Ring Closure Reactions Involving 1-Hydrazinophthalazine [1]. Reactions with 1,2,4-Tricarbonyl and 1,3-Dicarbonyl Compounds

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Annelation reactions of six-membered rings to 1-hydrazinophthalazine, **1**, were investigated. With aroyl(acyl)pyruvates, **2**, the desired system was obtained. It was found that the course of the reaction depends on the reaction condition as well as the substituted pyruvates. Thus, 3-(2-oxo-2-substituted ethyl)-4*H*-*as*-triazino[3,4-*a*]phthalazin-4-one, **4**, was the product when **1** reacted with **2** in alcoholic medium. The side chain tautomerism of **4** was studied by using ir, ^{1}H-nmr, and ms spectral methods. When **1** hydrochloride instead of **1** was reacted with **2**, 3-ethoxycarbonyl-*s*-triazolo[3,4-*a*]phthalazine, **6**, was the major product. The reaction of **1** with benzoylacetone in ethanol afforded the hydrazalone, **9**. By ir, ^{1}H-nmr, and ^{13}C-nmr methods it was shown that in solution it is inolved in an enhydrazine-hydrazone as well as a ring-chain tautomerism. Compound **9** upon the action of PPA underwent dehydrative cyclization to 3-methyl-*s*-triazolo[3,4-*a*]phthalazine, **10**, and 3-methyl-5-phenyl-1-(1-phthalazinyl)pyrazole, **7**. The reaction of **1** with ethyl phenylpropiolate in ethanol was reported by others to give 1-(1-phthalazinyl)-3-phenyl-5-pyrazolone, **8**. Upon reinvestigation of this reaction it is shown that the product actually is ethyl β-(1-phthalazinylhydrazono)benzenepropanoate, **11**. Attempts to synthesize **8** were unsuccessful by this method. In the reaction of **1** with ethyl benzoylacetate the expected hydralazone **11** was easily formed which upon reaction with PPA yielded the desired species **8**.

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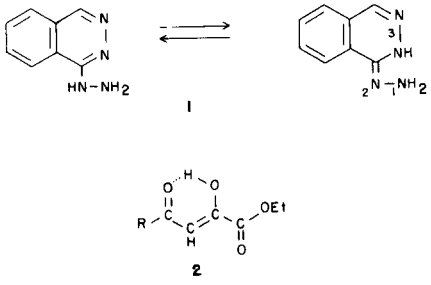
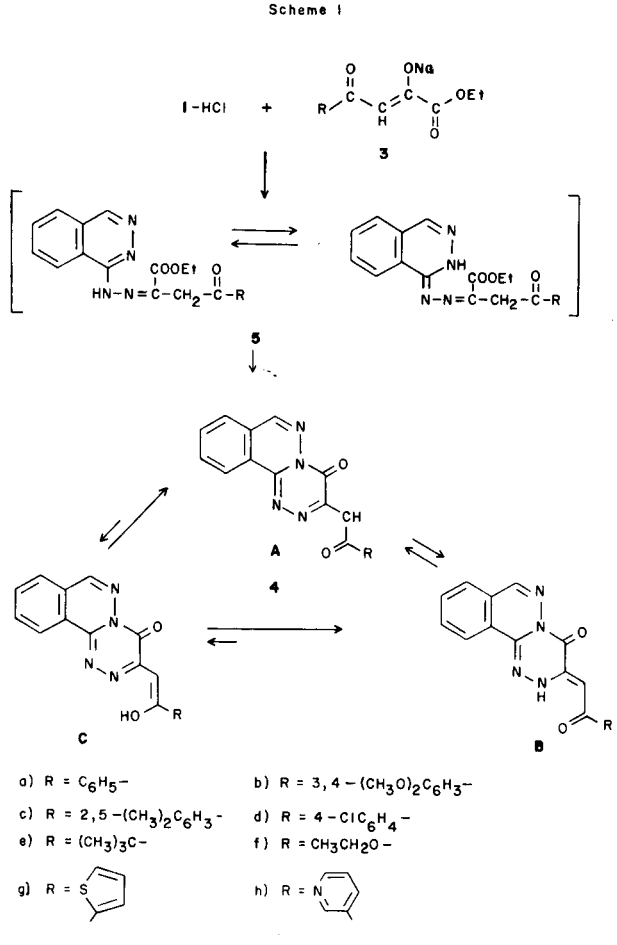
In connection with our work concerning the human metabolism [3a-c] of 1-hydrazinophthalazine **1** (hydralazine, a potent antihypertensive agent), we found that **1** upon acylation undergoes a very facile ring closure with a large number of mono-, di-, tri- and tetracarboxylic acids to yield the *s*-triazolo[3,4-*a*]phthalazine system [4].



