(2) This is also part VII in the series entitled Terpenes. Part VI: R. T. Gray and H. E. Smith, *Tetrahedron*, **25**, 3161 (1969).
(3) Taken in part from the Ph.D. Thesis of E.H.M., Vanderbilt University, Jan 1966.
(4) (a) Vanderbilt University; (b) Tennessee State University.
(5) National Defense Education Act Fellow, 1961–1964.
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Synthesis of Condensed Heterocyclic Systems. VI.[1a] Some Ring Closure Reactions Involving 1-Hydrazinophthalazine

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The acylation of 1-hydrazinophthalazine (**1**, hydralazine) with mono-, di-, tri-, and tetracarboxylic acids and acid derivatives gave 3-substituted *s*-triazolo[3,4-*a*]phthalazines; use of *p*-nitrophenol esters of carboxylic acids facilitates the dehydrative cyclization reaction and enlarges the scope of this type of reaction considerably. Though the annelation of five-membered rings to the phthalazine ring proceeds with exceptional ease, fusion of a six-membered ring to this system proceeds with difficulties only. Annelation of larger rings met with failure.

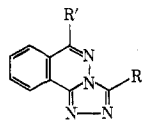
As the result of work by our group[2–5] and others[6–8] on the determination and clarification of the structure of human metabolites of **1**, a common hypotensive agent, we were prompted to investigate in detail the reaction between **1** and a variety of acylating agents. Originally,[7] it had been proposed that **1** undergoes enzymatic acetylation to give 1-(2-acetylhydrazino)phthalazine (**2**, R = CH_3; R′ = H). However, it has subsequently been shown independently by two groups[3,8] that enzymatic acetylation instead leads to 3-methyl-*s*-triazolo[3,4-*a*]phthalazine (**3**, R = CH_3; R′ = H). It has also been found that attempts to synthesize **2** under a variety of conditions[3] failed and always yielded the cyclized product **3**. This seems to be unique for the phthalazine system. In other cases, e.g., the acylation of 1-aminomethylisoquinoline[9] and corresponding benzoisoquinoline and benzoquinoline compounds,[10] the expected amides were obtained as stable and isolable compounds. These amides underwent dehydrative cyclization only upon catalysis by strong mineral or Lewis acids. It was, therefore, decided to investigate the acylation of **1** with a variety of acids and acid derivatives to determine whether ring closure to 3-substituted *s*-triazolo[3,4-*a*]phthalazines is in all cases the product in this type of reaction or if it is only typical for the acetylation reaction. Consequently, the acylation of **1** was studied using a variety of mono-, functional mono-, and dicarboxylic acids and derivatives as well as a tri- and a tetracarboxylic acid ester. In addition, attempts were made to fuse six-, seven-, and eight-membered rings to the phthalazine system.

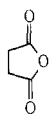
In agreement with earlier investigators[11] we also found that the acid chloride–$POCl_3$ method for achieving dehydrative cyclization to yield the *s*-triazolo system is not a general one and often not suitable at all owing to instability of the acid chlorides. We found that *p*-nitrophenol esters of such acids are excellent materials for the projected reaction, undergoing amide formation and ring closure under very mild conditions. Use of these esters extends the scope of this cyclization reaction considerably.

***s*-Triazolo[3,4-*a*]phthalazines from Monocarboxylic Acid Derivatives.** In every case, the reaction of monocarboxylic acids or acid derivatives with widely varying R groups (Table I) led to the formation of 3-substituted *s*-triazolo[3,4-*a*]phthalazines (**3**, R′ = H) (Scheme I). The scope of this reaction is shown by the substituents in **3** shown in Table I. A unique acylation agent, trichloroacetonitrile, was also used to prepare 3-trichloromethyl-*s*-triazolo[3,4-*a*]phthalazine although in poorer yield than with the acid. This reaction involving the nitrile is analogous to the formation of **3** (R = NH_2; R′ = H) from cyanogen bromide.[11]

In agreement with previous work,[11] the acylation of 1,4-dihydrazinophthalazine (**1**, R = R′ = $NHNH_2$) does not yield by a double ring closure reaction the bis-*s*-triazolo[3,4-*a*:4,3-*c*]phthalazine system (**4**, R = CF_3), but a mixture of

