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1,2,4-Triazoles. XXII. Derivatives of the s-Triazolo[3,4-a]phthalazine and Related Ring Systems[1]

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Cyclization of 1-hydrazino-4-alkyl(aryl)phthalazines with aliphatic acids, ortho esters, cyanogen bromide, urea, or carbon disulfide gave the appropriate 3-substituted 6-alkyl(aryl)-*s*-triazolo[3,4-*a*]phthalazines in good yield. The tetracyclic bis-*s*-triazolo[3,4-*a*:4,3-*c*]phthalazine system was readily available from 1,4-dihydrazinophthalazine, and the *s*-triazolo[4,3-*b*]-*s*-triazolo[3,4-*a*]phthalazine system was prepared by cyclization of 3-hydrazino-*s*-triazolo[3,4-*a*]phthalazine. Oxidation of *s*-triazolo[3,4-*a*]phthalazine gave *s*-triazole-3-carboxylic acid. The *s*-triazolo[3,4-*a*]phthalazine system was reduced by metal hydrides at the 5,6 position, but catalytic hydrogenation was unsuccessful. When treated with base, it underwent ring opening to 3-substituted 5-(2-cyanophenyl)-*s*-triazoles but was stable to hot mineral acid, whereas the bis-*s*-triazolo[3,4-*a*:4,3-*c*]phthalazine system underwent ring opening and subsequent hydrolysis to 6-hydrazino-*s*-triazolo[3,4-*a*]phthalazine with hot mineral acid. Alkylation of *s*-triazolo[3,4-*a*]phthalazine occurred exclusively at the 2 position under reflux conditions, whereas at room temperature alkylation occurred at both the 1 and 2 positions. Several electrophilic and nucleophilic reactions undergone by the nucleus are described, together with spectral characteristics of the fused system.

In a continuation of our interest in the chemistry of ring-fused *s*-triazole systems, we have studied the *s*-triazolo[3,4-*a*]phthalazine system and a variety of its derivatives. This communication describes their synthesis, their behavior toward oxidizing and reducing agents, their acid and base hydrolysis, electrophilic and nucleophilic substitution reactions, and the position of alkylation. This ring system was first reported[2a] in 1951, and several other 3-substituted derivatives were described[2b] in 1965, interest being directed mainly toward their antihypertensive properties. One other related bridgehead nitrogen ring system, the tetrazolo[1,5-*a*]phthalazine system, is known[3] but again there is no knowledge of the physical and chemical characteristics of this interesting nucleus.

Substituted *s*-Triazolo[3,4-*a*]phthalazines.—In this present study, 3- and 6-alkyl(aryl)-*s*-triazolo[3,4-*a*]-phthalazines were prepared by treating the appropriate 1-hydrazino-4-substituted phthalazine[4] (1) with either an aliphatic acid or the corresponding ortho ester, procedures well documented for the synthesis of fused *s*-triazole systems.[2a,5] The products obtained are described in Table I. Considerable flexibility is possible in the choice of cyclization agent; *e.g.*, 3-dichloromethyl-*s*-triazolo[3,4-*a*]phthalazine (2, R^1 = H; R^2 = $CHCl_2$) was prepared by cyclization of the hydrazine **1** with dichloroacetic acid, whereas 3-chloromethyl-*s*-triazolo-[3,4-*a*]phthalazine (2, R^1 = H; R^2 = CH_2Cl) was prepared utilizing cyclization with triethyl orthochloroacetate.[6] The use of ortho esters usually gave better yields and were the reagents of choice in the preparation of most of the above derivatives.

Reaction of 1-hydrazinophthalazine with carbon disulfide and aqueous sodium hydroxide gave *s*-triazolo-[3,4-*a*]phthalazine-3-thiol (2, R^1 = H; R^2 = SH) in excellent yield. The thiol, on treatment with methyl iodide and aqueous base, was converted into methyl-*s*-triazolo[3,4-*a*]phthalazin-3-yl sulfide (2, R^1 = H; R^2 = SCH_3), readily characterized through its nmr data listed in Table II. Use of carbon disulfide and chloroform as the reaction medium gave the same thiol, except that under the former conditions the reaction was much faster, presumably because of the homogeneous reaction conditions. The infrared spectrum of the thiol indicated that it existed mainly in the thioamide form (ν_{CS} 1250 cm^{-1}) since no appreciable S–H stretching absorption was detected (ν_{SH} 2600 cm^{-1}).

(1) (a) Support of this work by U. S. Public Health Service Research Grant CA 08495 National Cancer Institute is gratefully acknowledged. (b) Abstracted from the Ph.D Thesis of C. L., Rensselaer Polytechnic Institute, Jan 1969. (c) National Science Foundation Trainee 1966–1968. (d) Presented in part as a preliminary communication: K. T. Potts and C. Lovelette, *Chem. Commun.*, 845 (1968).

(2) (a) J. Druey and B. H. Ringier, *Helv. Chim. Acta*, **34**, 195 (1951). (b) P. Kubrokonski, J. Majcherczyk, and J. Szyrokska, *Acta Physiol. Polon.*, **16**, 254 (1965); N. Biniecki, A. Haase, J. Izdebski, I. Kesler, and L. Rylski, *Bull. Acad. Polon. Sci.*, **6**, 227 (1958); *Chem. Abstr.*, **52**, 18424 (1958).

(3) R. Stolle and H. Storch, *J. Prakt. Chem.*, **135**, 128 (1932).

(4) Several comprehensive reviews of synthetic procedures used to obtain the phthalazine intermediates utilized are available: (a) R. E. Simpson, "Condensed Pyridazine and Pyrazine Rings, Cinnolines, Phthalazines and Quinoxalines," Interscience Publishers, Inc., New York, N. Y., 1953; (b) R. C. Elderfield and S. H. Wythe, "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1957.

(5) (a) K. T. Potts and H. R. Burton, *J. Org. Chem.*, **31**, 251 (1966); (b) K. T. Potts and S. W. Schneller, *J. Heterocycl. Chem.*, **5**, 485 (1968).

(6) S. M. McElvain and J. W. Nelson, *J. Amer. Chem. Soc.*, **64**, 1825, (1942).

TABLE I

SOME *s*-TRIAZOLO[3,4-*a*]PHTHALAZINE DERIVATIVES (2)

Registry no.	R^1	R^2	Mp, °C	Method[a]	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Ultraviolet data,[b] λ_{max} (log ϵ)
234-30-0	H	H	184–185	A	66								267[c] (3.60), 237 (4.53)
			193–194[d]	B	95								
21516-99-4			261–263 dec[e]		100	$C_9H_7ClN_4$	52.31	3.42	27.12	52.44	3.46	27.21	
20062-41-3	H	CH_3	166[f]	A	44								239 (4.44), 231 (4.53)
			175	B	98								
21517-01-1	Ph	H	197	B	45	$C_{15}H_{10}N_4$	73.14	4.10	22.75	72.97	4.01	22.68	237 (4.48)
21517-02-2	Ph	CH_3	210–211	B	50	$C_{16}H_{12}N_4$	73.82	4.66	21.53	73.95	4.90	21.46	250 (4.50), 244 (4.52)
21517-03-3	CH_3	H	184–186	A	70	$C_{10}H_8N_4$	65.20	4.38	30.42	64.99	4.45	30.25	227 (4.53)
21517-04-4			270 dec[e]			$C_{10}H_9ClN_4$	54.43	4.11	25.40	54.16	4.23	24.41	
21517-05-5	CH_3	CH_3	236	B	60	$C_{11}H_{10}N_4$	66.64	5.08	28.27	66.52	5.11	28.25	247 (4.60), 240 (4.69)
21517-06-6	H	SH	305	C	98	$C_9H_6N_4S$	53.44	2.99	27.71	53.29	2.91	27.58	284 (4.34), 257 (4.67), 220 (4.62)
21517-07-7	H	SCH_3	192–193		80	$C_{10}H_8N_4S$	55.53	3.73	25.91	55.53	3.81	26.12	266 (4.53), 257 (4.53), 214 (4.63)
21517-08-8	H	NH_2	291	D	30	$C_9H_7N_5$	58.36	3.82	37.82	58.17	4.04	37.58	265 (4.42), 209 (4.53)
21517-09-9	H	OH	280[g]	E	80								264 (4.45), 254[c] (4.32), 205 (4.54)
21517-10-2	H	CH_2Cl	188[h]	B	60								274[c] (3.76), 249 (4.50), 234 (4.48)
21517-11-3	H	$CHCl_2$	224[i]	A	75								272 (4.02), 248 (4.72), 240 (4.76)

[a] A, carboxylic acid; B, ortho ester; C, carbon disulfide; D, cyanogen bromide; E, urea. [b] Methanol. [c] Shoulder. [d] Lit.[2a] mp 191°. [e] Hydrachloride. [f] Lit.[2a] mp 171–172°. [g] Lit.[2a] mp 275–276°. [h] Lit.[2a] mp 188–189°. [i] Lit.[2a] mp 213–215.

TABLE II

NMR SPECTRAL DATA FOR SOME 3- AND 6-SUBSTITUTED *s*-TRIAZOLO[3,4-*a*]PHTHALAZINES[a]

Substituent	Chemical shifts, ppm δ_3	δ_6	δ_{10}	$\delta_{7,8,9}$[b]
Unsubstituted	9.00	8.63	8.63	7.92
	9.61 (DMSO-d_6)	9.06	8.98	7.98
6-Methyl	8.91	*2.81*	8.69	8.00
6-Phenyl	9.36	*8.14*	8.65	7.83
3-Methyl	*2.81*	8.45	8.51	7.91
3,6-Dimethyl	*2.82*	*2.80*	8.64	7.88
3-Methyl-6-phenyl	*2.80*	*8.14*	8.69	7.83
3-Methylthio	*2.90*	8.46	8.43	7.89
3-Bromo[c]		8.70	8.65	7.90
3-Acetyl[d]	2.82	8.39		7.83
3-Formyl[e]	*10.04*	8.92		8.05

[a] Methyl, phenyl, and formyl absorptions are italicized. Spectra were determined in $CDCl_3$ except where indicated otherwise. [b] Nonresolved multiplets. [c] Registry no: 21537-95-1. [d] Registry no: 21517-12-4. [e] Registry no: 21517-13-5.

This is consistent with the behavior of similar ring-fused *s*-triazole-3-thiols.[5a,7]

Fusion of 1-hydrazinophthalazine (1) with urea afforded an excellent yield of *s*-triazolo[3,4-*a*]phthalazin-3-ol (2, R^1 = H; R^2 = OH). Ethyl chloroformate was unsatisfactory as the cyclization agent in this system, no well-defined product being obtained. Infrared spectral data suggested that this product existed mainly in the keto form (ν_{CO} 1620 cm^{-1}) since only minor O–H stretching absorption (ν_{OH} 3500 cm^{-1}) was observed in the spectrum. On reaction of the hydrazine 1 with cyanogen bromide, 3-amino-*s*-triazolo[3,4-*a*]phthalazine hydrobromide was obtained. It was readily converted into the free base (2, R^1 = H; R^2 = NH_2) (ν_{NH} 3360, 3150, 1640 cm^{-1}) with aqueous sodium acetate.