The ease of this dehydrative cyclization is mainly due to the high nucleophilicity of the N-3 atom [1,5,6] of **1**. It was now of interest, especially in view of the untoward side effects suffered by about 10% of the patients on a regimen of **1**, to investigate its reaction with 1,3-dicarbonyl as well as other polycarbonyl compounds. The reaction with such compounds is of special interest as far as the interaction of **1** with the Krebs cycle carbonyl compounds in its human metabolism is concerned. It is also known that pyruvic acid, after first forming the expected hydrazone with **1**, undergoes this dehydrative cyclization when refluxed in a suitable solvent to yield 3-methyl-*as*-triazino[3,4-*a*]phthalazin-4-one [7], a compound in which a six-membered ring is annelated to the phthalazine system. The same system was also formed by refluxing **1** in excess diethyl oxalate; 2*H*-*as*-triazino[3,4-*a*]phthalazine-3,4-dione was the obtained compound [4]. Similar results were obtained by reacting **1** with the Krebs cycle compound α-ketoglutaric acid

Scheme I



a) R = C_6H_5– b) R = 3,4-$(CH_3O)_2C_6H_3$–
c) R = 2,5-$(CH_3)_2C_6H_3$– d) R = 4-ClC_6H_4–
e) R = $(CH_3)_3C$– f) R = CH_3CH_2O–
g) R =   h) R =

[8] with which it formed 3-(methyl propionate)-*as*-triazino-[3,4-*a*]phthalazin-4-one. Recently, it also was reported that **1** reacts with dimethyl acetylenedicarboxylate in an annelation reaction to give 2-(3,4-dihydro-4-oxo-2*H*-*as*-triazino-[3,4-*a*]phthalazine-3-ylidene)acetate [9].

In continuation of our interest to annelate rings to **1**, we set out to investigate whether this cyclization in reactions of **1** with α-carbonyl acids to yield the *as*-triazino[3,4-*a*]-phthalazine system is a general one. Also, especially in the light of a recent publication describing the reaction of cer-

Table I

Mass Spectral Data of Compounds **4a-4h**

Compound	M^+	M^+-1	M^+-CO	M^+-CO-1	M^+-R	M^+-R-H	M^+R-CO	Remaining intense peaks			
4a	316 (86)	315 (100)	288 (8)	287 (28)	239 (19)		211 (13)	172 (13) 128 (33)	145 (12) 114 (11)	144 (27) 105 (74)	129 (28) 77 (42)
4b	376 (74)	375 (96)	348 (7)	347 (17)	239 (3)	238 (4)	211 (5)	361 (14) 129 (11)	331 (4)	165 (100)	138 (12)
4c	344 (37)		316 (6.5)	315 (2)	239 (2.3)	238 (2)	211 (2)	329 (100) 185 (8) 146 (11) 129 (16)	301 (3) 172 (21) 145 (11.5) 128 (9.5)	264 (4) 159 (11) 133 (63) 105 (27)	212 (4) 158 (13) 132 (21)
4d	350 (100) 352 (64)	349 (99) 351 (92)	322 (17) 324 (7)	321 (65) 232 (27)	239 (8)		211 (27)	315 (4) 141 (25) 111 (33)	294 (2) 139 (77) 103 (15)	172 (8) 129 (7) 102 (28)	161 (4) 113 (12) 89 (28)
4e	296 (17)				239 (100)	238 (1)	211 (4)	195 (11) 115 (5)	194 (7) 102 (7)	129 (22) 57 (5.5)	128 (7.5)
4f	284 (77)					238 (77)	211 (64)	212 (100) 183 (31) 129 (69) 102 (28)	184 (14) 171 (7) 128 (12)	156 (8) 127 (16)	155 (8) 115 (16)
4g	322 (100)	321 (85)	294 (6)	293 (19)	239 (4.5)	238 (19)	211 (6.4)	289 (19) 129 (18.5) 83 (10)	238 (19) 128 (7) 73 (42)	210 (14) 111 (93)	147 (10.4) 102 (26)
4h	317 (100)	316 (96)	289 (38)	288 (23)	239 (10)		211 (23)	300 (15) 106 (52) (15)	160 (17) 103 (13) (47)	131 (11) 102 (33) (14)	129 (37) 89 (14) (12)

tain 1,3-dicarbonyl compounds with **1** to allegedly give rise to formation of 1-(pyrazolo-substituted) phthalazines [10,11], these latter reactions were reinvestigated and the results shown to be in error.

A. 1.2.4-Tricarbonyl Compounds.

In further exploration of the reactivity of the N-1 and N-3 atoms of **1** we studied its reactions with aroyl(acyl)-pyruvates **2** and/or their sodium salts **3** as a potential source of annelated triazinophthalazines. It was found that this reaction proceeded differently depending on the reaction conditions as well as the substituted pyruvates used. Also of crucial importance for the product formation is whether the free base **1** or its hydrochloride salt, **1** hydrochloride is employed. Thus, refluxing equivalent amounts of **1** hydrochloride for 8-10 hours in aqueous solution with **3a-3h** and thus neutralizing **1** hydrochloride *in situ* to **1** afforded solids whose ir, ^{1}H-nmr, mass spectra, and elemental analysis are compatible with structures of type **4** compounds (Scheme I). The position of the peaks of the infrared spectra (potassium bromide) of the carbonyl groups of compounds **4a** to **4h** suggests that these compounds exist predominantly in the tautomeric form **4A** in the solid state. According to mass spectral data, these compounds exist in the gas phase in the tautomeric form, **4B**, thus explaining the intense $[M-H]^+$, $[M-CO-H]^+$ and/or $[M-R-H]^+$ ions shown by these compounds (Table I). Since the H radical is one of the most unfavorable leaving groups in any fragmentation, the high intensity of the $[M-H]^+$ peak indicates efficient stabilization of the resulting ion which can be best explained by the expulsion of a hydrogen atom from the enamine N-H group (Scheme II). Compounds **4c** and **4e** occur in dimethyl sulfoxide-d_6 solution in two tautomeric forms, *viz* enamine and ketimine, as indicated by their ^{1}H-nmr spectra. While the ^{1}H-nmr spectrum (dimethyl sulfoxide-d_6) of compound **4f** indicated it to occur as the tautomer **4fA** exclusively. No further investigations by ^{1}H-nmr concerning details about existence of tautomers of all of the type **4** compounds could be done due to solubility problems. This type of ketimine-enamine tautomerism in side-chain substituted N-heterocycles is well documented by spectroscopic [2,12] and chemical evidence [2,13,14].

