Diaziridines. IV. Reaction of Some 1,1-Dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones with Nitrones

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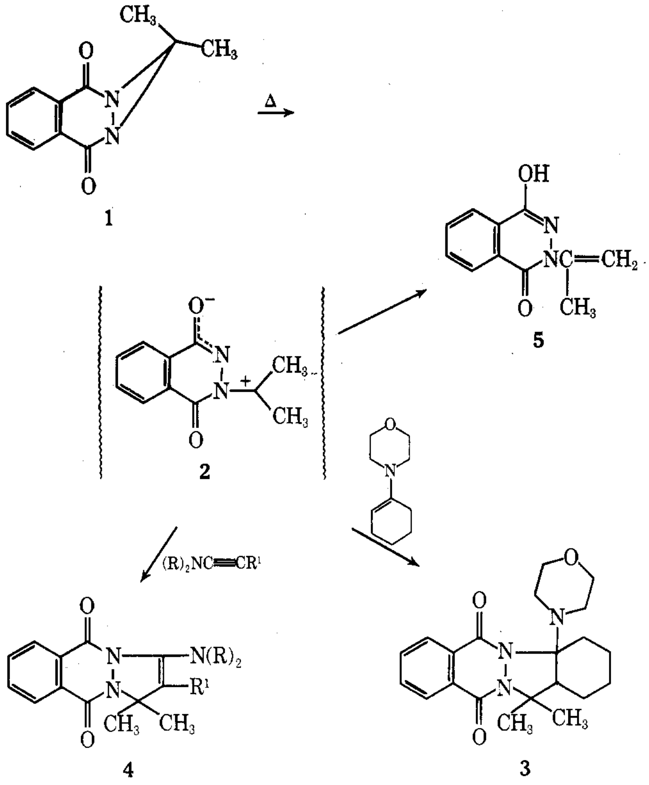
Received May 21, 1974

Reaction of 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones with nitrones in refluxing benzene gave 1*H*-[1,2,4,5]oxatriazino[4,5-*b*]phthalazine-6,11-diones. The latter compounds are hydrolyzed in aqueous methanol to 4-hydroxy-1(2*H*)-phthalazinone, ketones, and nitrones. It was also shown that 2-isopropenyl-4-hydroxy-1(2*H*)-phthalazinone reacted with nitrones in benzene to also form 1*H*-[1,2,4,5]oxatriazino[4,5-*b*]phthalazine-6,11-diones in low yields.

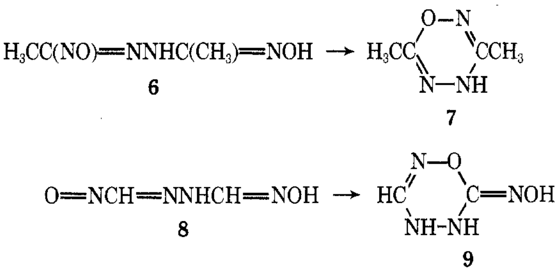
Recently reported reactions of 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones suggest that these substances are prone to form azomethine imines as reaction intermediates.[1] It appears, for example, that 1,1-dimethyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-dione (1) in boiling toluene or benzene is converted to 2, which then adds to enamines or ynamines to give 3 and 4, respectively, or in the absence of these reagents rearranges to 5 (Scheme I).[1]

Scheme I



The present paper deals with the reaction of 1,1-dialkyl-1*H*-diazirino[1,2*b*]phthalazine-3,8-diones with nitrones. The products are derivatives of the virtually unknown 1,2,4,5-oxatriazine system. Wieland was the first and perhaps the only one to synthesize 1,2,4,5-oxatriazines. He claimed that 6 was transformed into 7 in boiling water[2] and that 8 isomerized to 9 in acid[3] (Scheme II).