The ease of replacement of a 3-chloro or 3-bromo substituent in the tricyclic system 2 was of particular interest and a convenient synthetic route to these derivatives was necessary. Direct synthesis through ring closure of 1-hydrazinophthalazine was not feasible and alternative procedures involving reaction of *s*-triazolo[3,4-*a*]phthalazin-3-ol (2, R^1 = H; R^2 = OH) with phosphoryl chloride or treatment of 3-amino-*s*-triazolo[3,4-*a*]phthalazine (2, R^1 = H; R^2 = NH_2) under Sandmeyer reaction conditions have not been particularly successful in related ring systems.[5a] Two methods have now been established as more than adequate for the preparation of a chloro compound of this type. Oxidative chlorination[8] of *s*-triazolo[3,4-*a*]-phthalazine-3-thiol (2, R^1 = H; R^2 = SH) gave 3-chloro-*s*-triazolo[3,4-*a*]phthalazine (2, R^1 = H; R^2 = Cl) in good yield and this procedure is of particular importance for the preparation of chloro-substituted heterocycles of this type. It is far superior to the standard phosphorus oxychloride–phosphorus pentachloride reaction with appropriate hydroxyl derivatives. In the second procedure, treatment of *s*-triazolo[3,4-*a*]phthalazine (2, R^1 = R^2 = H) with sodium hypochlorite solution ("Clorox") gave an excellent yield[9] of the desired 3-chloro compound.

Attempts to prepare 3-formyl-substituted derivatives of the fused-ring system utilizing *n*-butyllithium and dimethylformamide were unsuccessful. Acid hydrolysis of the bis secondary amine derived from 3-dichloromethyl-*s*-triazolo[3,4-*a*]phthalazine (2, R^1 = H; R^2 = $CHCl_2$) and morpholine was, however, a successful synthetic route. The aldehyde 2 (R^1 = H; R^2 = CHO) was thermally stable and underwent a benzoin condensation, thus behaving as a typical aromatic-type aldehyde. It was readily oxidized with silver oxide and base to the corresponding carboxylic acid which, however, underwent decarboxylation to *s*-triazolo[3,4-*a*]phthalazine under the reaction conditions. The instability of the carboxylic acid is a characteristic feature of this ring system. From several reactions aimed at obtaining the 3-carboxylic acid, the only product isolated from the reaction was the decarboxylated product (2) (Scheme I).

The Bis-*s*-triazolo[3,4-*a*:4,3-*c*]phthalazine System.—1,4-Dihydrazinophthalazine (3), most conveniently prepared from *o*-phthalonitrile and an excess of hydrazine hydrate,[10] on refluxing with triethyl orthoformate formed bis-*s*-triazolo[3,4-*a*:4,3-*c*]phthalazine (4) in excellent yield. This represents the first successful cyclization of both hydrazino groups to a fully conjugated,

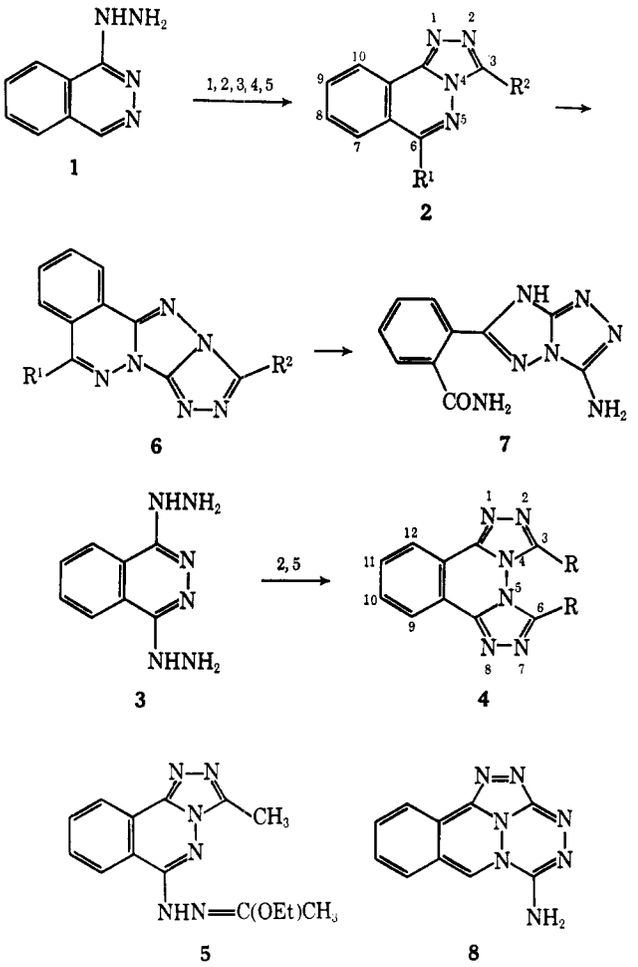
(7) N. N. Bereschangina and I. Va. Postowsbii, *Zh. Obshch. Khim.*, **34**, 1745 (1964).

(8) G. S. Sidhu, S. Naqui, and D. S. Iyanger, *J. Heterocycl. Chem.*, **3**, 158 (1966).

(9) We have found "Clorox" to be a particularly effective chlorinating agent in heterocycles and our use of this reagent will be described in a future publication.

(10) Cassella Farbwerke Mainkur Akt.-Ges., British Patent 707,337 (April 14, 1954); *Chem. Abstr.*, **49**, 7606 (1955).

SCHEME I[a]



[a] 1, R^2COOH; 2, $R^2C(OEt)_3$; 3, CS_2; 4, NH_2CONH_2; 5, CNBr.

tetracyclic system incorporating the phthalazine nucleus.[11] Several attempts[12] to synthesize systems of type **4** using formic acid as the cyclization agent resulted in ring closure of one hydrazine group only, the other being converted into its formyl derivative. Analogous results were obtained in attempts[3] to prepare the bistetrazolo system from 1,4-diazidophthalazine.

The structure of **4** was established on the basis of analytical and spectral data. Its molecular formula was determined to be $C_{10}H_6N_6$ and its nmr spectrum showed two equivalent protons at δ 10.03 corresponding to H_3 and H_6 of the tetracyclic system, consistent with the symmetrical character of the molecule. The absence of NH absorptions in the infrared spectrum, together with a –CH stretching absorption at 3040 cm^{-1} characteristic of the 3 hydrogen in s-triazolo[3,4-a]-phthalazine, further substantiated the proposed structure. When 1,4-dihydrazinophthalazine was refluxed in triethyl orthoacetate, the reaction failed to follow the expected course and, in this case, ethyl acetate (3-methyl-s-triazolo[3,4-a]phthalazin-6-yl)hydrazone (**5**) was obtained. The structure of **5** was determined mainly from its nmr spectrum (after establishment of the molecular formula from analytical and mass spectral data) which contained two nonequivalent methyl groups at δ 2.14 and 2.69, together with resonances attributable to an ethyl group at δ 1.38 (t, 3, J = 7.0 Hz, CH_3) and 4.32 (q, 2, J = 7.0 Hz, $-CH_2$). The infrared spectrum indicated the presence of an NH group (ν_{NH} 3200, 1590 cm^{-1}), a C=N group ($\nu_{C=N}$ 1650 cm^{-1}), and an ether linkage (ν_{COC} 1055 cm^{-1}), offering strong support for the proposed structure.

Models show that the methyl groups in 3,6-dimethylbis-s-triazolo[3,4-a:4,3-c]phthalazine would interact to a significant degree and it can be assumed that compound **5** results from steric control of the reaction. It is thus of interest that 3,6-diaminobis-s-triazolo[3,4-a:-4,3-c]phthalazine (**4**, R = NH_2) was obtained by cyclization of 1,4-dihydrazinophthalazine with cyanogen bromide. Spectral and analytical data were consistent with the assigned structure which is in accord with those of products obtained from cyanogen bromide cyclizations of this type.

The s-Triazolo[4,3-b]-s-triazolo[3,4-a]phthalazine System.—The extension of our present tricyclic system (**2**) in such a way as to obtain an essentially linear tetracyclic system which would contain the s-triazolo-s-triazole moiety described recently[13] was of interest and 3-hydrazino-s-triazolo[3,4-a]phthalazine (**2**, R^1 = H; R^2 = $NHNH_2$) was a particularly suitable intermediate for this purpose. However, the attempted cyclization of **2** (R^1 = H; R^2 = $NHNH_2$) with formic acid gave only 2-(3-hydrazino-s-triazolo[3,4-a]phthalazine)-formhydrazide (**2**, R^1 = H; R^2 = NHNHCHO). The infrared spectrum of the product was typical of a formhydrazide (N–H bending and stretching absorptions and carbonyl absorption) and this spectrum, combined with the nmr data, provided strong evidence for the assigned, open-chain structure. Similarly, reaction of the hydrazine with triethyl orthoformate likewise gave the (s-triazolo[3,4-a]phthalazin-3-yl)hydrazone of ethyl formate (**2**, R^1 = H; R^2 = NHN=CHOEt). Analytical and molecular weight data indicated that cyclization had not occurred and spectral data offered strong support for the assigned structure. The existence of an ethyl group (CH_3 triplet at δ 1.45, J = 7.0 Hz; CH_2 quartet at 4.22, J = 7.0 Hz) and a single proton resonating at 6.80 (the 6 proton of s-triazolo-[3,4-a]phthalazine occurs at 8.63), along with aromatic protons, was evident from the nmr spectrum and the infrared spectrum was similar to that of the hydrazone **5**. The hydrazone was susceptible to aerial oxidation, rapidly turning purple, a characteristic of s-triazolylhydrazones. However, a more effective cyclization agent such as cyanogen bromide did result in cyclization to the tetracyclic system, 3-amino-s-triazolo[4,3-b]-s-triazolo[3,4-a]phthalazine (**6**, R^1 = H; R^2 = NH_2) being formed in moderate yield. Confirmation of this structural assignment, originally made on the basis of spectral data, was obtained by alkali-induced ring opening of the product to 3-amino-6-(2-carboxamidophenyl)-5H-s-triazolo[5,1-c]-s-triazole (**7**) [$\lambda_{max}^{CH_3OH}$ 243 mμ (log ϵ 4.38)] and the corresponding 6-(2-cyanophenyl) derivative [$\lambda_{max}^{CH_3OH}$ 253 mμ (log ϵ 4.24)] which contain essentially the same chromophoric system present[13] in 3-amino-6-phenyl-5H-s-triazolo[5,1-c]-s-triazole [$\lambda_{max}^{CH_3OH}$ 248 mμ (log ϵ 4.48)]. This ring-opening

(11) The preparation of 9,10-dihydrobenzo[f]bis-s-triazolo[3,4-a:4,3-c]-phthalazine has been recently reported [B. Stanovnik, N. Tišler, and P. Škufca, *J. Org. Chem.*, **33**, 2910 (1968)].

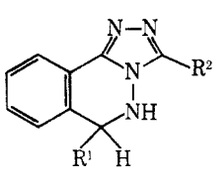
(12) G. A. Reynolds, J. A. VanAllan, and J. F. Tinker, *ibid.*, **24**, 1205 (1959).

(13) K. T. Potts and C. Hirsch, *ibid.*, **33**, 143 (1968).

reaction, discussed below, eliminates structure **8** from consideration for the cyclization product.

Oxidation and Reduction of the *s*-Triazolo[3,4-*a*]phthalazine System.—When *s*-triazolo[3,4-*a*]phthalazine was treated with a hot solution of potassium permanganate, *s*-triazole-3-carboxylic acid was the sole product isolated. This behavior is consistent with that of other ring-fused *s*-triazole systems such as *s*-triazolo[4,3-*a*]pyridine[5a] as well as pyrazolo[1,5-*a*]pyridine[14] and is in contrast to the behavior of indolizines[15] which yield substituted pyridines under analogous conditions.