Refluxing an aqueous solution of **1** hydrochloride and **3** for a brief period (5-10 minutes) resulted in the formation of the hydralazones **5**. These hydralazones could be cyclized to **4** either by prolonged refluxing in aqueous solution or dimethyl sulfoxide solution or by just heating them without a solvent.

It was found that when **1** hydrochloride was used instead of **1** in the reaction with **2a**, a colorless product was obtained along with **4a**. The colorless crystals were identified as 3-ethoxycarbonyl-*s*-triazolo[3,4-*a*]phthalazine, **6**, on the basis of elemental analysis and spectral data. The uv-spectrum of **6** resembles closely that of the 3-methyl-*s*-triazolo[3,4-*a*]phthalazine [1,3] which is another indication of **6** being an *s*-triazolo[3,4-*a*]phthalazine analog (Figure 1).

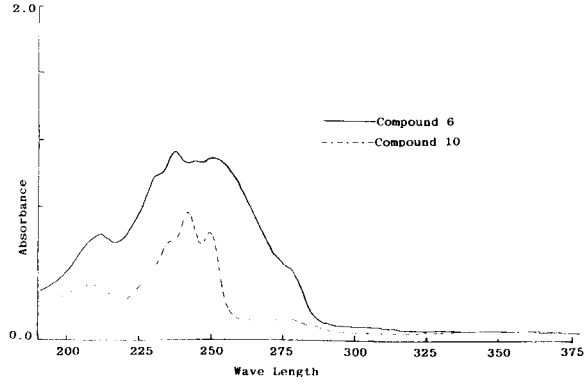
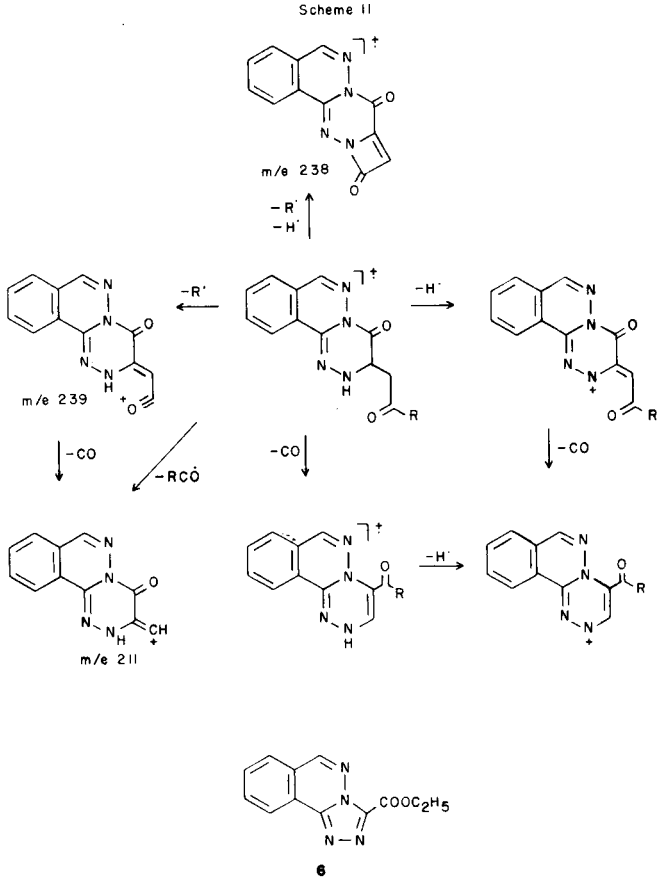


Figure 1

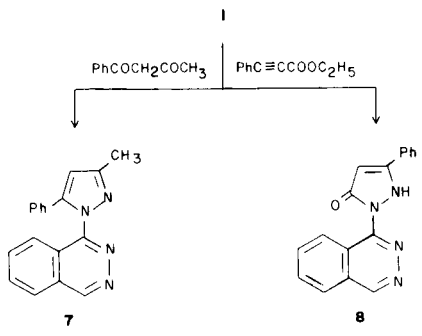
Scheme II



B. 1.3-Dicarbonyl Compounds.

R. Soliman and Feid-Allah reported on the reaction of **1** with benzoylacetone and ethyl phenylpropiolate and stated that the reaction products were 3-methyl-5-phenyl-1-(1-phthalazinyl)pyrazole **7** and 1-(1-phthalazinyl)-3-phenyl-5-pyrazolone, **8**, respectively (Scheme III) [11].

Scheme III



These structure assignments and results seemed improbable in the light of earlier findings [1,10].