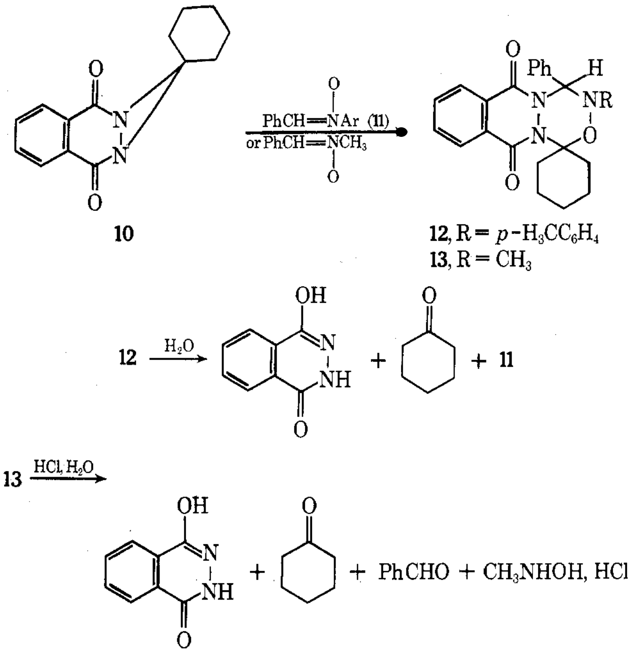
Scheme II



Results and Discussion

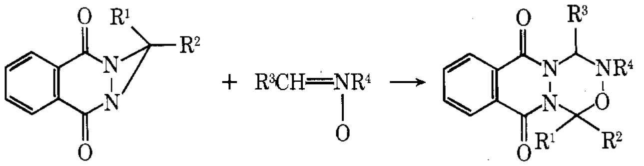
Heating of 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones with nitrones in benzene gives 1*H*-[1,2,4,5]oxatriazino[4,5-*b*]phthalazine-6,11-diones (Table I). Thus reaction of 10 with α-phenyl-*N*-*p*-tolylnitrone (11) and α-phenyl-*N*-methylnitrone gave 12 and 13, respectively (Scheme III).

Scheme III



The structure of 12 was established by mass spectroscopy, by nmr spectroscopy, and by the hydrolysis of 12 in aqueous methanol to 4-hydroxy-1(2*H*)-phthalazinone, cyclohexanone, and α-phenyl-*N*-*p*-tolylnitrone (11) (Scheme III). The acid hydrolysis of 13 gave analogous products, namely, 4-hydroxy-1(2*H*)-phthalazinone, cyclohexanone, benzaldehyde, and *N*-methylhydroxylamine hydrochloride. Most probably during the hydrolysis of 13, α-phenyl-*N*-methylnitrone was produced and subsequently hydrolyzed to benzaldehyde and *N*-methylhydroxylamine hydrochloride. *N*-Alkylnitrones have been reported to be far more susceptible to hydrolysis than *N*-arylnitrones.[4]

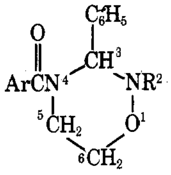
Table I
1*H*-[1,2,4,5]Oxatriazino[4,5-*b*]phthalazine-6,11-diones from the Reaction of Nitrones with 1,1-Dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones[a]



Compd	R^1	R^2	R^3	R^4	Crude yield, %	Mp, °C[b]
12	$-(CH_2)_5-$		Ph	p-$H_3CC_6H_4$	85	171–172
13	$-(CH_2)_5-$		Ph	Me	84	160–162
14	$-(CH_2)_5-$		Me	C_6H_{11}	71	139–141
15	Me	Me	Ph	p-$H_3CC_6H_4$	80	157–159
16	Me	Me	Ph	Me	66	137–140
17	n-Pr	n-Pr	Ph	p-$H_3CC_6H_4$	50	163–165

[a] Satisfactory analytical data for C, H, and N were obtained for all compounds listed in this table. Ed. [b] Compounds 12–17 were recrystallized from acetonitrile.

The nmr spectra of **12–17** were consistent with the proposed structures. The *N*-methyl groups of **13** and **16** appeared at δ 2.50 and 2.60, respectively, and the *gem*-dimethyl groups of **16** at δ 2.30 and 1.67. The *p*-tolylmethyl group of **15** appeared at δ 2.37 and the *gem*-dimethyl groups gave signals at δ 2.28 and 1.80. Those 1,2,4,5-oxatriazino derivatives bearing *N*-alkyl groups, *i.e.*, **13, 14,** and **16,** showed the methine hydrogens at δ 6.00, 6.10, and 6.01, respectively. The signals for the methine hydrogens of those 1,2,4,5-oxatriazines bearing *N*-aryl groups (**12, 15,** and **17**) were obscured by the absorption of the aromatic protons. The chemical shifts of the methine protons of **12–17** are analogous to those observed for the similar system, 4-aroyltetrahydro-2*H*-1,2,4-oxadiazines (**18**).[5] The methine hydrogen at C-3 absorbed in the aromatic region for those 1,2,4-oxadiazines substituted with aryl groups in the 2 position of the ring while those examples of **18** with methyl groups in the 2 position absorbed at δ 5.8.