This ring system has several possible reaction sites for the action of complex metal hydrides. *s*-Triazolo[3,4-*a*]phthalazine and its 3- and 6-methyl derivatives with an excess of lithium aluminum hydride in dry tetrahydrofuran underwent reduction at the 5,6 double bond. Thus, from 3-methyl-*s*-triazolo[3,4-*a*]phthalazine (**2**, R^1 = H; R^2 = CH_3), 5,6-dihydro-3-methyl-*s*-triazolo[3,4-*a*]phthalazine (**9**, R^1 = H; R^2 = CH_3) was the sole product isolated. The nmr spectrum contained a methyl singlet at δ 2.33, a methylene doublet at 4.25 (J = 9.0 Hz), and an NH triplet at 5.16 (J = 9.0 Hz). These data, particularly the singlet nature of the methyl resonance, lead to the conclusion that the 5,6 double bond was involved in the reduction. Similarly, **9** (R^1 = R^2 = CH_3) showed in its nmr spectrum a methyl singlet at δ 2.83, a methyl doublet at 1.38 (J = 7.0 Hz) together with an apparent methine quartet at 4.35 (J = 7.0 Hz), and an NH doublet at 5.05. The methine proton was not a simple quartet showing superimposed spin–spin splitting, probably due to some coupling with the hydrogen on the adjacent nitrogen atom. The doublet character of the methyl signal offered further evidence for reduction of the 5,6 double bond. This same product was also prepared by sodium borohydride reduction of the parent system with diminuition in yield. Similar reductions have been observed in the quinazoline series where 3,4-dihydroquinazolines were formed[16] and also with 2-alkylphthalazinium iodides[17] and isoquinolines.[18]



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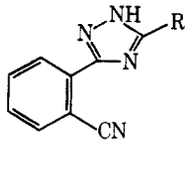

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In contrast to this facile reduction with complex metal hydrides, the tricyclic system was found to be completely resistant to reduction with nitrogen and Adams catalyst.

Base-Catalyzed Ring Opening of the *s*-Triazolo[3,4-*a*]phthalazine System.—*s*-Triazolo[3,4-*a*]phthalazine (**2**, R^1 = R^2 = H) and its 3-methyl derivative on treatment with alcoholic potassium hydroxide (aqueous sodium hydroxide or barium hydroxide) underwent an interesting ring opening to form 3-(2-cyanophenyl)-*s*-triazole (**10**, R = H) and its 5-methyl derivative (**10**, R = CH_3) as reported in our preliminary communication.[1d] Full details are described in the Experimental Section. This type of N–N bond fission[19] is analogous to N–O or N–N bond fission reported for isoxazoles, pyrazoles, and pyrazolines[20] as well as indazoles[21] and *v*-triazoles.[22] Though H–D exchange studies[23] indicated that the 3 proton was more acidic than the 6 proton, abstraction of the 6 proton results in elimination of the resonance-stabilized *s*-triazole anion with the formation of a stable entity. When a relatively acidic proton such as that found in *s*-triazolo[3,4-*a*]phthalazin-3-ol (**2**, R^1 = H; R^2 = OH) was present in the molecule, no ring opening occurred, presumably because of the negative charge residing on the *s*-triazole nucleus in the fused system.

s-Triazolo[3,4-*a*]phthalazine and its alkyl and phenyl derivatives were found to be stable toward hot mineral acid and readily formed the corresponding *s*-triazolo[3,4-*a*]phthalazine hydrochloride which on dissolution in water gave the free base. The weakly basic character of this ring system was demonstrated on potentiometric titration,[24] the pK_a (H_2O) for *s*-triazolo[3,4-*a*]phthalazine being *ca.* 2.51 and those of its 3- and 6-methyl derivatives being 2.90 and 2.61, respectively. They are thus weaker bases than phthalazine[25] which has a pK_a of 3.43.

Acid-Catalyzed Ring Opening of Bis-*s*-triazolo[3,4-*a*:4,3-*c*]phthalazine.—Bis-*s*-triazolo[3,4-*a*:4,3-*c*]phthalazine (**4**, R = H), on treatment with hot mineral acid, readily gave 6-hydrazino-*s*-triazolo[3,4-*a*]phthalazine (**2**, R^1 = $NHNH_2$; R^2 = H), presumably *via* a ring opening of the tetracyclic system to an intermediate 2-(*s*-triazolo[3,4-*a*]phthalazin-6-yl)formhydrazide, a type of compound which is known to hydrolyze in an acid environment.[12] The structure of **2** (R^1 = $NHNH_2$; R^2 = H) was established on the basis of its infrared spectrum which was typical of a hydrazine derivative (ν_{NH} 3400, 3300, 1510 cm^{-1}) and from its ultraviolet spectrum which indicated that the compound had the same chromophoric system as an *s*-triazolo[3,4-*a*]phthalazine derivative with an electron-releasing substituent at the 6 position (see Table I). Confirmation of the structure of **2** (R^1 = $NHNH_2$; R^2 = H) was obtained by its conversion into its tetracyclic progenitor (**4**) with hot triethyl orthoformate.

The tetracyclic system (**4**) was stable to base. It thus appears that an initial quaternization of N_1 in **4** is followed by hydration of the cation and, at the elevated temperatures employed, ring opening to the formhydrazide follows. This behavior of the tetracyclic ring system **4** is in direct contrast to that of the tricyclic ring system **2** and the facile ring opening indicates that there

(14) J. D. Bower and G. R. Ramage, *J. Chem. Soc.*, 4506 (1957).
(15) E. J. Borrows and D. O. Holland, *Chem. Rev.*, **42**, 636 (1948).
(16) R. F. Smith, P. C. Briggs, R. H. Kent, J. A. Albright, and E. J. Walsh, *J. Heterocycl. Chem.*, **2**, 157 (1965).
(17) R. F. Smith and E. D. Otremba, *J. Org. Chem.*, **27**, 879 (1962).
(18) L. M. Jackman and D. I. Packham, *Chem. Ind.* (London), 360 (1955); E. A. Braude, J. Hannah and R. P. Linstead, *J. Chem. Soc.*, 3249 (1960); see also J. L. Neumeyer, M. McCarthy, and K. K. Weinhardt, *Tetrahedron Lett.*, 1095 (1967).
(19) A useful compilation of references on this topic can be found in Y. A. Naumou and I. I. Grandberg, *Russ. Chem. Rev.* (Engl. Transl.), **35**, 9 (1966).
(20) R. Fusco, V. Rosnati, and G. Pagani, *Tetrahedron Lett.*, 1739 (1966); 4541 (1967).
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(23) At 34°, R = 2.54 × 10^{-2} min^{-1}; this datum was determined following integration values for the 3 proton in CH_3OD–Et_3N solution and the exchange reaction apparently followed first-order kinetics. The 6 proton did not show any appreciable exchange under these conditions but in CH_3OD–CH_3ONa solution 19% exchange occurred after 24 hr.
(24) We are indebted to Mr. B. Amoto for these determinations.
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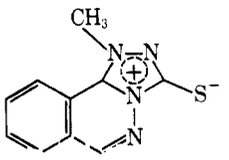
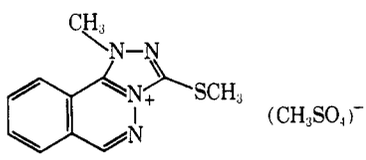
must be considerable strain involved in the essentially coplanar tetracyclic system.

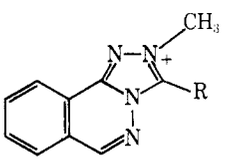
Alkylation of the s-Triazolo[3,4-a]phthalazine System.—As there is more than one nitrogen atom at which alkylation can occur in this system, it was of interest to determine the most basic nitrogen atom and whether rearrangement of the alkylation products occur as has been observed in the s-triazolo[4,3-a]pyridine system.[26] An unambiguous synthesis of a derivative with an N-alkyl group in a predetermined position was achieved in the following way. 1-Methyl-1-(1-phthalazinyl) hydrazine, prepared by treatment of 1-chlorophthalazine with methylhydrazine, on reaction with carbon disulfide gave anhydro-3-mercapto-1-methyl-s-triazolo[3,-4-a]phthalazinium hydroxide (**11**) in good yield. Reaction with dimethyl sulfate in benzene afforded a quantitative yield of 1-methyl-3-methylthio-s-triazolo[3,4-a]phthalazinium methosulfate (**12**) whose nmr spectrum showed an N-methyl resonance at δ 4.39 and an S-methyl resonance at 2.88. Treatment of s-triazolo-[3,4-a]phthalazin-3-yl sulfide (**2**, R^1 = H; R^2 = SCH_3) with dimethyl sulfate under these conditions resulted in a methosulfate salt which was not identical with **12**. Its nmr spectrum showed an N-methyl signal at δ 4.62 and an SCH_3 at 2.92. These data exclude alkylation of the nucleus at the 1 position and the following evidence indicated that this product is best represented as **13** (R = SCH_3). The nmr spectrum showed that there was no appreciable deshielding[26] of the 6 proton, thus excluding alkylation at the 5 position. Alkaline potassium ferricyanide oxidation gave 2-methyl-s-triazolo[3,4-a]phthalazin-3-one (**14**) which could only have arisen from alkylation at the 2 position.



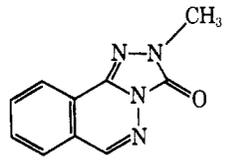
11



12



13



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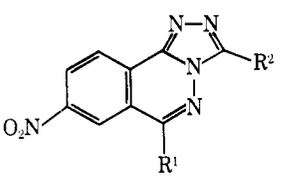

15

s-Triazolo[3,4-a]phthalazine (**2**, R^1 = R^2 = H) and methyl iodide in boiling methanol gave a methiodide salt whose nmr spectrum showed an N-methyl signal at δ 4.38 and a single proton signal at 10.12. The 3 proton in s-triazolo[3,4-a]phthalazine, though concentration dependent, has a characteristic absorption at *ca.* δ 9.00, and the downfield shift of 1.12 ppm obtained in this methiodide can be attributed to a deshielding effect of an adjacent positive charge and is consistent with alkylation at N_2. Alkaline potassium ferricyanide oxidation of this methiodide again gave 2-methyl-s-triazolo[3,4-a]phthalazin-3-one (**14**), indicating that the methylation product is best represented as 2-methyl-s-triazolo[3,4-a]phthalazinium iodide (**13**, R = H). When the reaction was carried out at room temperature, the nmr spectrum of the crude product indicated the presence of another isomer (18%) (N-methyl at δ 4.46), most likely the result of alkylation at the 1 position. Analogous results were obtained with 3-methyl-s-triazolo[3,4-a]phthalazine (**2**, R^1 = H; R^2 = CH_3) and methyl iodide in boiling methanol and also at room temperature, and these data are described in the Experimental Section. As expected, 2-methyl-s-triazolo-[3,4-a]phthalazin-3-one was readily obtained from s-triazolo[3,4-a]phthalazin-3-ol and diazomethane or by reaction with methyl iodide and potassium carbonate in acetone.