Thus, when repeating the reaction of **1** with benzoylacetone by following the reported conditions [11], an orange compound, **9**, was isolated, mp = 132-134° (methanol) (lit [11] mp = 125° (ethanol)). On the basis of its elemental analysis and the exact mass value of m/e 304.1336 (RI = 32.82%) for the molecular ion, this compound has the molecular formula $C_{18}H_{16}N_4O$, that is one molecule of water less than the sum of the two reactants. Due to its ir spectroscopic behavior, it is necessary to consider separately the results obtained for this compound when in the solid state or when in solution (Figure 2). In the solid state,

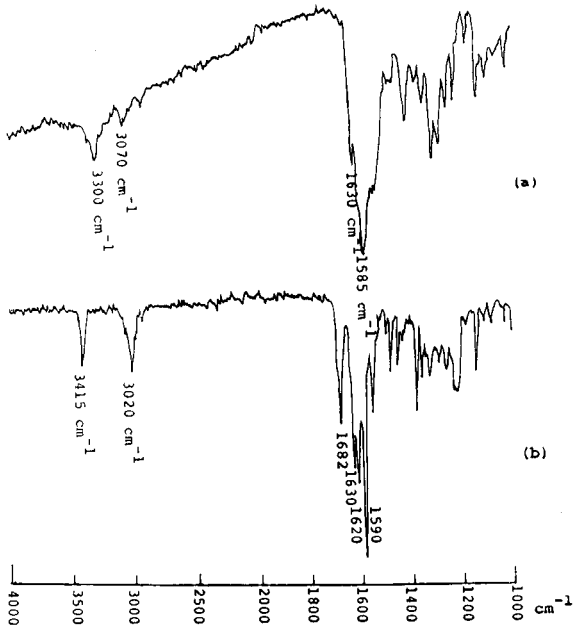
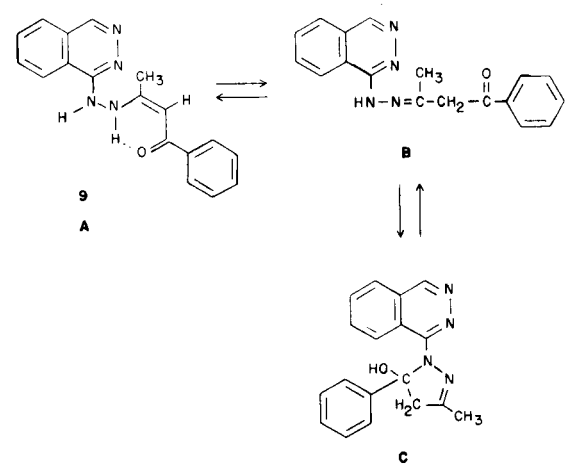


Figure 2. The ir-spectra of the orange crystals, mp = 132.134° (from the reaction of **1** + $PhCOCH_2COCH_3$); (a) in potassium bromide; (b) in chloroform solution.

the enhydrazine tautomer **9A** can be recognized by the presence of a C=O band at 1630 cm^{-1} and a NH band at 3300 cm^{-1}. The rather low frequency of the peak due to the carbonyl group is caused by intramolecular hydrogen bonding between the carbonyl and the amino group.



Evaluation of the ir spectral data of **9** in chloroform solution, namely the appearance of the two carbonyl bands at 1682 cm^{-1} (hydrazone) and 1630 cm^{-1} (enhydrazine), point to the existence of at least two side chain tautomers, **9A** and **9B**. The occurrence of a ring-chain tautomer, **9C**, in addition to the enhydrazine-hydrazone tautomers becomes evident by the ^{1}H-nmr spectrum of **9**. The presence of two CH_2 signals and one =C*H* signal is best explained by assuming that **9A, 9B**, and **9C** are present in solution. Moreover, ^{13}C-nmr evidence corroborates on these structural assignments. The ^{13}C-nmr exhibits 42 signals indicating the presence of three C_{14} species. It shows signals for three different CH_3 groups at δ 17.219, 18.524, and 24.210 (q), signals for two -CH_2-groups at 42.644 and 49.383 (t), and one signal caused by a CH group at 93.174 ppm (d). The two carbonyl carbon atoms are responsible for signals at 179.561 (s) and 196.348 (s) ppm for tautomers **9B** and **9A**, respectively.

A quantitative study by ^{1}H-nmr spectrosocopy showed that, in non-polar solvents like deuteriochloroform, the ring tautomer **9C** is the predominant species, but its abundance decreases in dipolar aprotic solvents like dimethyl sulfoxide-d_6 (Table II). These results agree with results of our previous studies [5] in this area.

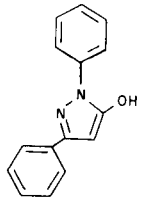
The chemical behavior of **9** also is best interpreted in terms of this tautomeric equilibrium. Thus, **9** is converted to a mixture of 3-methyl-5-phenyl-1-(1-phthalazinyl)pyrazole, **7**, and 3-methyl-*s*-triazolo[3,4-*a*]phthalazine, **10**, by the action of acid (Scheme IV). Using *p*-toluene sulfonic acid and benzene as a solvent, **10** was found to be the major product >90% yield; traces of **7** were detected by tlc. However, a significant amount of **7** (32% yield) was formed utilizing PPA, though **10** still represented a large portion of the yield (37%).

Table II

^{1}H-NMR Spectra of Compound **9** [a]

Solvent	CH_3	CH_2	=C*H*	Ar*H*	Deuterium oxide exchangeable protons (N*H*, O*H*)	Relative Abundance %
Deuteriochloroform	2.167	4.033	5.800	7.167-8.1	9.667	A 25.2
	2.267	4.333			10.100	B 31
	2.333				10.400	C 43.8
					14.633	
Dimethyl Sulfoxice-d_6	2.167	4.167	5.967	7.367-8.4	11.333	A 22.0
	2.183	4.317			11.533	B 52.5
	2.317				11.667	C 25.5
					14.033	

[a] Concentration of **9** was 0.252 mole/ℓ.