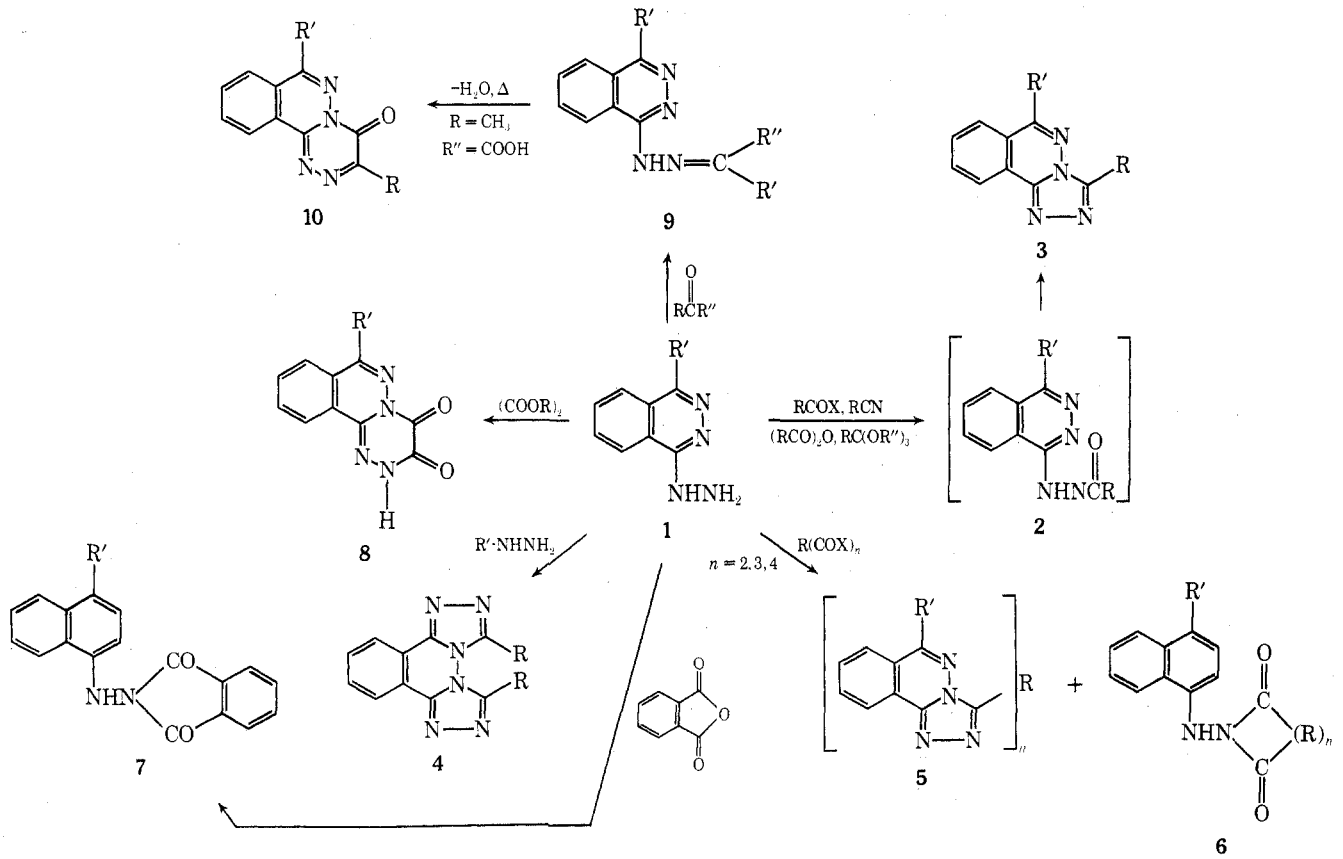
Table I
Reactions of Hydralazine with Various Acids and Acid Derivatives[a]



Acid derivative	Registry no.	R	R'	Molecular formula	Mp, °C	Yield, %	Method of prepn[g]
$Cl_3CC{\equiv}N$	545-06-2	CCl_3	H	$C_{10}H_5Cl_3N_4$	252–253	61[b]	A-1
Cl_3CCOOH	76-03-9	CCl_3	H	$C_{10}H_5Cl_3N_4$	252–253	82[b]	B-1
CF_3COCCF_3 (O O)	407-25-0	CF_3	H	$C_{10}H_5F_3N_4$	309–310	80[b]	C
$HSCH_2COOH$	68-11-1	CH_2SH	H	$C_{10}H_8N_4S$	170–171 dec	53[f]	A-2
PhCHOHCOOH	611-72-3	CHOHPh	H	$C_{16}H_{12}N_4O$	208–209	72[b]	B-2
	108-30-5	$(CH_2)_2COOH$	H	$C_{12}H_{10}N_4O_2$	302–304 dec	81[c]	B-3
$(CH_3)_3COCl$	3282-30-2	$C(CH_3)_3$	H	$C_{13}H_{14}N_4$	192–193	22[d]	D
$CF_3CCOCCF_3$ (O O)	96-63-9	CF_3	$N_2H_2COCF_3$	$C_{12}H_6F_6N_6O$	309.5–310.5	43[d]	A-1
		CF_3	N_2H_3	$C_{10}H_7F_3N_6$	324 dec	23[e]	

