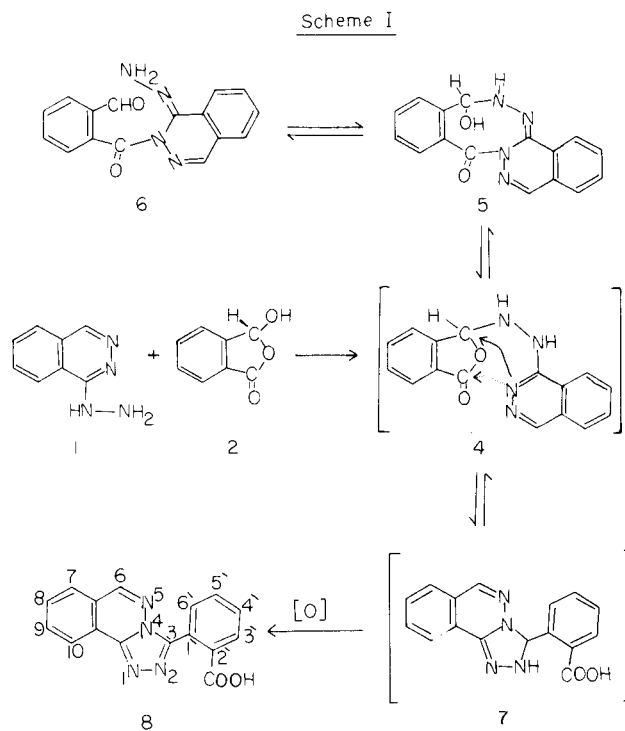
In a recent paper (3) we reported on the acylation of **1** by mono-, di-, tri-, and tetracarboxylic acids. All these reactions yielded *via* hydrazone formation followed by dehydrative cyclization the *s*-triazolo[3,4-*a*]phthalazine system. Reactions which were designed to utilize **1** to give heterocyclic systems with six-, seven-, and eight-membered rings annelated to phthalazine were successful only to give phthalazine with a fused six-membered ring; the desired fused seven- and eight-membered ring systems could not be obtained. Thus, reaction of **1** with pyruvic acid gave the corresponding hydrazone, which upon simple heating underwent dehydrative cyclization to form 3-methyl-*s*-triazino[3,4-*a*]phthalazin-4-one (**3**).



The present work describes the results of our renewed efforts towards this goal, namely to annelate rings larger than six-membered to phthalazine. We concentrated our efforts towards the synthesis of systems having an eight-membered ring fused to this heterocycle. Toward this end the reaction between hydralazine and phthalaldehydic acid (**2**) which potentially should lead to the formation of an eight-membered ring fused to phthalazine, was studied.

The aldehyde function of **2** is known to undergo normal derivatization, *e.g.*, its forms an oxime with hydroxylamine (**5**). Consequently, it should react with **1** to give the "hydralzone" which potentially could undergo dehydrative cyclization to yield **3**.

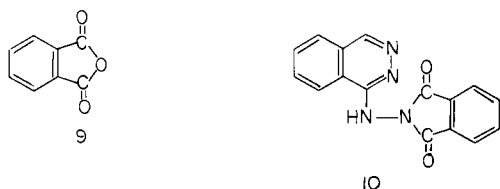
The experimental results, however, showed that **3** is not formed; instead the reaction, if performed in aqueous medium, gave a pale yellow material with spectral data not compatible with **3**. Recrystallization from ethanol resulted first in precipitation of yellow crystals, followed by