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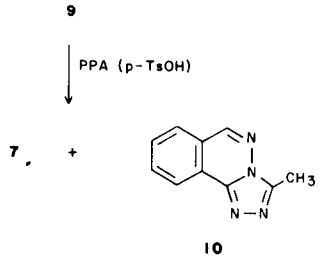
Scheme IV



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Treatment of **1** with ethyl phenylpropiolate, under the conditions reported previously [11] afforded in our hands an orange compound **11**, mp = 118° (methanol) (lit [11] mp = 122°, ethanol) (Scheme V). However, neither the elemental analysis nor spectroscopic data of the product isolated by us is compatible with the structural assignment as a pyrazolone, **8** [11]. The mass spectrum of our compound showed the molecular ion at m/e 334 $(C_{19}H_{18}N_4O_2)^{+\cdot}$; RI = 10.74% whereas **8**, should show a molecular ion at m/e 288. Our compound undergoes further loss of $C_2H_5O\cdot$ and C_2H_5OH to give ions at m/e 289 (6.55%) and m/e 288 (12.03) as a result of a typical ethyl ester fragmentation. The base peak at m/e 247 $(C_{15}H_{11}N_4)^+$ was attributed to an elimination process involving C_2H_5OH and C_6H_5. Further conclusive evidence in support of the structure of this orange product as ethyl β-(1-phthalazinylhydrazono)benzenepropanoate, **11**, is provided by its ^{1}H-nmr-spectrum in dimethyl sulfoxide-d_6 solution (see Experimental).

Since several pyrazolones possess valuable analgesic, antipyretic as well as antiinflammatory activities [15] we attempted the synthesis of **8**.

As anticipated, **11** is formed more conveniently and in higher yield when **1** as the free base reacts with ethyl benzoylacetate in alcoholic solution. A dehydrative cyclization by the action of PPA on **11** afforded the desired **8** in nearly quantitative yield (Scheme V). This compound is completely different from **11** and thus, we suspect that Soliman and Feid-Allah [11] did not synthesize the pyrazolone **8**, but mistakenly assigned a pyrazolone structure to **11**. The basis for the structural assignment of **8** synthesized by us is as follows. First, the high-resolution mass spectrum shows the expected molecular ion at m/e 288.0998 $(C_{17}H_{12}N_4O)^{+\cdot}$. The fragmentaion pattern is summarized in Table III.

Table III

Exact Mass Spectral Data of Compound **8**

m/e (Experimental)	M/e (Theoretical)	Relative Intensity, %	Elemental Composition
288.0998	288.10126	100	$C_{17}H_{12}N_4O$
247.0977	247.09853	46.18	$C_{15}H_{11}N_4$
211.0605	211.06211	25.55	$C_{11}H_7N_4O$
144.0522	144.05628	2.72	$C_8H_6N_3$
129.0451	129.04535	18.84	$C_8H_5N_2$
104.0494	104.05008	11.61	C_7H_6N
103.0423	103.04225	62.72	C_7H_5N
89.0390	89.03915	18.36	C_7H_5

Second, its ^{13}C-nmr (dimethyl sulfoxide-d_6) shows as expected 13 signals. For comparison, the corresponding pyrazolone derived of phenylhydrazine, **12**, also was synthesized and its ^{13}C-nmr spectrum taken. Both spectra are very similar (Table IV). The absence of a signal in the carbonyl region of both compounds is noteworthy and permits assignment of their structures as being the OH tautomers [16,17].

Table IV

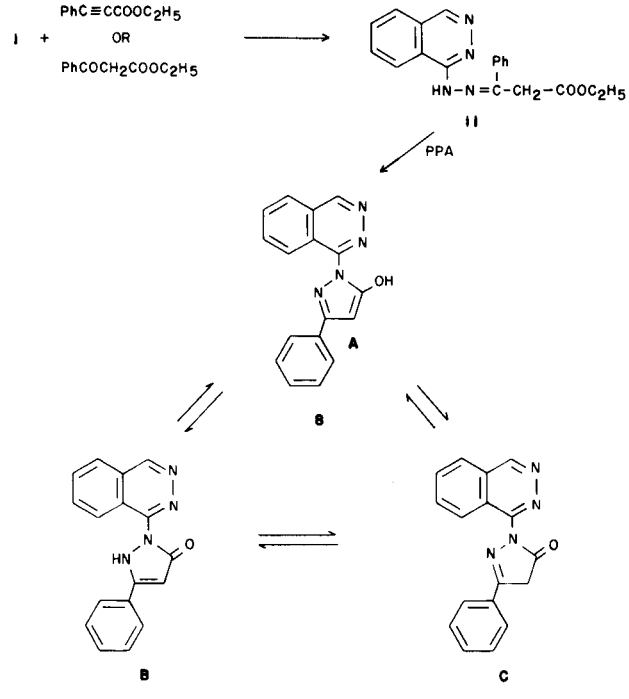
Decoupled ^{13}C-NMR Spectra of Compounds **8** and **12**

# of peak	Chemical Shifts in PPM	
	8	**12** [18]
1	156.950	154.253
2	152.204	149.938
3	151.934	139.151
4	134.028	133.650
5	133.812	128.796
6	133.165	128.095
7	128.904	125.883
8	128.688	125.398
9	127.178	121.353
10	125.614	85.486
11	125.128	
12	122.863	
13	85.055	

According to ir spectral evidence **8** occurs in the solid state either as a mixture of two tautomers, **8A** and **8B**, or as an intermediate structure between these two forms which is caused by a proton transfer in the crystal [18].