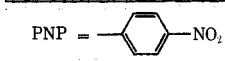
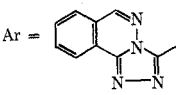
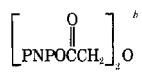
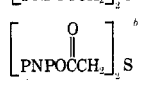
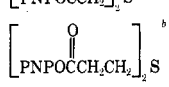
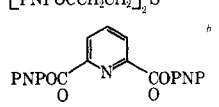
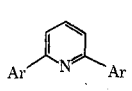
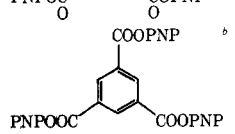
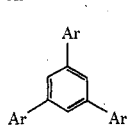
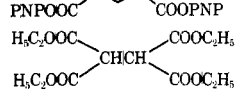
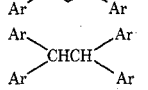
[a] Satisfactory analytical data (±0.4% in C, H, N) for all compounds in Tables I–III were submitted for review: Ed. [b] Recrystalized from ethanol. [c] From dimethylformamide. [d] From ethanol–water. [e] From methanol–water. [f] Vacuum sublimation at 140° (0.1 mm). [g] A-1, refluxed in acid derivative for 24 hr; A-2, refluxed in acid for 90 min; B-1, melt solution at 100° for 1 hr; B-2, melt solution at 130° for 1 hr; B-3, melt solution at 160–180° for 1 hr; C, stirred with anhydride at 5° for 2 hr; D, stirred with acid chloride in THF in presence of sodium acetate.

Scheme I
Some Compounds Derived from 1-Hydrazinophthalazine



3-trifluoromethyl-*s*-triazolo[3,4-*a*]phthalazin-6-yltrifluoroacetic acid hydrazide (**3**, R = CF_3; R' = $NHNHCOCF_3$) and 3-trifluoromethyl-6-hydrazino-*s*-triazolo[3,4-*a*]phthalazine (**3**, R = CF_3; R' = $NHNH_2$), the latter compound presumably arising from basic hydrolysis during work-up. Evidently, the steric repulsion between two trifluoromethyl groups at C_3 and C_6 in **4** prohibits annelation of a second *s*-triazolo ring; thus steric hindrance rather than electronic effects seemed to have prevented the ring formation in this case. However, use of the bulky pivaloyl chloride as acylat-

Table II
Reaction of Hydralazine with Esters and Activated Esters

Acid derivative	Registry no.	Product	Molecular formula	Mp, °C	Yield, %	Method of prepn[g]
PNP =  Ar = 						
PNPOC(CH$_2$)$_n$COPNP						
n = 1[a]	141-82-2	ArCH$_2$Ar	C$_{19}$H$_{12}$N$_8$	337–338	82[c]	A
n = 2[a]	110-15-6	Ar(CH$_2$)$_2$Ar	C$_{20}$H$_{14}$N$_8$	330–331	95[c]	A
n = 3[a]	110-94-1	Ar(CH$_2$)$_3$Ar	C$_{21}$H$_{16}$N$_8$	272–273	97[c]	A
n = 4[a]	124-04-9	Ar(CH$_2$)$_4$Ar	C$_{22}$H$_{18}$N$_8$	261–262	94[c]	A
n = 5[a]	111-16-0	Ar(CH$_2$)$_5$Ar	C$_{23}$H$_{20}$N$_8$	215–216	80[c]	A
	56173-23-0	ArCH$_2$OCH$_2$Ar[e]	C$_{20}$H$_{14}$N$_8$O·$^1/_4$H$_2$O	312–313	83[c]	A
	56173-24-1	ArCH$_2$SCH$_2$Ar	C$_{20}$H$_{14}$N$_8$S	283–284 dec	72[c]	A
	56173-25-2	ArCH$_2$CH$_2$SCH$_2$CH$_2$Ar	C$_{22}$H$_{18}$N$_8$S	241–243	72[c]	A
	56173-26-3		C$_{23}$H$_{13}$N$_9$	342–343 dec	76[c]	A
	56173-27-4		C$_{33}$H$_{18}$N$_{12}$	341–343 dec	96[c]	A
	632-56-4		C$_{38}$H$_{22}$N$_{16}$·2H$_2$O	≥200 dec	28[d]	B

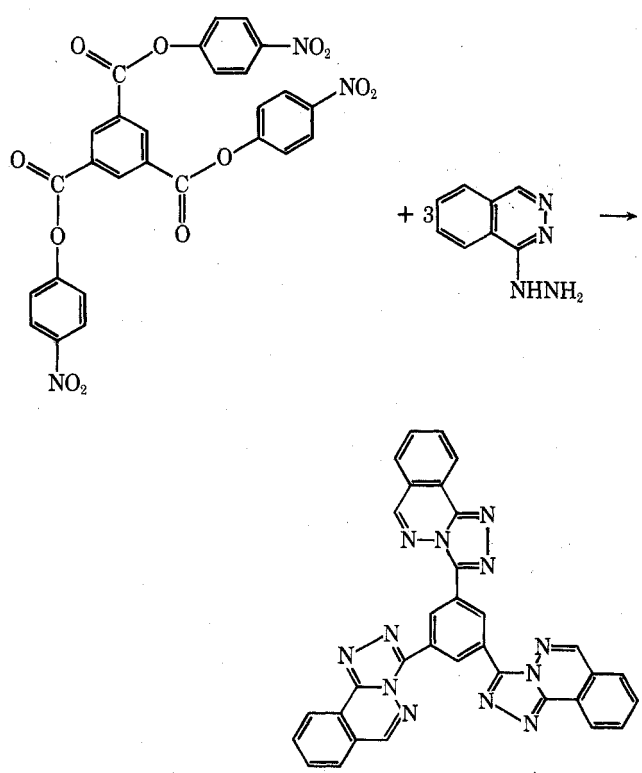
[a] Prepared from acid chloride and *p*-nitrophenol. [b] Prepared from acid and *p*-nitrophenyltrifluoroacetate in pyridine. [c] Recrystalized from dimethylformamide. [d] From dimethylformamide–water. [e] Anal. Calcd for C$_{20}$H$_{14}$N$_8$O·$^1/_4$H$_2$O: C, 61.91; H, 3.77; N, 29.62. Found: C, 61.92; H, 3.64; N, 29. [f] Anal. Calcd for C$_{38}$H$_{22}$N$_{16}$·2H$_2$O: C, 6178; H, 3.55; N, 30.34. Found: C, 61.97; H, 3.53; N, 29. [g] A, dimethylformamide solvent at 30° for 24 hr; B, dimethylformamide solvent at reflux for 24 hr.