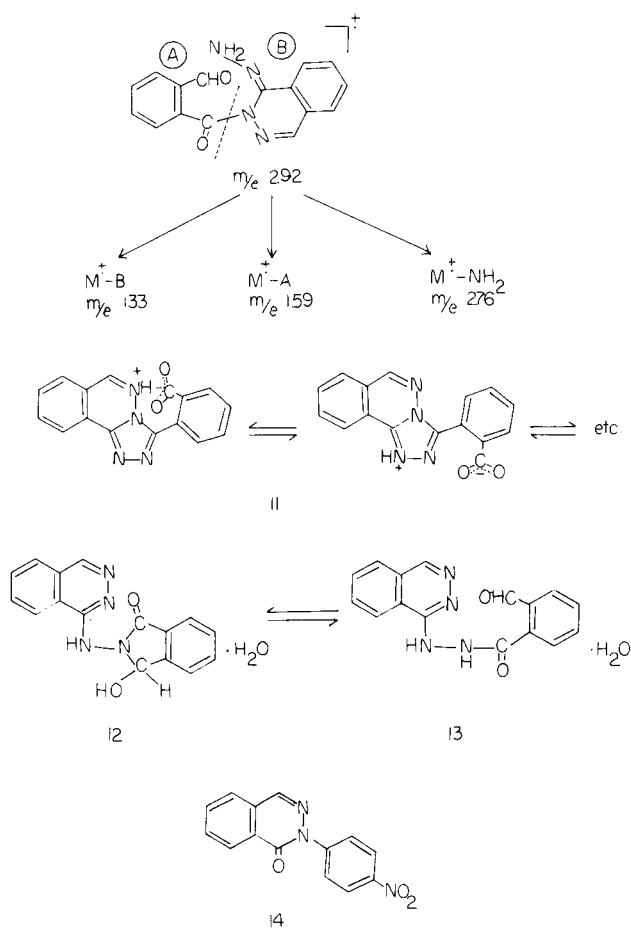
precipitation of colorless crystals. The yellow crystals were isolated carefully, and recrystallized again. The results of the second crystallization were the same as of the first one, yellow crystals precipitated first, followed by depositing of colorless crystals. When recrystallized mixture of yellow and colorless crystals was left to stand for a period of time (about two weeks) in the presence of ethanol, eventually only colorless crystals were present.

On the basis of spectroscopic evidence, these observations can best be explained by assuming that one is dealing with a mixture of two isomers, **5** and **6**, that easily interconvert and which are ring-chain tautomers (Scheme 1). The identification of the pale yellow product as a

tautomeric mixture of **5** and **6** is based on elemental analysis and the following spectral evidence. The infrared spectrum (potassium bromide) of the yellow crystals exhibited two broad bands centered at  $3400\text{ cm}^{-1}$  and  $3060\text{ cm}^{-1}$  (OH, NH), another band at  $3000\text{-}2000\text{ cm}^{-1}$  could be attributed to hydrogen transfer in the system (**6**),  $1710\text{ cm}^{-1}$  (w) (aldehyde CO, indicating the low abundance of **6** in the solid state),  $1620\text{ cm}^{-1}$ ,  $1600\text{ cm}^{-1}$  and  $1580\text{ cm}^{-1}$ . The nmr spectrum of this compound in dimethyl sulfoxide showed a multiplet at  $\delta$  7.5-8.67 (9H, ArH), singlet at  $\delta$  9.1 (1H, CHO), 12.3 (2H, NH<sub>2</sub>). However there was no signal in the region of  $\delta$  5-6 indicating the absence of methine H and therefore of tautomer **5**.



Scheme II



This is similar to the behavior of another ring-chain pair of tautomers, namely 3-hydroxyphthalide and

phthalaldehydic acid where we also find that the open-chain tautomer, having a free aldehydic group, is the

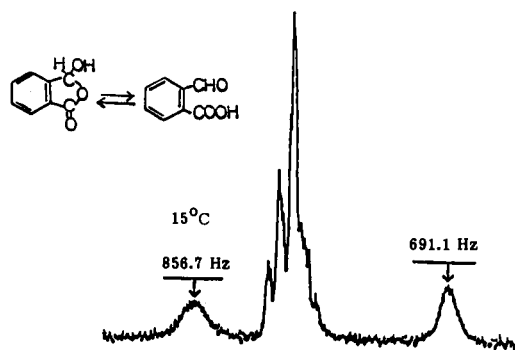


Fig. 1: NMR Spectrum (100 MHz) of phthalaldehydic acid (0.312 gm in 0.3 ml DMSO-d<sub>6</sub>).

predominant tautomer if dimethyl sulfoxide is used as a solvent (Figure 1). This is probably due to the solvation of the carbonyl group by this solvent, thus decreasing the ability of the CH=O group to undergo semiacetal formation with the hydroxyl moiety of the carboxylic acid group. Our findings agree only partly with earlier work (7) where it was stated that the closed form is the predominant if not the only tautomer in a number of solvents including chloroform (Figure 2), acetone and dimethyl sulfoxide.