The possibility that the ir spectrum of **8** can be interpreted in terms of a chelation as in **8A** involving the OH group of the pyrazole moiety and the N-atom of the 2-position in the phthalazine ring, as was suggested for a similar compound [19], also has to be considered. However, we feel that our data are not sufficient to decide between these possibilities.

Scheme V



EXPERIMENTAL

General.

Melting points were determined with a Fischer-Johns and/or Melt-Temp melting point apparatus and are uncorrected. Infrared spectra (ir) were recorded using a Perkin-Elmer Model 599 spectrometer calibrated against 1601 cm^{-1} band of polystyrene. The ^{1}H-nmr spectra were recorded on a Varian T-60 spectrometer. The ^{13}C-nmr spectra were recorded on a Bruker HFX-90 (22.6 MHz) with MODCOMP-II data system and/or a Nicolet NT300 narrow-bore spectrometer (75.5 MHz), with 1180 E data system. Chemical shifts are expressed in δ relative to tetramethylsilane as internal standard; ms data were obtained on a Perkin-Elmer RMU-7 mass spectrometer and/or a Kratos MS80 instrument with a DS-55 data system. Elemental analyses were performed at M-H-W Laboratories, Phoenix, Arizona.

General Procedures for the Preparation of 3-(2-Oxo-2-substituted ethyl)-4*H*-*as*-triazino[3,4-*a*]phthalazin-4-one (**4A**) and/or Tautomer (**4B**).

A) To an aqueous solution of **1** hydrochloride was added an equivalent amount of the sodium salt of a type **3** compound. The reaction mixture was allowed to reflux for 8-10 hours. After cooling, the resulting solid was filtered off and recrystallized from a suitable solvent.

B) A solution of an equivalent amount of **1** and a type **2** compound in ethanol was refluxed for 30 minutes. The material that separated was filtered off and washed with ethanol. This product was identical with the one obtained by method (A).

C) The hydralazone type **5** was placed in an oil-bath at 150° for 15 minutes. After cooling, the residue was triturated with ethanol, filtered off and recrystallized from a suitable solvent. Again, the product was identical with the products prepared by methods (A) and (B).

3-(2-Oxo-2-phenylethyl)-4*H*-*as*-triazino[3,4-*a*]phthalazine-4-one (**4a**).

Compound **4a** was obtained in a yield of 32% (method B), mp = 299-300° (*N,N*-dimethylformamide); ir (potassium bromide): 1710, 1665 cm^{-1}.

Anal. Calcd. for $C_{18}H_{12}N_4O_2$: C, 68.34; H, 3.82; N, 17.71. Found: C, 68.15; H, 4.04; N, 17.72.

3-[2-Oxo-2-(3,4-dimethoxyphenyl)ethyl]-4*H*-*as*-triazino[3,4-*a*]phthalazin-4-one (**4b**).

Compound **4b** was obtained in a yield of 68% (method A), mp = 305° (*N,N*-dimethylformamide); ir (potassium bromide): 1715 cm^{-1}.

Anal. Calcd. for $C_{20}H_{16}N_4O_4$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.69; H, 4.31; N, 14.89.

3-[2-Oxo-2-(2,5-dimethylphenyl)ethyl]-4*H*-*as*-triazino[3,4-*a*]phthalazin-4-one (**4c**).

Compound **4c** obtained in a yield of 67% (method A), mp = 192° (methanol); ir (potassium bromide): 1720 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 2.3, 2.4 (2s, 6H, 2C*H*$_3$), 4.63 (s, 0.44H, -C*H*$_2$-), 6.27 (s, 0.77H, =C*H*), 7.27, 7.9 (2m, 8H, Ar*H*), 14.1 (br s, 0.77H, N*H* is deuterium oxide exchangeable).

Anal. Calcd. for $C_{20}H_{16}N_4O_2$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.78; H, 4.66; N, 16.14.

3-[2-Oxo-2-(4-chlorophenyl)ethyl]-4*H*-*as*-triazino[3,4-*a*phthalazin-4-one (**4d**).

Compound **4d** was obtained in a yield of 78% (method A), mp = 273-275° (*N,N*-dimethylformamide); ir (potassium bromide): 1718 cm^{-1}.

Anal. Calcd. for $C_{18}H_{11}ClN_4O_2$: N, 15.97. Found: N, 15.98.

3-(2-Oxo-3,3-dimethylbutyl)-4*H*-*as*-triazino[3,4-*a*]phthalazin-4-one (**4e**).

Compound **4e** was obtained in a yield of 92% (method C), mp = 205° (methanol): ir (potassium bromide): 1720, 1696 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 1.17, 1.23 (2s, 9H, (C*H*$_3$)$_3$C-), 4.22 (s, 0.74H, -C*H*$_2$-), 6.1 (s, 0.63, H, =C*H*), 7.70, 7.93, 8.50, 9.03 (m, m, s, s, resp. 5H, Ar*H*), 13.7 (s, 0.63H, N*H* is deuterium oxide exchangeable).

Anal. Calcd. for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.76; H, 5.53; N, 18.71.

Ethyl 2-(4-Oxo-4*H*-*as*-triazino[3,4-*a*]phthalazin-3-yl)acetate (**4f**).

Compound **4f** was obtained in a yield of 62% (method A), mp = 210° (methanol); ir (potassium bromide): 1728, 1690 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 1.23 (t, 3H, -O-CH_2-CH_3), 4.00 (s, 2H, -CH_2-CO), 4.2 (q, 2H, -O-CH_2-CH_3), 8.35, 9.03, 9.40 (m, m, s, 5H, Ar*H*).