ing agent gave only 3-*tert*-butyl-*s*-triazolo[3,4-*a*]phthalazine (**3**, R = Me$_3$ C; R′ = H), indicating that mono ring closure is not prone to steric hindrance.

***s*-Triazolo[3,4-*a*]phthalazines from Di-, Tri-, and Tetracarboxylic Acid Derivatives.** A series of α,ω-bis(3-*s*-triazolo[3,4-*a*]phthalazinyl)alkanes [**5**, R = (CH$_2$)$_{1-5}$, n = 2] was prepared from *p*-nitrophenyl esters of malonic, succinic, glutamic, adipic, and pimelic acid, respectively, by treating 1 equiv of the ester with 2 equiv of **1** at 30° in dimethylformamide as solvent. Similarly, from *p*-nitrophenyl diglycolate, *p*-nitrophenyl thiodiglycolate, *p*-nitrophenyl thiodipropionate, and *p*-nitrophenyl dipicolinate were obtained 1,1′-bis(3-*s*-triazolo[3,4-*a*]phthalazinyl)dimethyl ether (**5**, R = –CH$_2$OCH$_2$–, n = 2), 1,1′-bis(3-*s*-triazolo[3,4-*a*]phthalazinyl)dimethyl sulfide (**5**, R = –CH$_2$SCH$_2$–, n = 2), 2,2′-bis(3-*s*-triazolo[3,4-*a*]phthalazinyl)diethyl sulfide (**5**, R = –CH$_2$CH$_2$SCH$_2$CH$_2$–, n = 2), and 2,6-bis(3-*s*-triazolo[3,4-*a*]phthalazinyl)pyridine [**5**, R = 2,6-C$_5$H$_3$N$_2$, n = 2].

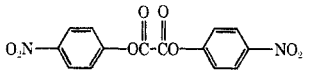
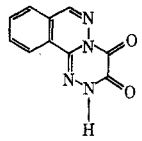
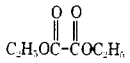
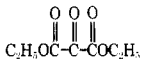
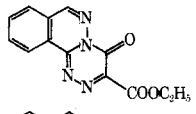
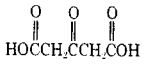
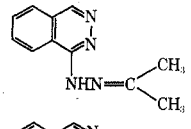
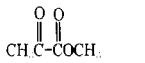
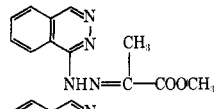
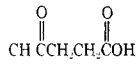
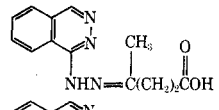
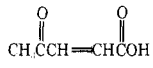
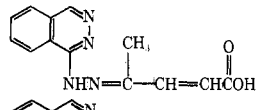
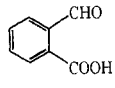
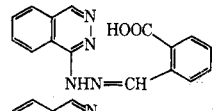
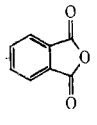
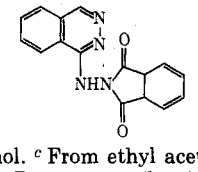
Finally, reaction of **1** with a tricarboxylic acid ester, *p*-nitrophenyl trimesitylate, in a similar fashion gave 1,3,5-tri(3-*s*-triazolo[3,4-*a*]phthalazinyl)benzene [**5**, R = 1,3,5-C$_6$H$_3$, n = 3] and with a tetracarboxylic acid ester, tetraethyl 1,1′,2,2′-ethanetetracarboxylate, in refluxing dimethylformide gave 1,1,2,2-tetra(3-*s*-triazolo[3,4-*a*]phthalazinyl)ethane dihydrate (R = >CHCH<, n = 4) (Table II).

The reactions involving the *p*-nitrophenyl esters of di- and tricarboxylic acids in ring closure reaction with **1** are rather remarkable. To our knowledge there is in the field of heterocyclic synthesis no other reaction known in which in a very high yield (up to 96%, see Table II) three cyclizations with formation of heterocyclic rings occur simultaneously, e.g.