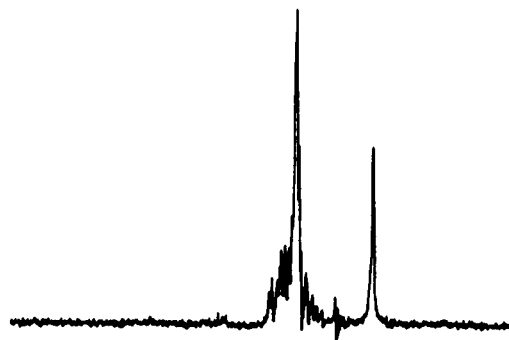


Fig. 2: NMR Spectrum (60 MHz) of phthalaldehydic acid in deuteriochloroform

The mass spectrum provides additional strong evidence for the presence of the mixture of the ring-chain tautomers **5** and **6**. It exhibited the expected molecular-ion peak at  $m/e$  292. Compound **5** should readily thermo-eliminate water and cause a peak at  $m/e$  274; this peak actually is observed as the base peak. Presence of **6** on the other hand readily explains the occurrence of the observed mass spectrum (Scheme II). The most characteristic fragmentation may be explained by assuming that the ring tautomer **5** represents the major constituent of the mixture. (See experimental).

The colorless crystals were identified as **8**, again on the basis of elemental analysis, spectral data as well as by an undepressed mixture melting point with independently synthesized material which was prepared from the reac-

tion between **1** and phthalic acid anhydride **9**. The later reaction led also to the formation of *N*-(1-aminophthalazino)phthalimide (**10**) as already previously reported (3).

A plausible explanation for the formation of **8** from the reaction between **1** and **2** is an air oxidation of the intermediate **7** during the prolonged standing of the reaction mixture while it is formed by a dehydrative cyclization reaction of 1-[2-(2-carboxybenzoyl)hydrazino]phthalazine, an intermediate in the reaction between **1** and **9**.

The infrared spectrum of **8** exhibits bands at  $1690\text{ cm}^{-1}$  (CO),  $1615\text{ cm}^{-1}$  (C=N) and a number of broad bands at  $3400\text{--}2300\text{ cm}^{-1}$  and  $1900\text{ cm}^{-1}$  which suggests that it exists as a mixture of zwitterionic species **11**. The nmr spectrum of **8** dimethyl sulfoxide showed eight protons causing a multiplet at  $\delta$  7.5-8.3 for hydrogens at positions 7, 8, 9, 10, 3', 4', 5' and 6' a singlet at  $\delta$  8.7 (1H) for positions 6, and a broad singlet centered at  $\delta$  12.7 (1H) for the acidic proton. The ms-spectrum of **8** showed the expected molecular ion peak at  $m/e$  290 ( $\text{C}_{16}\text{H}_{10}\text{N}_3\text{O}^+$ ); the base peak at  $m/e$  245 ( $\text{C}_{15}\text{H}_9\text{N}_4^+$ ) was attributed to elimination processes involving OH and CO.

Using ethanol instead of water as solvent for the reaction between **1** and **2** a yellow product was obtained which was different from the tautomeric mixture of **5** and **6**. On the basis of infrared and nmr spectral evidence, this material also is best formulated as a mixture of ring-chain tautomers, **12** and **13**. The infrared spectrum of this mixture exhibits a variable band centered at  $3260\text{ cm}^{-1}$  (OH, NH), and a weak band at  $1690\text{ cm}^{-1}$  (aldehydic CO) indicating that **13** represents the minor constituent of the mixture. The interpretation of the nmr spectrum of the mixture can be done on the basis as was discussed for 3-hydroxyphthalide/phthalaldehydic acid pair of ring-chain tautomers.

Thus, in dimethyl sulfoxide only the open-chain tautomer **13**, exists as is definitely proven by the singlet present at  $\delta$  9.3 (1H, CHO), in addition there appears in its spectrum only a multiplet centered at  $\delta$  8.1 (11H, 9ArH plus 2NH). The ms-spectrum (50 ev) of the reaction product showed a molecular-ion at  $m/e$  292 ( $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}_2^+$ ); RI 2.07%, the base peak appears at  $m/e$  273 and was attributed to processes involving OH and 2H.