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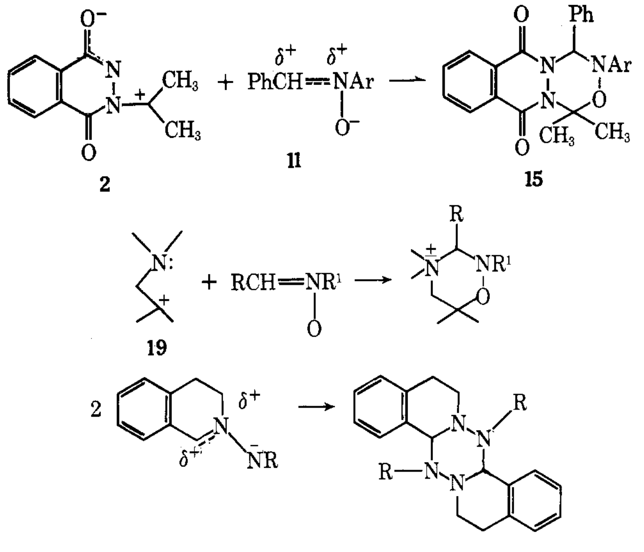
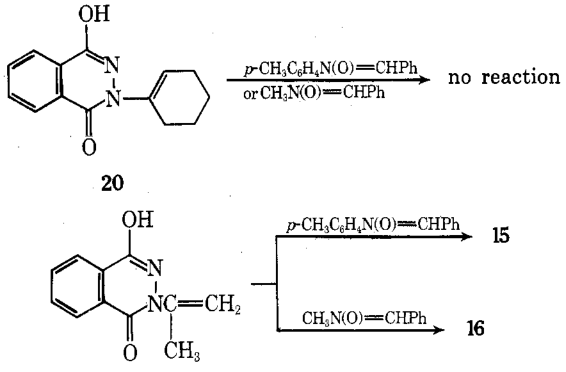
The 1,2,4,5-oxatriazines may be regarded as arising from the cycloaddition of two different 1,3-dipolar species, namely, the azomethine imine generated from the 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones (*e.g.*, **2**) and the nitrone (Scheme IV). Few examples of cycloaddition reactions between dissimilar 1,3-dipoles are known, although an interesting case of a cycloaddition of a nitrone with the 1,3-polar moiety **19** formed from an aziridinium ring has recently been reported by Leonard[6] and his colleagues (Scheme IV). Cycloadditions of similar 1,3-dipoles, such as the cyclodimerizations of azomethine imines, have been observed[7–10] (Scheme IV).

Since nitrones are known to react with alkenes to yield isoxazolidines[11–13] and since 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones isomerize into 2-(1-alken-1-yl)-4-hydroxy-1(2*H*)-phthalazinones (*e.g.*, **1** → **5**, Scheme I), experiments were conducted to see if the latter compounds would react with nitrones. There was no reaction when mixtures of **20** and α-phenyl-*N*-*p*-tolylnitrone or α-phenyl-*N*-methylnitrone were heated in benzene for 7.5 hr. Treatment of **5** with the above nitrones for 7.5 hr did not form isoxazolidines but surprisingly did give small yields ($\simeq$15%) of **15** and **16** (Scheme V). This is to be contrasted with the high yields of **15** and **16** (80 and 66%, Table I) that were obtained when mixtures of **1** and α-phenyl-*N*-*p*-tolylnitrone and **1** and α-phenyl-*N*-methylnitrone were heated in benzene for 6 hr.

Scheme IV



Scheme V

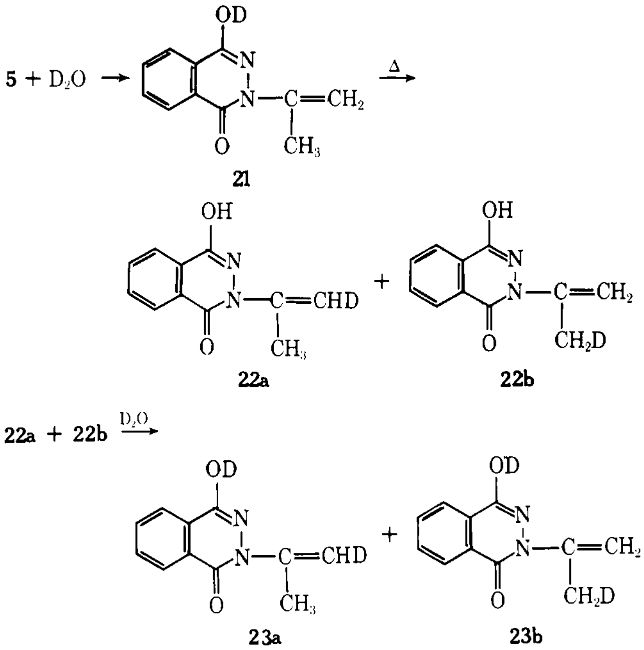


That **5** interacts with α-phenyl-*N*-*p*-tolylnitrone and α-phenyl-*N*-methylnitrone to give small amounts of **15** and **16** is explicable if **5** is in equilibrium with the azomethine imine **2** which undergoes a cycloaddition reaction with the nitrones.