Anal. Calcd. for $C_{14}H_{12}N_4O_3$: C, 59.15; H, 4.26; N, 19.71. Found: C, 59.21; H, 4.29; N, 19.82.

3-[2-Oxo-2-(2-thionyl)ethyl]-4*H*-*as*-triazino[3,4-*a*]phthalazin-4-one (**4g**).

Compound **4g** was obtained in a yield of 60% (method A), mp = 282° (*N,N*-dimethylformamide): ir (potassium bromide): 1710 cm^{-1}.

Anal. Calcd. for $C_{16}H_{10}N_4O_2S$: C, 59.61; H, 3.13; N, 17.38. Found: C, 59.39; H, 3.36; N, 17.17.

3-[2-Oxo-2-(3-pyridinyl)ethyl]-4*H*-*as*-triazino[3,4-*a*]phthalazin-4-one (**4h**).

Compound **4h** was obtained in a yield of 56% (method A), mp = 301° (*N,N*-dimethylformamide): ir (potassium bromide): 1720 cm^{-1}.

Anal. Calcd. for $C_{17}H_{11}N_5O_2$: C, 64.35; H, 3.49; N, 22.07. Found: C, 64.13; H, 3.28; N, 21.92.

General Procedure for the Preparation of Ethyl 4-Oxo-2-(1-phthalazinylhydrazono)-substituted butanoate (**5**).

(A) The general procedure is the same as method A above except that the reaction mixture was allowed to warm for 5-10 minutes.

(B) It was obtained from the mother liquor together with the *as*-triazinophthalazine prepared by method B above.

Ethyl 4-Oxo-2-(1-phthalazinylhydrazono)benzenebutanoate (**5a**).

Compound **5a** was obtained in a yield of 70% (method A), 47% (method B), mp = 160° (methanol); ir (potassium bromide): 3230, 1695, 1670 cm^{-1}; ms: M$^+$ = 362 (34), 343 (16), 316 (17), 289 (100), 257 (44), 211 (12), 183 (10), 158 (14), 131 (19), 105 (70), 77 (23); ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 1.3 (t, 3H, -O-CH_2-CH_3), 4.3 (q, 2H, -O-CH_2-CH_3), 4.6 (s, 2H, -CH_2CO-), 7.83 (m, 10 H, Ar*H*), 12.07 (s, 1H, N*H* is deuterium oxide exchangeable).

Anal. Calcd. for $C_{20}H_{18}N_4O_3$: C, 66.28; H, 5.01; N, 15.46. Found: C, 66.24; H, 5.07; N, 15.56.

Ethyl 5,5-Dimethyl-4-oxo-2-(1-phthalazinylhydrazono)hexanoate (**5e**).

Compound **5e** was obtained in a yield of 66% (method A); mp = 158° (methanol); ir (potassium bromide): 3230, 1728, 1700 cm^{-1}; ms: M$^+$ = 343 (10), 296 (19), 269 (20), 258 (11), 257 (32), 240 (16), 239 (85), 212 (18), 211 (28), 185 (17), 184 (12), 144 (100), 131 (23), 129 (23), 128 (17), 115 (15), 103 (17), 80 (18), 57 (18); ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 1.1 (s, 9H, $(CH_3)_3$-C-), 1.2 (t, 3H, -O-CH_2-CH_3), 4.13 (s, 2H, -CH_2-CO), 4.17 (q, 2H, -OCH_2-CH_3), 7.77, 8.23 (2m, 5H, Ar*H*), 11.8 (s, 1H, N*H* is deuterium oxide exchangeable).

Anal. Calcd. for $C_{18}H_{22}N_4O_3$: C, 63.14; H, 6.48; N, 16.36. Found: C, 63.13; H, 6.32; N, 16.55.

Diethyl 2-(1-Phthalazinylhydrazono)succinate (**5f**).

Compound **5f** was obtained in a yield of 7% (method A); upon filtering off the reaction product and washing it with methanol compound **5f** went in solution and was isolated upon evaporation of the filtrate, the remaining, in methanol insoluble residue, proved to be the triazinophthalazine **4f**, mp = 111° (methanol-water); ir (potassium bromide): 3220, 1720, 1690 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.23, 1.4 (2t, 6H, 2 CH_3CH_2O-), 4.03 (s, 2H, =C-CH_2-CO-), 4.17, 4.4 (2q, 4H, 2 CH_3CH_2O-), 7.7, 8,07, 8.47 (m, s, m, 5H, Ar*H*); 11.1 (s, 1H, NH deuterium oxide exchangeable); ms: M$^+$ = 330.1334 (Calcd. 330.13294).

Anal. Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.04; H, 5.26; N, 17.07.

3-Ethoxycarbonyl-*s*-triazolo[34,-*a*]phthalazine (**6**).

A hot solution of **2a** 0.5 g (0.002 mole) in 25 ml methanol was treated with **1** hydrochloride 0.4 g (0.002 mole) and the reaction mixture was refluxed for 2 hours. While still hot, a small amount or an orange precipitate which was identified as **4a** was filtered off and the filtrate concentrated. Upon cooling colorless crystals deposited (yield 52%). They were recrystallized from methanol, mp = 230°; ir (potassium bromide): 1730 cm^{-1}; ms: M$^+$ = 242 (11.46), 197 (16.27), 171 (10.26), 170 (46.70), 142 (7.24), 141 (6.33), 129 (8.33), 115 (100.00), 114 (20.90), 102 (6.89), 88 (16.51), 63 (10.91); ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 1.43 (t, 3H, CH_3-CH_2O-), 4.5 (q, 2H, CH_3-CH_2O-), 8.13-8.73 (m, 4H, Ar*H*), 9.3 (s, 1H, N=C*H*). Compound **6** has a R_f value of 0.772 from methanol:ether (8:2) mixture.