The possibility that the reaction of the bis esters with **1** might give rise to cyclic imides of type **6** was also considered. 1-Phthalazinyl-2-phthalimidohydrazine **7** was, therefore, prepared by refluxing **1** with phthalic anhydride in dimethylformamide. Comparison of the spectral properties of **7** with those of all of the isolated products showed that no

Table III
Reaction of Hydralazine Designed to Give Fused Six- and Seven-Membered Ring Systems

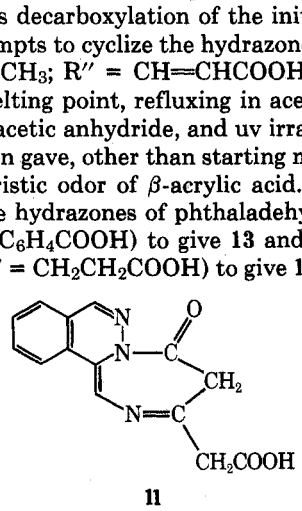
Acid derivative (aldehyde)	Registry no.	Product	Molecular formula	Mp, °C	Yield, %	Method of prepn[g]
	5070-15-5		$C_{10}H_6N_4O_2$	355[d]	91[a]	A
	95-92-1			355[d]	90[a]	B
	609-09-6		$C_{13}H_{10}N_4O_3$	233–234[d]	87[d]	C
	542-05-2		$C_{11}H_{12}N_4$	116–117[f]	98[e]	D
	600-22-6		$C_{12}H_{12}N_4O_2$	185–186	82[c]	D
	123-76-2		$C_{13}H_{14}N_4O_2$	194–195	84[c]	D
	4743-82-2		$C_{13}H_{12}N_4O_2$	202–203	81[d]	D
	119-67-5		$C_{16}H_{12}N_4O_2$	198	90[d]	D
	85-44-9		$C_{16}H_{10}N_4O_2$	297–298	40[a]	E

[a] Recrystalized from dimethylformamide. [b] From ethanol. [c] From ethyl acetate. [d] From 1-butanol. [e] Sublimed at 80° (0.1 mm). [f] Lit.[12] mp 114°. [g] A, solvent, dimethylformamide at 30° for 24 hr; B, ester at reflux for 1 hr; C, ethanol at 25° for 18 hr; D, methanol at 25° for 30 min; E, dimethylformamide at reflux for 30 min.

cyclic imides were formed in these reactions, not even when 1 was treated with large excesses of bis esters. The only product isolated beside the *s*-triazolo[3,4-*a*]phthalazines was an oxidation product of 1, namely 1,2-di(phthalazinyl)hydrazine.

The *as*-Triazino[3,4-*a*]phthalazine System. Recently[11] it was reported that the reaction of an excess of oxalic acid with 1 at 160° gave a 50% yield of *s*-triazolo[3,4-*a*]phthalazine (**3**, R = R′ = H), presumably arising from the decarboxylation of the originally formed *s*-triazolo[3,4-*a*]phthalazine-3-carboxylic acid (**3**, R = COOH; R′ = H). However, when we refluxed a solution of 1 in ethyl oxalate, the product isolated in 90% yield was not the expected ethyl *s*-triazolo[3,4-*a*]phthalazine-3-carboxylate (**3**, R = $COOC_2H_5$; R′ = H) but 2-*H*-*as*-triazino[3,4-*a*]phthalazine-3,4-dione (**8**), mp 355°, as evidenced by the analytical (Table III) and spectral data.

In 1954 Druey and Ringier[12] reported that the hydralazine hydrazone of pyruvic acid (**9**, R = CH_3; R[11] = COOH), when heated to its melting point or upon refluxing with acetic acid, undergoes cyclodehydration to give 3-methyl-*as*-triazino[3,4-*a*]phthalazine-4-one (**10**, R = CH_3), a system in which a six-membered ring has been fused to phthalazine. Formation of this system seems to be a general reaction because if 1 equv of 1 was treated with diethyl oxomalonate an 87% yield of 3-carbethoxy-*as*-triazino[3,4-*a*]phthalazin-4-one (**10**, R = $COOC_2H_5$) was obtained. However, when an attempt was made to prepare and cyclize the 1 hydralazone of β-ketoglutaric acid (**9**, R = R″ = CH_2COOH) analogously to a seven-membered fused ring system, **11**, the product isolated was found to be the 1 hydrazone of acetone, presumably arising from the spontaneous decarboxylation of the initially formed hydrazone. Attempts to cyclize the hydrazone of β-acetylacrylic acid (**9**, R = CH_3; R″ = CH=CHCOOH) to **12** by heating it to the melting point, refluxing in acetic acid, refluxing in trifluoroacetic anhydride, and uv irradiation of an ethanolic solution gave, other than starting material, an oil with a characteristic odor of β-acrylic acid. Similar attempts to cyclize the hydrazones of phthaladehydic acid (**9**, R = CH_3; R″ = O-C_6H_4COOH) to give **13** and levulinic acid (**9**, R = CH_3; R″ = CH_2CH_2COOH) to give **14** also failed.