Further if *p*-nitrophenylhydrazine was added to a dimethyl sulfoxide solution of **5** and **6** or **12** and **13** a precipitate formed which according to its elemental analysis, spectral data and undepressed mixture melting point with independently synthesized material (**9**) is 2-(4-nitrophenyl)-1-(2*H*)-phthalazinone, (**14**).

#### Acknowledgement.

We thank Mr. Donald Meyer of Dow-Merrell Pharmaceuticals, Inc., Cincinnati, Ohio for his assistance with the

nomenclature. A generous gift of hydralazine by CIBA-GEIGY Corp. (Dr. C. A. Brownley) assisted in the progress of this work.

#### EXPERIMENTAL

##### General.

Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra (ir) were recorded using a Perkin-Elmer Model 599 spectrometer calibrated against  $1601\text{ cm}^{-1}$  band of polystyrene.  $^1\text{H}$ -nmr spectra were recorded on a Varian HA 100 and/or a Varian T-60 spectrometer. Chemical shifts are expressed in  $\delta$  relative to tetramethylsilane as internal standard. Mass spectroscopical data were obtained on a Perkin-Elmer RMU-7 mass spectrometer. Elemental analyses were performed at M-H-W Laboratories, Phoenix, Arizona.

6,7-Dihydro-7-hydroxy-12*H*-phthalazino[2,1-*b*]2,4]benzodiazocin-12-one (**5**) and 2-(2-Formylbenzoyl)-1-hydrazono-1,2-dihydrophthalazine (**6**) Mixture.

A solution of 0.6 g of **2** in 7 ml of water was treated with an aqueous solution of 0.7 g of 1-hydrochloride. The reaction mixture was refluxed for 1/2 hour with formation of a yellow crystalline product (93%), mp  $200^\circ$  ethanol; ir (potassium bromide):  $3400, 3060, 3000\text{--}2000$  (br),  $1710, 1620, 1600, 1580\text{ cm}^{-1}$ ; nmr (dimethylsulfoxide- $d_6$ ):  $\delta$  7.5-8.67 (m, 9H), 9.1 (s, 1H), 12.3 (s, 2H, deuterium oxide exchangeable). Characteristic ms-peaks for **5**,  $m/e$  273 ( $\text{C}_{16}\text{H}_9\text{N}_4\text{O}^+$ ), ( $\text{M}^+[\text{H}_2\text{O}-1]$ ), RI = 48.87%;  $m/e$  247 ( $\text{C}_{15}\text{H}_9\text{N}_3\text{O}^+$ ), ( $\text{M}^+[\text{H}_2\text{O}-\text{HCN}]$ ), 10.77%;  $m/e$  246 ( $\text{C}_{15}\text{H}_{10}\text{N}_4^+$ ), ( $\text{M}^+[\text{H}_2\text{O}-\text{CO}]$ ), 27.64%;  $m/e$  245 ( $\text{C}_{15}\text{H}_9\text{N}_4^+$ ), ( $\text{M}^+[\text{H}_2\text{O}-\text{CO}-1]$ ), 84.26%;  $m/e$  219 ( $\text{C}_{14}\text{H}_8\text{N}_3^+$ ), ( $\text{M}^+[\text{H}_2\text{O}-\text{CO}-\text{HCN}]$ ), 5.98%;  $m/e$  218 ( $\text{C}_{14}\text{H}_8\text{N}_3^+$ ), (C-HCN), 17.38%;  $m/e$  190 ( $\text{C}_{14}\text{H}_8\text{N}^+$ ), (C-[HCN-N<sub>2</sub>]), 14.17%;  $m/e$  171 ( $\text{C}_9\text{H}_7\text{N}_4^+$ ), ( $\text{M}^+-\text{C}_6\text{H}_4-\text{CO}$ ), 31.68%;  $m/e$  145 ( $\text{C}_8\text{H}_7\text{N}_3^+$ ), 21.35% and 129 ( $\text{C}_8\text{H}_5\text{N}_2^+$ ), 13.10%; Characteristic peaks for **6**,  $m/e$  276 ( $\text{C}_{16}\text{H}_{10}\text{N}_3\text{O}_2^+$ ), ( $\text{M}^+-\text{NH}_2$ ), RI = 3.53% (**8**)  $m/e$  159 ( $\text{C}_8\text{H}_7\text{N}_4^+$ ), 2.08%;  $m/e$  133 ( $\text{C}_8\text{H}_5\text{O}_2^+$ ), 3.0% (Scheme II).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}_2$ : C, 65.75; H, 4.14; N, 19.17. Found: C, 65.62; H, 4.22; N, 19.21.