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.42; H, 4.23; N, 23.08.

Reaction of **1** with Benzoylacetone.

A solution of 1.6 g of **1** and 1.62 g of benzoylacetone in 30 ml ethanol was heated on a steam bath for 1 hour then concentrated and left to cool. The solid product, **9**, was filtered off, washed with cooled methanol and dried, yield = 80%; orange crystals mp = 132-134° (methanol); ir (potassium bromide): 3300, 3070, 1630, 1585 cm^{-1}; ir (chloroform): 3415, 3020, 1682, 1630, 1620, 1590 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.167, 2.267, 2.333 (2s, 3CH_3), 4.033, 4.33 (2s, 2-CH_2), 5.800 (s, =C*H*), 7.167-8.1 (m, Ar*H*), 9.667, 10.100, 10.400, 14.633 (4s br, N*H*, O*H* deuterium oxide exchangeable) [**9A:9B:9C** = 25.2:31:43.8]; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 2.167, 2.183, 2.317 (3s, 3CH_3), 4.167, 4.317 (2s, 2CH_2), 5.967 (s, =C*H*), 7.367-8.4 (m, ArH), 11.333, 11.533, 11.667, 14.033 (4s br, N*H*, O*H* deuterium oxide exchangeable) [**9A:9B:9C** = 22.0:52.5:25.5]; ms: M$^+$ = 304.1336 (32.82), 289.1095 (30.83), 287.1285 (13.51), 285.1145 (76.13), 274.1105 (21.57), 199.0991 (34.64), 185.0825 (70.29), 184.0730 (47.73), 120.0559 (13.53), 115.0430 (23.38), 105.0337 (38.76), 77.0384 (28.67).

Anal. Calcd. for $C_{18}H_{16}N_4O$: C, 71.03; H, 5.30; N, 18.41. Found: C, 71.26; H, 5.42; N, 18.42.

Reaction of **9** With Acids.

1. To a solution of 0.78 g of **9** in 80 ml of benzene, a few crystals of *p*-toluene-sulfonic acid were added. the reaction mixture was refluxed for 96 hours and the generated water collected. The benzene was distilled off, the residue was neutralized by an aqueos sodium bicarbonate solution and extracted with several portions of chloroform. After washing with water and drying over anhydrous sodium sulfate, the chloroform was evaporated *in vacuo* to give **10** in a yield of 90%.

2. Solid **9** (1.08 g) was treated with **3** g PPA and heated on a steam bath for 25 minutes, diluted with water, neutralized with sodium bicarbonate and extracted several times with chloroform. After washing with water, the chloroform solution was dried over anhydrous sodium sulfate and evaporated *in vacuo*. The tlc analysis of the remainder showed 5 spots. The two most intense ones were separated by hplc on silica gel using ether-methanol (9:1) as an eluent and shown to be the known 3-methyl-*s*-triazolo[3,4-*a*]phthalazine, **10** (yield = 37%) and 3-methyl-5-phenyl-1-(1-phthalazinyl)pyrazole, **7** (yield = 32%); mp = 129° (ether).

Anal. Calcd. for $C_{18}H_{14}N_4$: C, 75.50; H, 4.93; N, 19.57. Found: C, 75.42; H, 4.96; N, 19.59.

Ethyl β-(1-Phthalazinylhydrazino)benzenepropanoate (**11**).

(A) To a solution of 1.6 g of **1** in 25 ml ethanol was added 1.74 g of ethyl phenylpropiolate, refluxed for 1 hour and concentrated. After cooling, the product was filtered off and dried (yield = 52%); mp = 118° (methanol); ir (potassium bromide): 3280, 1730 cm^{-1}; ms (70 eV): M$^+$ = 334 (10.74), 289 (6.55), 288 (12.03), 247 (100), 211 (4.09), 131 (10.16), 104 (10.60), 103 (24.59), 77 (15.70); ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 1.13 (t, 3H, CH_3CH_2O-), 4.1 (q, 2H, CH_3CH_2O-), 4.13 (s, 2H, CH_2-), 7.43, 7.77, 8.17 (3m, 10H, Ar*H*), 12.07 (s 1H, N*H* is deuterium oxide exchangeable).

Anal. Calcd. for $C_{19}H_{18}N_4O_2$: C, 68.24; H, 5.42; N, 16.76. Found: C, 68.13; H, 5.28; N, 16.80.

(B) A solution of 2 g of **1** and 2.4 g of ethyl benzoylacetate in 50 ml ethanol was refluxed for 2 hours. After cooling, the product was filtered off and dried; yield = 74%. It was found to be identical in all respects with that synthesized by method A.

1-(1-Phthalazinyl)-3-phenyl-5-hydroxypyrazole (**8**).

A 1 g amount of **11** was treated with 2 g of PPA. The mixture was heated on a steam bath for 16 minutes and diluted with water. The resulting precipitate was filtered off and dried (yield 90%); mp = 180° (ligroin 90-120°); ir (potassium bromide): 3600-2000 cm^{-1} (broad band), 1620, 1600, 1580 cm^{-1}.

Anal. Calcd. for $C_{17}H_{12}N_4O$: C, 70.82; H, 4.20; N, 19.44. Found: C, 70.81; H, 4.32; N, 19.66.

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