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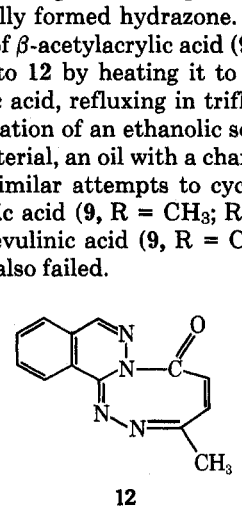

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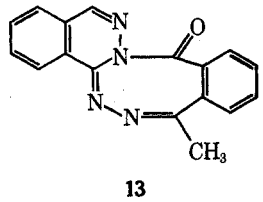

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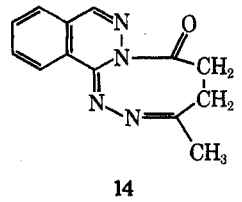

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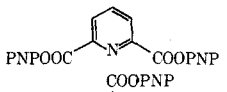
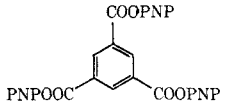
Table IV
***p*-Nitrophenyl Esters**

Ester[a]	Molecular formula	Mp, °C	Yield, %
$[PNPOOCCH_2]_2O$	$C_{16}H_{12}N_2O_9$	116–167	82
$[PNPOOCCH_2]_2S$	$C_{16}H_{12}N_2O_8S$	114.5–115.5	83
$[PNPOOCCH_2CH_2]_2S$	$C_{18}H_{16}N_2O_8S$	106.5–107.5	92
	$C_{19}H_{11}N_3O_8$	233–234	73
	$C_{27}H_{15}N_3O_{12}$	287–290	70

[a] PNP = O_2N–C$_6$H$_4$–

The exceptional ease of formation of the *s*-triazolo[3,4-*a*]phthalazine ring system in comparison to the imidazo[5,1-*a*]isoquinoline which needs strong acid catalysis to occur could be explained by a markedly higher nucleophilicity of the N atom in the 2 position of the 1-acylhydrazinophthalazines as compared to the ring nitrogen atom in acylated 1-aminomethylisoquinolines.

Experimental Section

General. All melting points were determined on a Fisher-Jones apparatus and are uncorrected. Infrared, nuclear magnetic resonance, and ultraviolet spectra were taken on a Perkin-Elmer 700, Varian T-60 or Bruker HFX-10, and a Unicam SP-800 spectrophotometer, respectively. All C, H, N analyses were obtained by Chemalytics, Tempe, Ariz. The observed values for all new compounds in Tables I–IV agreed within 0.4% with the calculated values.

Preparation of *s*-Triazolo[3,4-*a*]phthalazines from Monocarboxylic Acid Derivatives. 3-Trichloromethyl-*s*-triazolo[3,4-*a*]phthalazine. The brief procedures given in Table I in most cases should give sufficient information to achieve the preparation of the desired *s*-triazolo[3,4-*a*]phthalazines derived of monocarboxylic acids.

General Method for the Preparation of α,ω-Bis(3-*s*-triazolo[3,4-*a*]phthalazinyl)alkanes. 3-*s*-Triazolo[3,4-*a*]phthalazinyl Substituted Aromatics and 1,1,2,2-Tetra(3-*s*-triazolo[3,4-*a*]phthalazinyl)ethane (Table II). Method A. To 40 ml of DMF was added 1.0 molar equiv of the appropriate bis(*p*-nitrophenyl) ester and 2.2 molar equiv of 1·H_2O. The mixture was stirred for 24 hr at 30° (additional dimethylformamide added if the resulting slurry was too thick), and the precipitate was filtered, washed with DMF and ether, and recrystallized from DMF.

Method B. Exactly as method A, except that the DMF solution was refluxed for 24 hr.

Reactions of Hydralazine Designed to Give Six- and Seven-Membered Rings Annelated to the Phthalazine Ring System (Table III). 1-*H*-*as*-Triazino[3,4-*a*]phthalazine-3,4-dione. A. A slurry of 6.64 g (0.02 mol) of di-*p*-nitrophenyl oxalate[13] and 7.83 g (0.044 mol) of 1 in 40 ml of DMF was stirred at 30° for 24 hr, filtered, and washed with DMF and ether to yield 3.9 g (91%), based on the ester, recrystallized from DMF: mp 335° dec; ir (KBr) 3175 (N–H), 3030 (ArH), 2925 (C–H), 1720, 1670 (C=O), 1600 cm^{-1} (C=N); NMR (Me_2SO-d_6) δ 7.7–8.4, 8.7 (m, s, ArH); uv max (MeOH) sh 252, 260, 274, 286, sh 312, 328, sh 350.