Nucleophilic–Electrophilic Substitution Reactions.—A 3-chloro or 3-bromo substituent in s-triazolo[3,4-a]-phthalazine underwent an extremely facile displacement by hydrazine forming 3-hydrazino-s-triazolo[3,4-a]-phthalazine (**2**, R^1 = H; R^2 = $NHNH_2$) in excellent yield. This behavior is similar to that observed for halogen-substituted derivatives of the isoquinoline system,[8] the imidazo[1,2-a]pyridine system,[27] and the indolizine system[28] but, interestingly enough, not to the s-triazolo[4,3-a]pyridine system.[29]

Reaction of s-triazolo[3,4-a]phthalazine (**2**, R^1 = R^2 = H) with either N-bromosuccinimide in carbon tetrachloride or bromine in acetic acid at reflux temperatures afforded 3-bromo-s-triazolo[3,4-a]phthalazine (**2**, R^1 = H; R^2 = Br) in good yield. The structure of the bromo product was evident from its nmr spectrum in which the downfield, single proton signal at δ 8.70 was a doublet (J = 1.0 Hz), clearly the 6 proton, and the 3 proton was absent. The infrared spectrum confirmed the structural assignment since the absorption at 3100 cm^{-1}, attributed to the 3 hydrogen was absent. When the 3 position was blocked with a methyl substituent, no reaction occurred with either brominating reagent. Attempts to effect bromination of **2** with bromine in methanol or bromine in aqueous sodium hydroxide always resulted in incomplete bromination.

6-Methyl-s-triazolo[3,4-a]phthalazine (**2**, R^1 = CH_3; R^2 = H) underwent reaction with fuming nitric acid–concentrated sulfuric acid at room temperature and gave a mononitro derivative. The nmr spectrum of this product showed that both the 3 proton and the C_5-methyl group were present and the C_6-methyl group had essentially the same chemical shift as the C_6-methyl group in the starting material. This excludes nitration at the 7 position, since a nitro group in this position would be expected to influence the chemical shift of the C_6-methyl group by a *peri* interaction. The chemical shift of the 10 proton in **2** (R^1 = R^2 = H) was deshielded by the *ortho* effect of the nitrogen atoms in the adjacent triazole ring and appeared downfield from

(26) W. W. Paudler and R. J. Brumbough, *J. Heterocycl. Chem.*, **5**, 29 (1968); see also W. W. Paudler and L. S. Helmick, *ibid.*, **5**, 691 (1968).

(27) V. K. Matueev, *Bull. Acad. Sci. URRS Classe Sci. Math. Nat. Ser. Chem.*, 2521 (1957).

(28) N. Scholtz, *Ber.*, **45**, 734, 1718 (1912).

(29) K. T. Potts, H. R. Burton, and S. K. Roy, *J. Org. Chem.*, **31**, 265 (1966).

the other aromatic protons. As the 10 proton was present in the nitration product and was slightly more shielded (δ 8.61 *vs.* 8.51), nitration at the 9 and 10 position can be excluded because, with a 9-nitro substituent, the 10 proton would have been deshielded relative to the starting material. In addition, the complex splitting of H_{10} was retained in the spectrum of the nitration product suggesting that *ortho* coupling was still an important factor. On the basis of these data, it is clear that nitration most likely occurred in the 8 position and the structure of the product is best represented as **15** ($R^1 = CH_3$; $R^2 = H$). The remaining aromatic protons were centered at δ 8.12 and were deshielded by 0.22 ppm from the center of the aromatic protons in **2** ($R^1 = R^2 = H$) (δ 7.90), consistent with the above interpretation. In a similar fashion 3-methyl-8-nitro-*s*-triazolo[3,4-*a*]phthalazine (**15**, $R^1 = H$; $R^2 = CH_3$) and 8-nitro-*s*-triazolo[3,4-*a*]phthalazine (**15**, $R^1 = R^2 = H$) were prepared by nitration of the appropriate precursor.

When *s*-triazolo[3,4-*a*]phthalazine was treated with acetic anhydride and copper nitrate at room temperature, the product obtained was identified as 3-acetyl-*s*-triazolo[3,4-*a*]phthalazine. The presence of a carbonyl group was evident from an infrared absorption at 1720 cm^{-1} and, after analytical data had established a molecular formula of $C_{11}H_8N_4O$, the nmr spectrum showed that substitution had occurred in the 3 position (Experimental Section). It should be noted that acetic anhydride alone did not effect acetylation of this ring system.

Formylation reactions, using the Vilsmeier procedure or the Fisher–Schwartz method, were unsuccessful when applied to *s*-triazolo[3,4-*a*]phthalazine.

Experimental Section[30]

The various phthalazine derivatives utilized were prepared by literature procedures[31] or as described below.

1-Methyl-1-(1-phthalazinyl)hydrazine.—1-Chlorophthalazine[2a] (1.0 g, 0.006 mol) in methanol (15 ml) and methylhydrazine (5 ml) were refluxed for 1 hr. The yellow solution was concentrated under reduced pressure until a red viscous oil remained and the oil was taken up in aqueous sodium carbonate (10% solution). The aqueous solution was extracted with chloroform; the combined chloroform layers were dried (Na_2SO_4) and then evaporated to dryness. Recrystallization of the residue from benzene afforded yellow needles: 0.75 g (70%); mp 119–120°; ir ($CHCl_3$) 3370, 3000, 2890, 1615, 1590, 1360 cm^{-1}.

Anal. Calcd for $C_9H_{10}N_4$: C, 62.04; H, 5.79; N, 32.17. Found: C, 61.79; H, 5.90; N, 31.94.

The preparations below illustrate the general synthetic procedures used.

The Preparation of 6-Methyl-*s*-triazolo[3,4-*a*]phthalazine. A. Using Formic Acid.—1-Hydrazino-4-methylphthalazine (1.0 g, 0.006 mol) in formic acid (50 ml, 98%) was refluxed for 4 hr. The excess formic acid was removed under reduced pressure giving brown irregular prisms which, after recrystallization from benzene–petroleum ether (85–100°), afforded cream irregular prisms: 0.75 g (70%); mp 184–186°.

B. Using Triethyl Orthoformate.—The hydrazine (2.0 g, 0.01 mol) in triethyl orthoformate (50 ml) was refluxed for 1.5 hr. Excess triethyl orthoformate was removed under reduced pressure giving brown irregular prisms which, after recrystallization from benzene, afforded cream plates: 1.5 g (75%); mp 185°; ir (KBr) 3110, 3070, 2990, 2960, 1610, 1520, 1450, 1318, 930, 770, 760 cm^{-1}; uv max (CH_3OH) 254 mμ (log ϵ 3.74), 227 (4.45), 205 (4.15); mass spectrum (70 eV) *m/e* (rel intensity) 184 (100), 129 (13), 128 (10), 104 (5), 103 (4), 102 (9), 76 (4); nmr ($CDCl_3$) δ 2.81 (s, 3, CCH_3), 8.91 (s, 1, H_3), 8.30 (m, 4, aromatic).

1-Hydrazino-4-methylphthalazine hydrochloride (2.0 g, 0.01 mol) and triethyl orthoformate under the above reaction conditions gave 6-methyl-*s*-triazolo[3,4-*a*]phthalazine [1.1 g (55%)]. Its hydrochloride was isolated from the hot mother liquor. Recrystallization from methanol afforded cream irregular prisms: 0.3 g (15%); mp 270° dec; ir (Nujol) 1175, 1740, 1200, 990, 880, 730, 695 cm^{-1}.

***s*-Triazolo[3,4-*a*]phthalazine-3-thiol. A. Using Chloroform as Solvent.**—1-Hydrazinophthalazine (2.0 g, 0.02 mol), chloroform (100 ml), and carbon disulfide (10 ml) were heated under reflux until hydrogen sulfide evolution ceased (48 hr). Upon cooling, the product separated from the reaction mixture as yellow irregular prisms, and a second crop was obtained by evaporation of the mother liquor to dryness under reduced pressure. Recrystallization of the combined products from ethanol afforded yellow needles of the thiol: 1.95 g (98%); mp 305°.

B. Using Aqueous Potassium Hydroxide.—The hydrazine (1.59 g, 0.001 mol), ethanol (30 ml), potassium hydroxide (0.56 g) in water (5 ml), and carbon disulfide (1.45 g) were heated under reflux for 3 hr. The reaction mixture was evaporated to dryness under reduced pressure, the residue was dissolved in sodium hydroxide (10% solution) and filtered, and the product was obtained by acidification of the clear solution. Recrystallization from ethanol afforded the thiol as yellow plates: 1.35 g (85%); mp 305°; ir (KBr) 3050, 2120, 1620, 1600, 1550, 1500, 1450, 1320, 1250, 900, 770 cm^{-1}; uv max (CH_3OH) 283 mμ (log ϵ 4.39), 257 (4.07), 220 (4.62).

Methyl-*s*-triazolo[3,4-*a*]phthalazin-3-yl Sulfide.—The above thiol (0.1 g, 0.001 mol) dissolved in sodium hydroxide (20 ml, 1.5 *N* solution), was treated with methyl iodide (15 ml) and the heterogeneous mixture was stirred at room temperature for 25 min and then extracted with chloroform. The chloroform layer was dried (Na_2SO_4) and evaporated to dryness. The crude residue was recrystallized from benzene giving pale yellow irregular prisms: 0.08 g (80%); mp 192–193°; ir (KBr) 3060, 3020, 2920, 1620, 1520, 1460, 1280, 980, 910, 790, 705, 695 cm^{-1}; uv max (CH_3OH) 266 mμ (log ϵ 4.53), 257 (4.53), 214 (4.64); nmr ($CDCl_3$) δ 2.90 (s, 3, S-CH_3), 8.46 (d, 1, J = 0.5 Hz, H_6), 7.90 (m, 4, aromatic), impurity 2.14 (s, probably SH).

3-Amino-*s*-triazolo[3,4-*a*]phthalazine.—1-Hydrazinophthalazine (0.5 g, 0.003 mol) and cyanogen bromide (0.53 g, 0.005 mol) in methanol (50 ml) were refluxed for 2 hr. The reaction mixture was then evaporated to dryness under reduced pressure, the resulting hydrobromide was taken up in water, and the solution was made basic with ammonium carbonate (10% solution). The product was recrystallized from water yielding the amino compound as yellow irregular prisms: 0.15 g (30%); mp 291°; ir (KBr) 3440, 3150, 3025, 1640, 1610, 1560, 1520, 1460, 1455, 980, 740 cm^{-1}; uv max (CH_3OH) 266 mμ (log ϵ 4.43), 258 (4.41), 209 (4.53).

***s*-Triazolo[3,4-*a*]phthalazin-3-ol.**—1-Hydrazinophthalazine (1.0 g, 0.006 mol) and urea (1.1 g, 0.002 mol) were heated to 180°. A solid formed in the melt and the temperature of the bath was then raised to 210° and held there for 1 hr. The residue was recrystallized from ethanol yielding yellow needles: 0.9 g (80%); mp 280° (lit.[2a] mp 276°); ir (KBr) 3500, 3400, 3050, 2800, 1720, 1620, 1550, 1470, 1380, 1125, 1085, 900, 810, 750 cm^{-1}; uv max (CH_3OH) 264 mμ (log ϵ 4.45), 254 (4.32), 207 (4.53); mass spectrum (70 eV) *m/e* (rel intensity) 187 (36), 186 (83), 157 (9), 130 (22), 129 (100), 115 (26), 114 (12), 103 (93), 102 (37), 98 (5), 88 (8), 76 (7).