$$\mathbf{5} \rightleftharpoons \mathbf{2}$$

The following experiments suggest that such an equilibrium exists. When a chloroform solution of **5** was treated with deuterium oxide, the nmr absorption for the OH proton at δ 10.00 disappeared immediately. This peak reappeared after heating **21** at reflux in toluene overnight owing to exchange of the OD with the protons of the isopropenyl group. The latter material was probably a mixture of **22a** and **22b** and some **21** (Scheme VI). The mixture of **22a** and **22b** was then treated again with D_2O to give a mixture of **23a** and **23b** (Scheme VI). The latter mixture was analyzed by mass spectroscopy and its mass spectrum was compared to that of some untreated **5.** Significant quantities of the mixture **23a** and **23b** showed a molecular ion *m/e* 204 (*i.e.*, 18.6% relative to the standard **5** which gave only 1.1% of *m/e* 204).

Scheme VI



That the reaction of **5** with α-phenyl-*N*-*p*-tolylnitrone and α-phenyl-*N*-methylnitrone results in only about 15% of **15** or **16** is probably due to the greater basicity of **15** and **16** relative to the alkene moiety of **5.** As **15** and **16** accumulate in the reaction mixture they capture the acidic proton of **5**, thus preventing further formation of the azomethine imine **2.**

Experimental Section

Materials. The nitrones were prepared by reaction of N-substituted hydroxylamines with aldehydes according to literature procedures[14,15] and were known compounds.

Syntheses of 1*H*-[1,2,4,5]Oxatriazino[4,5-*b*]phthalazine-6,11-diones 12–17 (Table I). A mixture of 2 mmol of the nitrone and 2 mmol of the 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-dione in 15 ml of anhydrous benzene was refluxed for 6 hr. The cooled reaction mixture was filtered and the solvent was evaporated. The residue was slurried with a small quantity of cold methanol and the crude crystalline **12–17** were filtered and recrystallized from acetonitrile.

Hydrolysis of 12. A solution of 453 mg (1 mmol) of **13** in 10 ml of CH_3OH containing 6 drops of water was refluxed for 2 hr. The cooled reaction mixture was filtered to give 120 mg (77%) of the 4-hydroxy-1(2*H*)-phthalazinone. Evaporation of the filtrate gave 150 mg (71%) of α-phenyl-*N*-tolylnitrone.

Hydrolysis of 13. A solution of 377 mg (1 mmol) of **13** in 10 ml of CH_3OH containing 1 drop of hydrochloric acid was refluxed for 1 hr. The solution was cooled and the 4-hydroxy-1(2*H*)-phthalazinone (130 mg, 81%) was filtered. A solution of 2,4-dinitrophenylhydrazine was added to the filtrate and the precipitate (450 mg) of a mixture of 2,4-dinitrophenylhydrazones of benzaldehyde and cyclohexanone was filtered. Separation of the 2,4-dinitrophenylhydrazones was easily achieved by recrystallizing from ethanol. The benzaldehyde 2,4-dinitrophenylhydrazone precipitated selectively from the hot solvent and was filtered. The cooled filtrate yielded the cyclohexanone 2,4-dinitrophenylhydrazone.

The *N*-methylhydroxylamine hydrochloride was isolated by repeating the hydrolysis of **13**, filtering the 4-hydroxy-1(2*H*)-phthalazinone, and evaporating the filtrate to dryness. The residue weighed 50 mg (60%) and its infrared spectrum was identical with that of a commercial sample of *N*-methylhydroxylamine hydrochloride.

Acknowledgment. We thank Professor Charles C. Sweeley for the mass spectra of some of the compounds reported in this paper. Financial support from the Henry and Camille Dreyfus Foundation and the National Institutes of Health is gratefully acknowledged.

Registry No.—**1**, 52165-36-3; **1** *n*-Pr analog, 52165-37-4; **10**, 52165-38-5; **12**, 52165-39-6; **13**, 52165-40-9; **14**, 52165-41-0; **15**, 52165-42-1; **16**, 52165-43-2; **17**, 52165-44-3; α-phenyl-*N*-*p*-tolylnitrone, 19064-77-8; α-phenyl-*N*-methylnitrone, 3376-23-6; α-methyl-*N*-cyclohexylnitrone, 3376-30-5.

References and Notes

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