B. A solution of 3.56 g (0.02 mol) of 1 in 50 ml of ethyl oxalate was refluxed for 1 hr and cooled, and the precipitate was filtered to give 3.9 g (90%), recrystallized from DMF, identical in all respects with compound prepared according to A.

3-Carboethoxy-*as*-triazino[3,4-*a*]phthalazin-4-one. To a solution of 8.7 g (0.05 mol) of diethyl oxomalonate in 10 ml of ethanol was added 8.9 g (0.05 mol) of 1 in 30 ml of ethanol. The solution was stirred for 18 hr at 25° and then refluxed for 2 hr after the addition of 20 ml of ethanol. After cooling, the yellow precipitate was filtered to give 11.75 g (87%), recrystallized from ethanol: mp 233–234° dec; ir (KBr) 3050 (ArH), 2975 (C–H), 1740 (C=O, ester), 1700 cm^{-1} (C=O); uv max (MeOH) sh 288 nm (log ε 4.04), 297 (4.17), 375 (4.16).

Hydralazine Hydrazones. These compounds were prepared according to Druey et al.[12]

Phthalaldehydic acid hydralazone was prepared from 1 and phthaldehdic acid, yield 90%, mp 198° (1-butanol). Anal. Calcd for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.53; H, 4.22; N, 19.03.

Levulinic acid hydralazone was prepared analogously from 1 and levulinic acid, yield 84%, mp 194–195° (ethyl acetate). Anal. Calcd for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.70. Found: C, 60.41; H, 5.41; N, 21.56.

β-Acetylacrylic acid hydralazone was prepared from 1 and β-acetylacrylic acid, yield 81%, mp 202–203° (1-butanol). Anal. Calcd for $C_{12}H_{12}N_3O_2$: C, 60.93; H, 4.72; N, 21.87. Found: C, 61.34; H, 4.85; N, 21.66.

Attempted Cyclizations of Hydralazine Hydrazones of β-Acetylacrylic Acid, Phthalaldehydic Acid, and Levulinic Acid. The following cyclization attempts were done with these three hydrazones. (1) The compounds were refluxed in glacial acetic acid and an equivalent amount of aquous HCl; the only observed reaction was a cleavage of the hydrazone linkage. (2) The compounds were heated and kept for about 30 min at their melting temperature. Only severe degradation was observed. (3) The compounds were irradiated in alcoholic solution with a mercury lamp with or without sensitizer, and with or without a Pyrex filter; in all cases only degradation but no cyclization was observed.

***N*-(1-Aminophthalazino)phthalimide.** A slurry of 1.0 g (0.0056 mol) of 1 and 0.83 g (0.0056 mol) of phthalic acid anhydride in 10 ml of dimethylformamide was refluxed for 30 min. The solution was cooled and the yellow precipitate filtered, digested with ethanol, filtered, and washed to give 0.65 g (40%), recrystallized from DMF: mp 297–298°; ir (KBr) 3250 (N–H), 1710, 1690 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 7.8–9.0 (m, ArH).

General Method for the Preparation of *p*-Nitrophenyl Esters of Dicarboxylic Acids (Table IV). A solution of 1.0 molar equiv of the appropriate bis acid and 2.0 molar equiv of *p*-nitrophenyl trifluoroacetate in 10–30 ml of dry pyridine was stirred at 30° for 15–30 min, diluted with water to precipitate the ester, and filtered. The precipitate was slurried in ethanol, ether was added and filtered before being recrystallized from an appropriate solvent.

Acknowledgment. We gratefully acknowledge financial support of this work through Department of Health, Education and Welfare Grant 2-R01 AM12297-03 and the Geyer Fund (Department of Medicine, University of Cincinnati). We thank CIBA-GEIGY Corp. (Dr. C. A. Brownly) for a gift of 1 hydrochloride.

Registry No.—1 (R′ = H), 86-54-4; 1 (R′ = $NHNH_2$), 484-23-1; 3 (R = CCl_3, R′ = H), 56172-99-7; 3 (R = CF_3, R′ = H), 53551-55-6; 3 (R = CH_2SH, R′ = H), 56173-00-3; 3 [R = $CH(C_6H_5)OH$, R′ = H], 56173-01-4; 3 [R = $(CH_2)_2COOH$, R′ = H], 56173-02-5; 3 [R = $C(CH_3)_3$, R′ = H], 56173-03-6; 3 [R = CF_3, R′ = $N_2H_2COCF_3$], 56173-04-7; 3 (R = CF_3, R′ = N_2H_3), 56173-05-8; 5 (R = CH_2), 56173-06-9; 5 [R = $(CH_2)_2$], 56173-07-0; 5 [R = $(CH_2)_3$], 56173-08-1; 5 [R = $(CH_2)_4$], 56173-09-2; 5 [R = $(CH_2)_5$], 56173-10-5; 5 (R = CH_2OCH_2), 56173-11-6; 5 (R = CH_2SCH_2), 56173-12-7; 5 (R = $CH_2CH_2SCH_2CH_2$), 56173-13-8; 5 (R = 2,6-$C_5H_3N_2$), 56173-14-9; 5 (R = 1,3,5-C_6H_3), 56173-15-0; 5 (R = >CHCH<), 56173-16-1; 8 (R′ = H), 56173-17-2; 9 (R = R′ = CH_3), 56173-18-3; 9 (R = $COOCH_3$, R″ = CH_3), 56173-19-4; 9 [R = $(CH_2)_2CO_2H$, R″ = CH_3], 56173-20-7; 9 (R = CH=$CHCO_2H$, R″ = CH_3), 56173-21-8; 9 (R = C_6H_4-o-CO_2H, R″ = H), 7211-69-0; 10 (R = $COOC_2H_5$), 56173-22-9; diglycolic acid, 110-99-6; thiodiglycolic acid, 123-93-3; *p*-nitrophenyl trifluoroacetate, 658-78-6; thiodipropionic acid, 111-17-1; dipicolinic acid, 499-83-2; trimesic acid, 554-95-0.