3-Dichloromethyl-*s*-triazolo[3,4-*a*]phthalazine.—1-Hydrazinophthalazine (5.0 g, 0.3 mol) and dichloroacetic acid (10 ml) were heated on a steam bath for 1 hr. The addition of water (50 ml) caused the product to precipitate. Recrystallization from methanol afforded yellow needles of the dichloro compound: 4.0 g (75%); mp 224° (lit.[2a] mp 215°); ir (KBr) 3050, 1620, 1520,

(30) Infrared spectra were determined using either a Perkin-Elmer Model 421 or Perkin-Elmer 337 recording spectrophotometer and ultraviolet spectra were recorded on a Cary 14 spectrophotometer. Nmr spectra were determined using a Varian A-60 spectrometer and chemical shifts are reported in δ units using tetramethylsilane as an internal standard and standard calibration procedures. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6E recording mass spectrometer with samples being introduced *via* a direct inlet (*ca.* 200°) system. Microanalyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn. The standards for product equivalency for any compounds reported in this work were superimposable infrared spectra and less than 2° depression in a mixture melting point determination.

(31) S. Gabriel and A. Newmann, *Ber.*, **26**, 525, 705 (1893); V. Rothenburgh, *J. Prakt. Chem.*, **51**, 152 (1895); A. Lieck, *Ber.*, **38**, 3922 (1905); M. Hartmann and J. Druey, U. S. Patent, 2,484,029 (Oct 11, 1949); *Chem. Abstr.*, **44**, 4046 (1950); ref 2a.

1450, 1220, 830, 780, 765, 750, 715, 700, 680 cm^{-1}; uv max (CH_3OH) 272 mμ (log ε 4.02), 248 (4.76), 234 sh (4.68), 209 (4.43); mass spectrum (70 eV) *m/e* (rel intensity) 253 (8), 251 (11), 218 (45), 217 (15), 216 (100), 171 (9), 170 (76), 129 (13), 115 (28), 114 (11), 102 (7), 76 (6).

When the above reactants were shaken at room temperature for 1 hr, water (30 ml) was added, and the shaking was continued for an additional hour, 2-(1-phthalazinyl)dichloroacethydrazide precipitated as yellow irregular prisms. Two recrystallizations from methanol gave pale cream needles: 4.8 g (95%); mp 166–168°; ir (KBr) 3250, 3210, 2950, 1650, 1590, 1350, 1170, 1090, 980, 810, 790, 660 cm^{-1}.

Anal. Calcd for $C_{10}H_8Cl_2N_4 \cdot H_2O$: C, 41.54; H, 3.49; N, 19.38. Found: C, 41.58; H, 3.25; N, 19.36.

3-Chloro-s-triazolo[3,4-a]phthalazine.—s-Triazolo[3,4-a]-phthalazine-3-thiol (0.2 g, 0.001 mol) in water and chloroform at 0° was treated with a gentle stream of chlorine for 3 hr. The two-phase system was separated and the aqueous portion was extracted with chloroform. The chloroform portions were combined, dried (Na_2SO_4), and evaporated to dryness. The crude product was recrystallized from water yielding colorless needles of the chloro compound: 0.15 g (70%); mp 223–224°; ir (KBr) 3040, 3020, 1620, 1510, 1450, 1420, 1340, 1310, 1200, 1010, 890, 750, 690 cm^{-1}; uv max (CH_3OH) 274 mμ sh (log ε 3.83), 249 (4.63), 241 (4.70), 234 sh (4.58), 209 (4.33).

Anal. Calcd for $C_9H_5ClN_4$: C, 52.86; H, 2.47; N, 27.38. Found: C, 53.00; H, 2.60; N, 27.32.

3-Hydrazino-s-triazolo[3,4-a]phthalazine.—3-Bromo-s-triazolo[3,4-a]phthalazine (1.5 g, 0.004 mol) and hydrazine hydrate (40 ml, 85%) were refluxed for 3 hr. The product precipitated from the reaction mixture as yellow needles unchanged on recrystallization from methanol: 1.3 g (90%); mp 224–225°; ir (KBr) 3290, 1600, 1550, 1470, 1320, 1270, 1200, 900, 860, 695, 590 cm^{-1}; uv max (CH_3OH) 264 mμ (log ε 4.26), 213 (4.43); mass spectrum (70 eV) *m/e* (rel intensity) 200 (30), 186 (23), 185 (55), 171 (22), 170 (45), 130 (32), 129 (55), 128 (12), 116 (12), 115 (98), 114 (12), 103 (100), 102 (56), 101 (10), 89 (20), 88 (58), 76 (50).

Anal. Calcd for $C_9H_8N_6$: C, 53.93; H, 4.03; N, 41.98. Found: C, 54.02; H, 3.99; N, 42.10.

3-Formyl-s-triazolo[3,4-a]phthalazine.—3-Dichloromethyl-s-triazolo[3,4-a]phthalazine (1.0 g, 0.004 mol) and morpholine (5 ml) were heated on a steam bath for 5 hr. The excess morpholine was removed by distillation under reduced pressure and the crude salt was treated with aqueous hydrochloric acid (25% solution) at room temperature for 1 hr. The crude product was filtered and, after air drying, recrystallized from water giving pale yellow irregular prisms: 0.7 g (60%); mp 237–238°. An analytical sample was recrystallized from benzene: mp 242–243°; ir (KBr) 3050, 2890, 1700, 1640, 1540, 1490, 1455, 1350, 1250, 1160, 1110, 1070, 990, 830, 770, 740, 710, 650 cm^{-1}; uv max (CH_3OH) 272 mμ sh (log ε 3.85), 263 sh (3.88), 246 (4.60), 239 (4.69), 233 sh (460), 206 (4.30); nmr ($CDCl_3$) δ 8.92 (d, 1, J = 1.0 Hz, H_6), 8.05 (m, 4, aromatic), 10.04 (s, 1, CHO).

Anal. Calcd for $C_{10}H_6N_4O$: C, 60.60; H, 3.06; N, 28.27. Found: C, 60.43; H, 3.01; N, 28.26.

Bis-s-triazolo[3,4-a:4,3-c]phthalazine.—1,4-Dihydrazinophthalazine (1.0 g, 0.007 mol) and triethyl orthoformate (50 ml) were refluxed for 17 hr. The product was filtered from the cold reaction mixture and obtained as pale green irregular prisms. Recrystallization from methanol–dimethylformamide gave pale green irregular prisms: 1.7 g (80%); mp 342° dec; ir (KBr) 3040, 1500, 1455, 1420, 1200, 1120, 1080, 1015, 940, 860, 780, 700, 645 cm^{-1}; uv max (CH_3OH) 260 mμ (log ε 4.25), 235 (4.82), 227 (4.88), 220 (4.77); nmr (DMSO-d_6) δ 8.20 (m, 4, aromatic), 10.03 (s, 2, H_3, H_6); mass spectrum (70 eV) *m/e* (rel intensity) 211 (47), 210 (100), 170 (10), 129 (21), 128 (51), 127 (6), 101 (16), 99 (8), 88 (16), 77 (14), 76 (37).

Anal. Calcd for $C_{10}H_6N_6$: C, 57.13; H, 2.88; N, 39.99. Found: C, 57.22; H, 2.95; N, 40.40.

3,6-Diaminobis-s-triazolo[3,4-a:4,3-c]phthalazine.—1,4-Dihydrazinophthalazine[10] (2.0 g, 0.001 mol) in methanol (100 ml) and cyanogen bromide (2.5 g) were refluxed for 36 hr. The product was filtered from the reaction mixture, washed with hot butanol followed by hot dimethylformamide, and air dried giving pale green irregular prisms: 1.7 g (80%); mp 345° dec; ir (KBr) 3310, 3100, 1620, 1560, 1470, 1450, 970, 870, 700, 685, 600 cm^{-1}; uv max (CH_3OH) 267 mμ (log ε 4.51), 205 (4.26); mass spectrum (70 eV) *m/e* (rel intensity) 239 (7.5), 210 (45.5), 209 (100), 184 (7.5), 182 (23), 156 (53), 155 (15), 143 (13), 130 (15.5), 129 (91.5), 128 (43), 127 (15.5), 116 (9.5), 115 (7.5), 101 (17), 89 (12.5), 77 (55), 76 (32).

Anal. Calcd for $C_{10}H_8N_8$: C, 49.99; H, 3.36; N, 46.65. Found: C, 49.86; H, 3.37; N, 46.66.

Ethyl Acetate (3-Methyl-s-triazolo[3,4-a]phthalazin-6-yl)hydrazone.—1,4-Dihydrazinophthalazine (1.0 g, 0.007 mol) and triethyl orthoacetate (30 ml) were refluxed for 48 hr. The triethyl orthoacetate was removed under reduced pressure and the crude product was recrystallized from benzene affording the hydrazone as tan needles: 0.75 g (60%); mp 195–196°; ir (KBr) 3200, 3150, 2950, 1650, 1620, 1500, 1360, 1310, 1060, 940, 765, 700 cm^{-1}; nmr ($CDCl_3$) δ 1.39 (t, 3, J = 7.0 Hz), 2.15 (s, 3), 2.78 (s, 3), 4.30 (q, 2, J = 7.0 Hz), 7.85 (m, 4).

Anal. Calcd for $C_{14}H_{16}N_6O$: C, 59.13; H, 5.68; N, 29.56; mol wt, 284. Found: C, 59.18; H, 5.66; N, 29.50; mol wt, 284.

Ethyl Formate (s-Triazolo[3,4-a]phthalazin-3-yl)hydrazone.—3-Hydrazino-s-triazolo[3,4-a]phthalazine (0.7 g, 0.004 mol) and triethyl orthoformate (25 ml) were refluxed for 17 hr. The product was filtered from the reaction mixture and recrystallized from benzene affording buff irregular prisms of the hydrazone: 0.45 g (60%); mp 205–206°; ir (KBr) 3160, 3050, 2960, 1850, 1600, 1510, 1480, 1450, 1350, 1250, 1130, 1090, 905, 845, 770, 600 cm^{-1}; nmr ($CDCl_3$) δ 1.45 (t, 3, J = 7.0 Hz), 4.40 (q, 2, J = 7.0 Hz), 6.75 (s, 1), 7.85 (m, 1).

Anal. Calcd for $C_{12}H_{12}N_6O$: C, 56.23; H, 4.73; N, 32.80; mol wt, 256. Found: C, 56.38; H, 4.58; N, 32.75; mol wt, 256.

2-(3-s-Triazolo[3,4-a]phthalazin-3-yl)formhydrazide.—3-Hydrazino-s-triazolo[3,4-a]phthalazine (1.0 g, 0.005 mol) and formic acid (17 ml, 98%) were refluxed for 2 hr and the product was isolated by addition of ammonium hydroxide. Recrystallization from ethanol afforded the hydrazide as colorless needles: 0.8 g (85%); mp 277–278°; ir (KBr) 3290, 3150, 2900, 1690, 1605, 1530, 1480, 1290, 1230, 1190, 1065, 905, 780, 765, 700 cm^{-1}; nmr (DMSO-d_6) δ 8.20 (m, 7), 8.95 (s, 1).

Anal. Calcd for $C_{10}H_8N_6O$: C, 52.62; H, 3.54; N, 36.83; mol wt, 228. Found: C, 52.79; H, 3.68; N, 37.04; mol wt, 228.