##### 3-(2-Carboxyphenyl)-s-triazolo[3,4-*a*]phthalazine (**8**).

Method A: When the mixture of **5** and **6** in ethanol stands for an extended period of time (at least two weeks) **5** and **6** changed to colorless crystals of **8**, mp  $298^\circ$  (ethanol); ir (potassium bromide):  $3400\text{--}2300$  (br),  $1900$  (br),  $1690, 1615\text{ cm}^{-1}$ ; nmr (dimethylsulfoxide- $d_6$ ):  $\delta$  7.5-8.3 (m, 8H), 8.7 (s, 1H), 12.7 (s, 1H, deuterium oxide exchangeable); (ms) (70 ev) 290 ( $\text{M}^+$ , 2.08), 273 (1.73), 246 (71.14), 245 (100), 220 (3.71), 190 (4.03), 147 (3.44), 143 (2.05), 130 (5.35), 129 (5.98), 128 (17.75), 117 (6.84), 116 (3.59), 155 (16.65), 114 (10.82), 105 (3.44), 104 (4.05), 103 (8.82), 102 (8.89), 101 (4.44), 89 (10.57), 88 (20.51), 76 (13.02), 75 (6.74).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{10}\text{N}_4\text{O}_2$ : C, 66.20; H, 3.47; N, 19.30. Found: C, 66.43; H, 3.76; N, 19.44.

Method B: Compound **8** was obtained in a 40% yield by reducing the volume of the mother liquor of a preparation of *N*-(1-aminophthalazino)phthalimide (**2**). It was identical in all respects with the product prepared by method A.

2-(1-Aminophthalazino)-3-hydroxy-1-oxoisindole (**12**) and 1-[2-(2-Formylbenzoyl)hydrazino]phthalazine (**13**) Mixture.

A solution of 1.5 g of **2** in 100 ml of ethanol was treated with a solution of 1.96 g of 1-hydrochloride and 0.83 g of sodium acetate in 50 ml of ethanol. The reaction mixture was refluxed for 2 hours. The precipitated product was filtered off and dried (88%), yellow crystals, mp  $205^\circ$  (ethanol-dioxane); ir (potassium bromide):  $3260, 1690, 1610\text{ cm}^{-1}$ ; nmr (dimethylsulfoxide- $d_6$ ):  $\delta$  8.1 (m, 11H, 2H were deuterium oxide exchangeable), 9.3 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}_2 \cdot \text{H}_2\text{O}$ : C, 61.93; H, 4.55; N, 18.06. Found: C, 61.54; H, 4.08; N, 17.77.

## REFERENCES AND NOTES

- (1) Paper VII of the series: Condensed Heterocyclic Rings, preceeding paper see reference 3.
- (2) Projected Ph.D. thesis, University of Cincinnati.
- (3) Hans Zimmer, J. M. Kokosa and K. J. Shah, *J. Org. Chem.*, **40**, 2901 (1975).
- (4) J. Druoy and H. Ringier, *Helv. Chem. Acta*, **34**, 195 (1951).
- (5) E. Bernatek, *Acta. Chem. Scand.*, **14**, (1960).
- (6) For a theoretical treatment of hydrogen shifts vs. hydrogen bonds see, V. A. Kurmitsky and K. N. Solovyov, *J. Mol. Struct.*, **65** 219 (1980).
- (7) J. Kogan, *J. Org. Chem.*, **32**, 4060 (1967).
- (8) This peak also has a contribution of the P + 2 peak (m/e 274).
- (9) L. Seckles, *Rec. Trav. Chim.*, **43**, 329 (1924).