Supplementary Material Available. Full NMR, ir, and uv data for all the novel triazolo compounds as well as ir data on all intermediates together with detailed experimental procedures will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St.,

N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2901.

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Basic Methanolysis of Anilides. Evidence for the Mechanism Applying to the Special Case of *N*-Methyl-4′-nitroanilides

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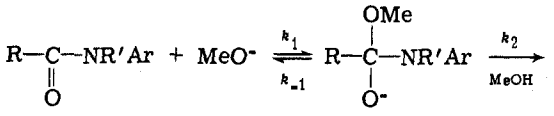
Evidence from activation parameters, solvent effects on rate, and solvent activity coefficients suggests that *N*-methyl-4′-nitroanilides undergo basic methanolysis by way of rate-determining methoxide addition to the amide. For other ring-substituted *N*-methyl and all NH anilides, decomposition of the tetrahedral intermediate is rate determining. Hammett data are discussed in terms of these mechanisms and an explanation of the behavior of the *N*-methyl-4′-nitroanilides is proposed.

The details of the mechanisms of basic anilide hydrolysis and alcoholysis are of current interest. To summarize (using methanolysis as the example and referring to eq 1), formation of 1 (mechanism A) or its decomposition to



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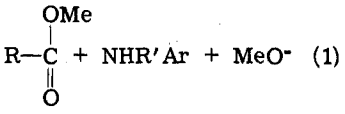
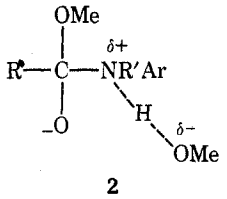
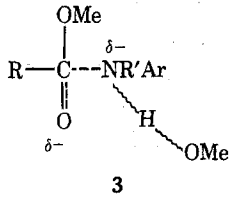


(1)

products can be rate determining. In the latter case, two extreme transition states are possible.[1] Where NR′Ar is a poor leaving group (mechanism B), protonation of the nitrogen is rate determining (transition state **2**) while for better leaving groups (mechanism C) solvent-assisted C–N cleavage is rate determining (transition state **3**).



2



3

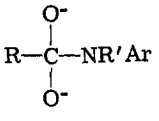
It appears that the mechanism is affected by many aspects of the structure of the anilide. For example, in acetanilides (R = Me[2] or CF_3;[1] R′ = H or Me) a gradual change from B to C occurs when the substituent on the benzene ring is changed from methoxy through to nitro. On the other hand, *N*-methylbenzanilides have been stated[3] to follow C irrespective of the nature of Ar.

Discussion of the possible occurrence of mechanism A has been limited to compounds containing the 4′-nitro substituent, the best leaving group studied to date, where decomposition of 1 to products might be so favored that A operates. It is our purpose here to summarize previous results, provide new data, and hopefully clarify the situation regarding this possibility.

Results and Discussion

pH–Rate Profiles in Basic Hydrolysis. Hydrolysis and methanolysis reactions are closely related and information about one can be related to the other with fair confidence.

Decomposition of the hydrolysis intermediate analogous to **1** can proceed via a dianionic intermediate (**4**). At high



4

pH, this route is fast and dominates for 4′-nitro-NH-anilides, formation of **1** becomes rate determining, and k_{obsd} tends to level off.[4,5] This behavior is not observed for analogous *N*-methyl compounds[4-6] and here the pH–rate profile is linear over the entire pH range. This has been variously interpreted as consistent[6] or not[5] consistent with mechanism A operating in this pH range for the *N*-methyl compounds.

Activation Parameters. Though *N*-methyl-4′-nitroacetanilide undergoes basic methanolysis only 1.5 times faster than the NH compound at 373 K, activation parameter measurements revealed a major difference between the two.[7] The much higher activation energy but more favorable entropy for the NH compound was ascribed to a predominant ground state solvation effect, it being assumed that both compounds reacted by mechanism C.

New rate data for reactions in methanol are collected in Table I. Activation parameters for other anilides have been calculated from some of the results and these, with the literature values for the 4′-nitro compounds, are listed in Table II.