3-Amino-s-triazolo[4,3-b]-s-triazolo[3,4-a]phthalazine.—3-Hydrazino-s-triazolo[3,4-a]phthalazine (0.8 g, 0.004 mol) and cyanogen bromide (0.6 g, 0.06 mol) in methanol (50 ml) were refluxed for 8 hr. The reaction mixture was evaporated to dryness under reduced pressure and the crude hydrobromide was recrystallized from methanol:ether forming pale yellow irregular prisms: 0.65 g (80%); mp 283°; ir (KBr) 3500, 3410, 3050, 1670, 1550, 1350, 1180, 1070, 920, 800, 700 cm^{-1}.

Anal. Calcd for $C_{10}H_8BrN_7 \cdot H_2O$: C, 37.10; H, 3.18; N, 30.21. Found: C, 37.09; H, 3.02; N, 30.06.

The above salt, dissolved in water (10 ml), was treated with sodium acetate and the resulting precipitate was collected, dried, and recrystallized from benzene–dimethylformamide forming yellow plates of the amino compound: 0.2 g (60%); mp 276°; ir (KBr) 3340, 2790, 1630, 1580, 1460, 1350, 1270, 1190, 920, 765, 705 cm^{-1}; mol wt, 225. 3-Amino-s-triazolo[4,3-b]-s-triazolo[3,4-a]phthalazine was too insoluble for any other spectral determinations to be made.

Ring-Opening of 3-Amino-s-triazolo[4,3-b]-s-triazolo[3,4-a]-phthalazine.—The above hydrochloride (0.7 g, 0.002 mol) and barium hydroxide (1.7 g, 0.01 mol) in water (30 ml) were refluxed for 5 hr. Ammonium carbonate (1.7 g) was then added and all solid material was removed. The mother liquor was evaporated to dryness, the residue was dissolved in water (5 ml) and the solution was made just acid to litmus. 3-Amino-6-(2-carboxamidophenyl)-5H-s-triazolo[5,1-c]-s-triazole separated as yellow, irregular prisms, which after recrystallization from water formed cream, irregular prisms: 0.18 g (25%); mp 282° dec; ir (KBr) 3380, 3260, 3250, 1660, 1600, 1500, 1400, 1200, 1150, 1095, 1050, 795, 710 cm^{-1}; uv max (CH_3OH) 243 mμ (log ε 4.38); mass spectrum M^+ 243.

Anal. Calcd for $C_{10}H_9N_7O \cdot {}^1/_4H_2O$: C, 48.59; H, 3.64; N, 38.50. Found: C, 48.74; H, 3.69; N, 38.00.

Use of alcoholic potassium hydroxide in the above reaction resulted in the formation of a small amount of 3-amino-6-(2-cyanophenyl-5H-s-triazolo[5,1-c]-s-triazole which was characterized spectroscopically: ir (KBr) 3300, 3120, 2230, 1600, 1310, 1200, 1150, 790 cm^{-1}; uv max (CH_3OH) 253 mμ (log ε 4.24).

Oxidation of s-Triazolo[3,4-a]phthalazine.—s-Triazolo[3,4-a]-phthalazine (1.0 g, 0.003 mol) in water (200 ml) was heated on a

steam bath with potassium permanganate (7.4 g) for 5 hr. The manganese dioxide was then removed by filtration and the filtrate was made acid with dilute hydrochloric acid (10% solution). On concentration of the mother liquor, the product separated as almost colorless irregular prisms: 0.43 g (40%); mp 140–142°. It was identical in all respects with an authentic sample of *s*-triazole-3-carboxylic acid.

Lithium Aluminum Hydride Reduction of *s*-Triazolo[3,4-*a*]phthalazines. The Formation of 5,6-Dihydro-*s*-triazolo[3,4-*a*]phthalazine.—*s*-Triazolo[3,4-*a*]phthalazine (0.5 g, 0.003 mol) in dry tetrahydrofuran (20 ml) was stirred at room temperature for 36 hr with an excess of lithium aluminum hydride (0.75 g). The reaction mixture was evaporated to dryness under reduced pressure, water (15 ml) was cautiously added dropwise, and the insoluble material was filtered. The aqueous solution was extracted with chloroform; the chloroform was dried (Na_2SO_4) and then evaporated to dryness. Recrystallization of the residue from benzene afforded golden needles of the dihydro compound: 0.29 g (65%); mp 159–160°; ir (KBr) 3190, 3100, 2970, 2900, 1620, 1500, 1430, 1200, 1190, 1150, 1100, 1050, 970, 940, 900, 860, 760, 710 cm^{-1}; uv max (CH_3OH) 286 sh mμ (log ε 3.15), 250 (4.14); mass spectrum (70 eV) *m/e* (rel intensity) 173 (21), 172 (59), 171 (100), 170 (22), 144 (5), 129 (4), 118 (7), 117 (54), 116 (60), 115 (17), 114 (6), 102 (7), 91 (10), 90 (97), 89 (48), 77 (10), 76 (18).

Anal. Calcd for $C_9H_8N_4$: C, 62.77; H, 4.69; N, 32.54. Found: C, 63.00; H, 4.50; N, 32.37.

Under analogous conditions, 5,6-dihydro-3-methyl-*s*-triazolo[3,4-*a*]phthalazine was obtained from the corresponding 3-methyl compound. It was recrystallized from benzene, affording colorless plates: 50%; mp 193°; ir (KBr) 3150, 2950, 1620, 1500, 1450, 1350, 1300, 1215, 1200, 1135, 1105, 1030, 980, 930, 780, 730, 685, 665, 610 cm^{-1}; uv max (CH_3OH) 291 mμ (log ε 3.24), 260 (4.00), 240 (4.32); nmr ($CDCl_3$) δ 2.34 (s, 3, C_3 CH_3), 4.21 (d, 2, J = 9.0 Hz, C_6 H_2), 5.17 (t, 1, J = 9.0 Hz, N_5 H), 7.61 (m, 4, aromatic).

Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.52; H, 5.43; N, 30.11. Found: C, 64.65; H, 5.50; N, 29.85.

Treatment of 3,6-dimethyl-*s*-triazolo[3,4-*a*]phthalazine (1.8 g, 0.01 mol) with lithium aluminum hydride as described above and recrystallization of the resultant product from water afforded the dihydro compound as colorless irregular prisms: 1.0 g (67%); mp 211–212°; ir (KBr) 3220, 2950, 2900, 1550, 1450, 1400, 1365, 1300, 1205, 1160, 1090, 1035, 990, 910, 870, 705 cm^{-1}; uv max (CH_3OH) 286 mμ (log ε 3.22), 254 (4.22), 205 (4.38); nmr ($CDCl_3$) δ 2.37 (s, 3, C_3 CH_3), 1.37 (d, 3, J = 7.0 Hz, C_6 CH_3), 4.37 (m, 1, J = 7.0 Hz, C_6 H), 5.02 (m, 1, NH), 7.45 (m, 4, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 201 (5), 200 (38), 199 (2), 186 (13.5), 185 (100), 156 (2), 144 (81), 131 (6), 130 (42), 129 (5), 128 (5), 117 (10), 116 (20), 115 (4.5), 104 (8), 103 (29), 102 (13), 101 (4), 90 (11), 89 (26), 88 (5), 77 (27), 76 (10).

Anal. Calcd for $C_{11}H_{12}N_4$: C, 65.96; H, 6.05; N, 27.98. Found: C, 66.22; H, 5.91; N, 28.14.

Use of sodium borohydride in the above reactions gave identical products.

Ring Opening of *s*-Triazolo[3,4-*a*]phthalazines with Base to 3-(2-Cyanophenyl)-*s*-triazole. A. Using Aqueous Barium Hydroxide.—*s*-Triazolo[3,4-*a*]phthalazine (1.2 g, 0.007 mol) and barium hydroxide (1.0 g) in water (50 ml) were refluxed for 24 hr. After the addition of ammonium carbonate (1.5 g), the barium carbonate was removed by filtration and the mother liquor was then evaporated to dryness under reduced pressure. The glassy residue was dissolved in water (3 ml), 1 drop of hydrochloric acid (10% solution) was added, and the crude product was filtered. Recrystallization from water afforded the triazole as colorless needles: 0.5 g (40%); mp 193°; ir (KBr) 3350, 3250, 3050, 2850–2750, 2210, 1640, 1590, 1450, 1410, 1395, 1310, 1250, 1160, 1090, 980, 960, 900, 860, 770, 740, 710 cm^{-1}; uv max (CH_3OH), 263 mμ (log ε 3.86), 230 (4.15), 210 (4.56); mass spectrum (70 eV) *m/e* (rel intensity) 170 (100), 142 (68), 130 (21), 129 (68), 115 (54), 114 (20), 102 (84), 88 (68), 76 (25).

Anal. Calcd for $C_9H_6N_4$: C, 63.51; H, 3.56; N, 32.93. Found: C, 63.28; H, 3.70; N, 32.73.

B. Using Ethanolic Potassium Hydroxide.—*s*-Triazolo-[3,4-*a*]phthalazine (1.0 g, 0.006 mol), anhydrous ethanol (30 ml), and potassium hydroxide (0.4 g) were refluxed for 12 hr. The solution was evaporated to dryness under reduced pressure, the crude salt was dissolved in water, and the solution was made just acid to litmus with hydrochloric acid (10% solution). Recrystallization of the triazole from water gave colorless needles [0.75 g (71%), mp 193°], identical in all respects with that obtained above.

Using procedure B, 3-methyl-*s*-triazolo[3,4-*a*]phthalazine (0.95 g, 0.005 mol) gave, after recrystallization from water, colorless needles of 3-methyl-5-(2-cyanophenyl)-*s*-triazole: 0.45 g (55%); mp 217°; ir (KBr) 3140, 3000, 2900–2500, 2210, 1610, 1580, 1490, 1400, 1200, 1180, 1070, 990, 905, 780, 750, 705 cm^{-1}; uv max (CH_3OH) 290 mμ (log ε 3.84), 255 sh (4.25), 223 (4.82); mass spectrum (70 eV) *m/e* (rel intensity) 185 (45), 184 (100), 155 (8), 129 (39), 128 (13), 115 (50), 102 (38), 101 (10), 89 (8), 88 (76), 76 (15).

Anal. Calcd for $C_{10}H_8N_4$: C, 65.19; H, 4.39; N, 30.42. Found: C, 64.95; H, 4.40; N, 30.29.

6-Phenyl-*s*-triazolo[3,4-*a*]phthalazine (1.0 g, 0.004 mol) was treated with alcoholic potassium hydroxide in a manner analogous to that above. The product isolated was identical in all respects with the starting material: 0.9 g (90%); mp 198–199°. Similarly, *s*-triazolo[3,4-*a*]phthalazin-3-ol (0.5 g, 0.003 mol), when treated as above, gave the starting material: 0.45 g (90%); mp 280°.

Acid Hydrolysis of Bis-*s*-triazolo[3,4-*a*:4,3-*c*]phthalazine.—The tetracyclic system (1.0 g, 0.005 mol) in methanol (20 ml) was refluxed with concentrated hydrochloric acid (3 ml) for 17 hr. The reaction mixture was then evaporated to dryness under reduced pressure and the crude salt was dissolved in water. The aqueous solution was made basic with ammonium hydroxide and the precipitate was collected and air dried. Recrystallization from benzene–dimethylformamide afforded pale purple needles of 6-hydrazino-*s*-triazolo[3,4-*a*]phthalazine: 0.6 g (65%); mp 319–320° dec; purple color lost upon heating; ir (KBr) 3300, 3200, 1650, 1620, 1600, 1500, 1400, 1330, 1145, 1085, 980, 845, 790, 705, 660 cm^{-1}; uv max (CH_3OH) 255 mμ (log ε 3.85), 229 (4.53), 223 sh (4.48).

Anal. Calcd for $C_9H_8N_6$: C, 53.98; H, 4.03; N, 41.98; mol wt, 200. Found: C, 54.00; H, 4.01; N, 41.89; mol wt, 200.

6-Hydrazino-*s*-triazolo[3,4-*a*]phthalazine was refluxed with triethyl orthoformate for 20 hr. The reaction mixture was cooled and the product that separated was removed by filtration. Recrystallization from methanol–dimethylformamide afforded buff irregular prisms (mp 342° dec), identical in all respects with an authentic sample of bis-*s*-triazolo[3,4-*a*:4,3-*c*]phthalazine.

2-Methyl-*s*-triazolo[3,4-*a*]phthalazinium Iodide.—*s*-Triazolo-[3,4-*a*]phthalazine (0.5 g, 0.003 mol) in methanol (90 ml) and methyl iodide (25 ml) were refluxed for 24 hr. The solution was cooled, ether was added and the resulting precipitate was collected. Recrystallization from methanol afforded colorless needles of the iodide: 0.45 g (80%); mp 246–248°; uv max (CH_3OH) 266 mμ (log ε 4.07), 220 (4.60); nmr (DMSO-d_6) δ 4.38 (s, 3, NCH_3), 10.12 (s, 1, H_3), 9.55 (d, 1, J = 1.5 Hz, H_5), 8.29 (m, 4, aromatic).

Anal. Calcd for $C_{10}H_9IN_4$: C, 38.48; H, 2.90; N, 17.95. Found: C, 38.28; H, 2.96; N, 18.02.

2,3-Dimethyl-*s*-triazolo[3,4-*a*]phthalazinium iodide was readily obtained from 3-methyl-*s*-triazolo[3,4-*a*]phthalazine (1.0 g, 0.006 mol) under these conditions. It crystallized from methanol as yellow needles: 1.6 g (80%); mp 284° dec; ir (KBr) 3000, 1620, 1590, 1530, 1440, 1400, 1230, 1020, 905, 855, 690 cm^{-1}; nmr (DMSO-d_6) δ 3.08 (s, 3, CCH_3), 4.34 (s, 3, NCH_3), 9.55 possible doublet, 1, H_5), 8.26 (m, 4, aromatic).

Anal. Calcd for $C_{11}H_{11}IN_4$: C, 40.50; H, 3.41; N, 17.18. Found: C, 40.70; H, 3.46; N, 17.09.

Treatment with methyl iodide (20 ml) at room temperature for 20 hr gave a precipitate of yellow needles: 1.6 g (80%); mp 275° dec; nmr (DMSO-d_6) δ 3.08 (s, 3, CCH_3), 4.34 (s, 3, NCH_3), impurities at 2.86 (s, CCH_3, starting material), 4.64 (s, NCH_3, N_1 isomer).

Potassium Ferricyanide Oxidation of 2-Methyl-*s*-triazolo[3,4-*a*]phthalazinium Iodide.—The above iodide (2.5 g) was dissolved in water (15 ml) and passed through an ion-exchange resin (IRA-400) pretreated with sodium hydroxide (10% solution). Potassium ferricyanide (11 ml, 1 N solution) was then added to the aqueous solution which was stirred at room temperature for 6 hr. The product that separated was removed by filtration and dried. Recrystallization from methanol afforded orange irregular prisms of 2-methyl-*s*-triazolo[3,4-*a*]phthalazin-3-one: 1.1 g (44%); mp 263°; ir (KBr) 3035, 2910, 1695, 1550, 1460, 1370, 1280, 900, 770, 710, 610 cm^{-1}; uv max (CH_3OH) 265 mμ (log ε 4.57), 255 (4.44), 208 (4.59); nmr ($CDCl_3$) δ 3.75 (s, 3, NCH_3), 7.67 (m, 4, aromatic), 8.22 (d, 1, J = 1.5 Hz, H_5).

Anal. Calcd for $C_{10}H_8N_4O$: C, 59.98; H, 4.00; N, 27.99; mol wt, 186. Found: C, 60.21; H, 4.06; N, 28.15; mol wt, 186.

2-Methyl-3-methylthio-*s*-triazolo[3,4-*a*]phthalazinium iodide (0.6 g) was treated with potassium ferricyanide in a manner analogous to that described above. A product (mp 260°) was isolated by continuous ether extraction (12 hr) of the mother liquor. The infrared spectrum was identical with that of 2-methyl-*s*-triazolo[3,4-*a*]phthalazin-3-one prepared below and there was no depression of the mixture melting point.

The Preparation of 2-Methyl-*s*-triazolo[3,4-*a*]phthalazin-3-one by Methylation Procedures. A.—*s*-Triazolo[3,4-*a*]phthalazin-3-ol (3.0 g, 0.002 mol) in methanol (50 ml) was treated with an ethereal alcohol solution of diazomethane (prepared from 5.0 g of Diazald). The reaction mixture was allowed to stand at room temperature for 72 hr, and the solvent was then removed under reduced pressure and the crude residue was recrystallized from ethanol. It formed pale yellow needles of 2-methyl-*s*-triazolo-[3,4-*a*]phthalazin-3-one [2.4 g (80%), mp 261°] and was identical with the product isolated from the above ferricyanide oxidation.

B.—*s*-Triazolo[3,4-*a*]phthalazin-3-ol (1.1 g, 0.006 mol), anhydrous potassium carbonate (1.1 g), acetone (50 ml), and methyl iodide (25 ml) were refluxed for 48 hr. The solution was then evaporated to dryness and the solid residue extracted with chloroform. Evaporation of the chloroform extract, followed by recrystallization of the residue from methanol, gave 2-methyl-*s*-triazolo[3,4-*a*]phthalazin-3-one identical in all respects with that prepared above.

Anhydro-3-mercapto-1-methyl-*s*-triazolo[3,4-*a*]phthalazinium Hydroxide.—1-Methyl-1-(1-phthalazinyl)hydrazine (1.0 g, 0.006 mol), water (15 ml) and carbon disulfide (10 molar excess) were refluxed for 72 hr during which the product separated as brown plates, not changing appreciably on recrystallization from water: 0.9 g (85%); mp 269°; ir (KBr) 3030, 1600, 1550, 1470, 1385, 1140, 1000, 900, 800, 770, 755 cm^{-1}; uv max (CH_3OH) 290 sh mμ (log ε 3.16), 280 sh (3.77), 265 (4.13), 255 (4.10), 243 sh (4.16), 210 (4.46).

Anal. Calcd for $C_{10}H_8N_4S$: C, 55.54; H, 3.74; N, 25.92. Found: C, 55.34; H, 3.89; N, 26.16.

1-Methyl-3-methylthio-*s*-triazolo[3,4-*a*]phthalazinium Methosulfate.—Anhydro-3-mercapto-1-methyl-*s*-triazolo[3,4-*a*]phthalazinium hydroxide (0.35 g, 0.001 mol) and anhydrous dimethyl sulfate (9 ml) were refluxed for 1 hr. The precipitate that separated was collected and twice recrystallized from methanol–ether yielding the methosulfate as colorless needles: 0.23 g (65%); mp 183°; ir (KBr) 3000, 2950, 1625, 1530, 1450, 1360, 1320, 1280, 1250, 1210, 1060, 1020, 900, 760, 690 cm^{-1}; uv max (CH_3OH) 290 sh mμ (log ε 3.93), 280 sh (4.06), 266 sh (4.42), 255 (3.39), 243 (4.46), 210 (4.57); nmr (D_2O) δ 2.92 (s, 3, SCH_3), 4.45 (s, 3, NCH_3), 9.35 (s, 1, H_6), 8.21 (m, 4, aromatic).

2-Methyl-3-methylthio-*s*-triazolo[3,4-*a*]phthalazinium Methosulfate.—Methyl-*s*-triazolo[3,4-*a*]phthalazin-3-yl sulfide (1.0 g, 0.005 mol), anhydrous dimethyl sulfate (1 ml), and benzene (30 ml) were refluxed for 1 hr. The resulting solid was collected and recrystallized from methanol forming colorless plates: 0.8 g (75%); mp 194–195°; ir (KBr) 3050, 2990, 2915, 1620, 1570, 1540, 1480, 1460, 1350, 1270, 1250, 1200, 1050, 1020, 1000, 915, 820, 770, 750, 730 cm^{-1}; uv max (CH_3OH) 268 mμ (log ε 4.43), 220 (4.73); nmr (D_2O) δ 2.90 (s, 3, SCH_3), 4.68 (s, 3, CCH_3), 9.37 (d, 1, J = 1.5 Hz, H_6), 8.45 (m, 4, aromatic).

Anal. Calcd for $C_{12}H_{14}N_4S_2O_4$: C, 42.10; H, 4.13; N, 16.47. Found: C, 42.28; H, 4.21; N, 16.24.

Reactions of 3-Formyl-*s*-triazolo[3,4-*a*]phthalazine. A. Benzoin Condensation.—3-Formyl-*s*-triazolo[3,4-*a*]phthalazine (1.5 g, 0.008 mol) in ethanol (50 ml) was treated with potassium cyanide (0.15 g) in water (10 ml). The reaction mixture was then refluxed for 2 hr. After the mixture had cooled, the solid which separated was removed by filtration and recrystallized from nitrobenzene giving colorless irregular prisms of the acyloin: 1.3 g (80%); mp 279°; ir (KBr) 3400, 3050, 1700, 1630, 1510, 1470, 1440, 1345, 1250, 1180, 1120, 1045, 990, 875, 850, 760, 745, 590 cm^{-1}. The material was too insoluble for further spectral characterization.

Anal. Calcd for $C_{20}H_{12}N_8O_2$: C, 60.60; H, 3.06; N, 28.27; mol wt, 396. Found: C, 60.43; H, 2.91; N, 28.16; mol wt, 396.

B. With Silver Oxide.—The formyl compound (1.0 g, 0.005 mol) was treated with a solution of silver nitrate (1.1 g, 0.01 mol) and sodium hydroxide (1.65 g, 0.04 mol) and the reaction mixture was stirred at room temperature for 1 hr. The elemental silver was removed by filtration and the mother liquor was made acidic with dilute hydrochloric acid (10% solution). The acid solution was extracted with methylene chloride, and the methylene chloride solution was evaporated to dryness under reduced pressure. The product isolated was identical in all respects with *s*-triazolo-[3,4-*a*]phthalazine: 0.6 g (70%); mp 192°.

In several other attempts to prepare *s*-triazolo[3,4-*a*]phthalazine-3-carboxylic acid, 1-hydrazinophthalazine (5.0 g, 0.003 mol) and oxalic acid (3.22 g) were heated at 160°. After reaction work-up in the usual manner, the product was identical in all respects with *s*-triazolo[3,4-*a*]phthalazine: 2.4 g (50%); mp 191°. The hydrazine (2.0 g, 0.001 mol) in dry tetrahydrofuran (70 ml) was treated with *n*-butyllithium in hexane (1.1 ml). Though a color change from yellow to red was noted upon the addition of *n*-butyllithium and this color was discharged when carbon dioxide was bubbled into the reaction mixture, the final product was shown to be identical in all respects with the starting material.

Bromination of *s*-Triazolo[3,4-*a*]phthalazine with N-Bromosuccinimide.—*s*-Triazolo[3,4-*a*]phthalazine (0.5 g, 0.003 mol) in carbon tetrachloride (50 ml) was treated with N-bromosuccinimide (0.523 g) and the mixture was refluxed for 5 hr. The solution was evaporated to dryness under reduced pressure and the crude product recrystallized from water giving 3-bromo-*s*-triazolo[3,4-*a*]phthalazine as pale yellow irregular prisms: 0.42 g (80%); mp 206–208°. An analytical sample was prepared by vacuum sublimation [160° (0.5 mm)]: mp 207–208°; ir (KBr), 3010, 1620, 1515, 1450, 1405, 1365, 1345, 1310, 1200, 1130, 1000, 960, 900, 750, 690 cm^{-1}; uv max (CH_3OH), 273 sh mμ (log ε 3.84), 250 (4.61), 243 (4.68); nmr ($CDCl_3$) δ 7.89 (m, 4, aromatic), 8.64 (d, 1, J = 1.0 Hz, H_6); mass spectrum (70 eV) *m/e* (rel intensity) 251 (10), 250 (94), 249 (10), 248 (95), 169 (8), 142 (6), 141 (22), 129 (12), 116 (10), 115 (100), 114 (24), 113 (83), 102 (9), 89 (13), 88 (44), 76 (10).

Anal. Calcd for $C_9H_5BrN_4$: C, 43.39; H, 2.03; N, 22.50. Found: C, 43.67; H, 2.19; N, 22.46.

Using bromine and acetic acid under reflux also gave 3-bromo-*s*-triazolo[3,4-*a*]phthalazine (50%). However, when this reaction was carried out at room temperature, *s*-triazolo[3,4-*a*]-phthalazine hydrobromide was obtained. It crystallized from methanol [0.45 g (80%); mp 289–290° dec] and was shown to be identical with an authentic sample of *s*-triazolo[3,4-*a*]phthalazine hydrobromide. Incomplete bromination was always obtained when methanol was used as a solvent.

Nitration of the *s*-Triazolo[3,4-*a*]phthalazine System.—6-Methyl-*s*-triazolo[3,4-*a*]phthalazine (0.3 g, 0.002 mol) was stirred at 0° with sulfuric acid (4 ml, 98%). Fuming nitric acid (1.85 ml) and sulfuric acid (8 ml, 98%) were slowly added over a 5-min period and the stirring was continued for 45 min at 0°, then 2 hr at room temperature. The reaction mixture was poured over crushed ice and made basic to litmus with ammonium hydroxide and the resulting crude nitro compound was filtered. Recrystallization from acetone afforded 6-methyl-8-nitro-*s*-triazolo[3,4-*a*]phthalazine as yellow irregular prisms: 0.16 g (50%); mp 315–316°; ir (KBr) 3140, 3080, 3050, 2900, 1610, 1530, 1440, 1375, 1360, 1290, 1200, 1170, 1040, 935, 815, 750, 685 cm^{-1}; uv max (CH_3OH) 240 mμ (log ε 4.35), 224 (4.40); nmr (DMSO-d_6) δ 2.86 (s, 3, C_6CH_3), 8.12 (m, 3, aromatic).

Anal. Calcd for $C_{10}H_7N_5O_2$: C, 52.40; H, 3.08; N, 30.77; mol wt, 229. Found: C, 52.60; H, 3.25; N, 30.52; mol wt, 229.

3-Methyl-*s*-triazolo[3,4-*a*]phthalazine (0.5 g, 0.002 mol), under analogous conditions, gave 8-nitro-*s*-triazolo[3,4-*a*]phthalazine as yellow irregular prisms from acetone: 0.23 g (43%); mp 280–282°; ir (KBr) 3060, 3020, 2900, 1620, 1525, 1440, 1360, 1230, 1140, 850, 815, 760, 720, 690 cm^{-1}.

Anal. Calcd for $C_{10}H_7N_5O_2$: C, 52.40; H, 3.08; N, 30.77; mol wt, 229. Found: C, 52.31; H, 3.27; N, 31.09; mol wt, 229.

Similarly, *s*-triazolo[3,4-*a*]phthalazine (0.5 g, 0.003 mol) gave 8-nitro-*s*-triazolo[3,4-*a*]phthalazine as yellow irregular prisms from acetone: 0.27 g (51%); mp 285°; ir (KBr) 3150, 3020, 1620, 1530, 1440, 1360, 1340, 1230, 1170, 1085, 980, 840, 815, 760, 690 cm^{-1}; nmr (DMSO-d_6) δ 7.95 (m, 3, aromatic), 8.76 (possible doublet, 1, H_6), 9.24 (s, 1, H_3).

Anal. Calcd for $C_9H_5N_5O_2$: C, 50.23; H, 2.35; N, 32.55; mol wt, 215. Found: C, 50.40; H, 2.25; N, 32.85; mol wt, 215.

When copper nitrate–acetic anhydride was used as the nitration medium, *s*-triazolo[3,4-*a*]phthalazine (1.0 g, 0.006 mol) in acetic anhydride (75 ml), after treatment with a stirred suspension of copper nitrate (1.6 g) in acetic anhydride (20 ml) over 72 hr, gave 3-acetyl-*s*-triazolo[3,4-*a*]phthalazine following dilution of the reaction mixture with water and extraction of the product with chloroform. It was recrystallized from water forming colorless, irregular prisms: 0.10 g (10%); mp 269°; ir (KBr) 3050, 1750, 1630, 1590, 1470, 1300, 1240, 1120, 780, 650 cm^{-1}; nmr ($CDCl_3$) δ 2.82 (s, 3, $COCH_3$), 7.81 (m, 4, aromatic), 8.39 (d, 1, J = 1.5 Hz, H_6).

Anal. Calcd for $C_{11}H_8N_4O \cdot H_2O$: C, 57.48; H, 3.50; N, 24.30. Found: C, 57.45; H, 3.43; N, 23.99.

Registry No.—**2** (R^1 = H; R^2 = Cl), 21517-16-8; **2** (R^1 = H; R^2 = $NHNH_2$), 21517-17-9; **2** (R^1 = H; R^2 = NHN=CHOEt), 21537-96-2; **2** (R^1 = H; R^2 = NHNHCHO), 21517-21-5; **2** (R^1 = $NHNH_2$; R^2 = H), 21517-30-6; **2** (R^1 = R^2 = H) (HBr), 21517-38-4; **4** (R^1 = R^2 = H), 21517-18-0; **4** (R^1 = R^2 = NH_2), 21517-19-1; **5**, 21517-20-4; **6** (R^1 = H; R^2 = NH_2), 21517-22-6; **6** (R^1 = H; R^2 = NH_2) (HBr), 21517-23-7; **7**, 21517-24-8; **9** (R^1 = R^2 = H), 21537-97-3; **9** (R^1 = H; R^2 = CH_3), 21517-26-0; **9** (R^1 = R^2 = CH_3), 21517-27-1; **10**, 21517-28-2; **11**, 12376-93-1; **12**, 21517-34-0; **13** (R = H) (iodide), 21517-31-7; **13** (R = SMe) (methosulfate), 21517-35-1; **14**, 21517-33-9; **15** (R^1 = Me; R^2 = H), 21517-39-5; **15** (R^1 = R^2 = H), 21517-40-8; acyloin of 3-formyl-*s*-triazolo-[3,4-*a*]phthalazine, 21517-36-2; 1-methyl-1-(1-phthalazinyl)hydrazine, 21517-14-6; 2-(1-phthalazinyl)dichloroacethydrazide, 21517-15-7; 3-amino-6-(2-cyanophenyl)-5H-*s*-triazolo[5,1-*c*]-*s*-triazole, 21517-25-9; 3-methyl-5-(2-cyanophenyl)-*s*-triazole, 20062-39-9; 2,3-dimethyl-*s*-triazolo[3,4-*a*]phthalazinium iodide, 21517-32-8; 1,3-dimethyl-*s*-triazolo[3,4-*a*]phthalazinium iodide, 21517-37-3.

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Oxidations with Lead Tetraacetate. III. Cyclization of Ketosemicarbazones to 2-Imino-Δ^3-1,3,4-oxadiazolines[1]

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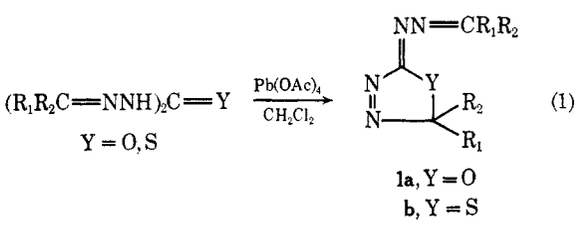
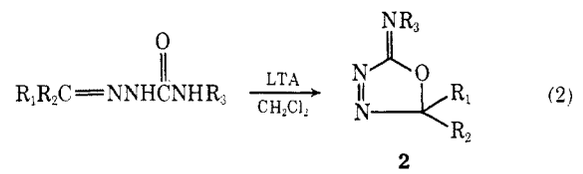
Acetone 4-benzylsemicarbazone is oxidized by lead tetraacetate (LTA) to 5,5-dimethyl-2-benzylimino-Δ^3-1,3,4-oxadiazoline. Eight other members of this new type of oxadiazoline were synthesized. Assignment of the gross structure is based on the spectra of the compounds and on their reactions. The geometry at the exocyclic imino function is not rigorously established but the *anti* (azo) configuration is suggested on the basis of some of the nmr spectra.

Oxidative cyclization of ketocarbohydrazones to oxadiazolines and of acetone thiocarbohydrazone to a thiadiazoline, according to eq 1, were reported recently.[2] We have explored the generality of that type of oxidative ring closure and we now report the synthesis and some properties of related oxadiazolines, eq 2, from semicarbazones and LTA.



(1)

1a, Y = O
b, Y = S

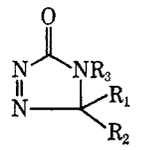


(2)

2

Results and Discussion

The oxadiazoline structure is assigned to the products on the basis of analytical data, molecular weights, spectra, and chemical behavior. The spectra of structures **1** were discussed in detail earlier in establishing those assignments, and the choice of the oxadiazoline structure (**2**) instead of the triazolinone structure (**3**), in the present case, is based largely on analogy.[2]



3

The infrared spectra (Table I) are characterized by a sharp, intense absorption in the region of 1694–1715 cm^{-1}, which can be assigned to the stretching frequency of the exocyclic C=N function.[2] Of the other absorptions noted in Table I, a band in the region of 1114–1156 cm^{-1} appears to be a common feature, regardless of the substituents. It may be caused by a ring vibration associated with the C—O—C function.

The compounds are characterized by two bands in the ultraviolet spectrum, with maxima ranging from 220 to 260 mμ and from 316 to 357 mμ. Both bands must arise from $\pi \rightarrow \pi^*$ transitions.[3] The band at longer wavelength shows fine structure with hydrocarbon solvents and it tails into the visible to obscure the expected weak, $n \rightarrow \pi^*$ (azo) absorption.[3]

(1) Taken, in part, from the Ph.D. Thesis of P. R. West, McMaster University, 1967.

(2) P. R. West and J. Warkentin, *J. Org. Chem.*, **33**, 2089 (1968).

(3) An exception is **4** in which R_3 is alkyl. Its $\pi \rightarrow \pi^*$ transition occurs at about 260 mμ and the weaker band at higher wavelength (329 mμ) is probably the $n \rightarrow \pi^*$ band. A shoulder on the high wavelength, $\pi \rightarrow \pi^*$ band in some of the spectra may be caused by an $n \rightarrow \pi^*$ transition.