Table III. First-Order Rate Constants and Product Distribution for the Hydrolysis of Phenyl N-Methylacetimidate at 25° and Ionic Strength 0.50[a]

pH	k_{obsd}, min^{-1}	Ester produced, %
0.35	0.055	50
0.53	0.053	53
0.67	0.055	55
0.75	0.055	55
1.0	0.052	54
1.22	0.050	50
1.7	0.053	35
2.0	0.052	28
2.5	0.052	24
3.0	0.053	20
3.5	0.052	20
4.0	0.053	20
4.5	0.053	18
5.0	0.052	17

[a] Ionic strength maintained with lithium chloride.

and methylamine in about equal amounts.[16] This interpretation requires that the break in the pH–rate profile previously observed must be the consequence of changes in activity coefficients with increasing acidity rather than a transition in rate-determining step. In view of these considerations, we have extended our previous investigations both to include product analysis under more acidic conditions and to study the reaction kinetics in solutions in which the ionic strength is maintained constant with lithium chloride.[9b] The results of these studies are collected in Table III. In the first place, our product analyses are clearly in substantial agreement with those of Jencks and Gilchrist although the higher ionic strength employed here tends to increase somewhat the tendency of the neutral and cationic tetrahedral intermediates to expel methylamine rather than phenol. It is important to note that the yields of ester below pH 2 are minimum yields since it is probable that phenyl acetate hydrolyzes to some extent as it is being formed. Jencks and Gilchrist did observe that the yield of ester in this reaction was time dependent under these conditions suggesting that such hydrolysis does occur.[16] In the second place, the rate constants measured in the presence of lithium chloride do not exhibit the break in the pH–rate profile observed for this reaction in the presence of potassium chloride. Clearly, then, the break is a consequence of a change in activity coefficients and not a consequence of a change in the rate-determining step.

Acknowledgment. We are indebted to Dr. Gaston Schmir for communicating pertinent results to us prior to publication and to Drs. Schmir and Jencks for helpful comments.

Reactions of Cyclic 1,3-Diketones with Hydrazine. The Mechanism of Cinnolino[5,4,3-*cde*]cinnoline Formation. An Unusual Oxidation as a Result of Steric Crowding[1]

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Contribution from the Department of Chemistry, University of Iowa, Iowa City, Iowa 52240. *Received June 28, 1968*

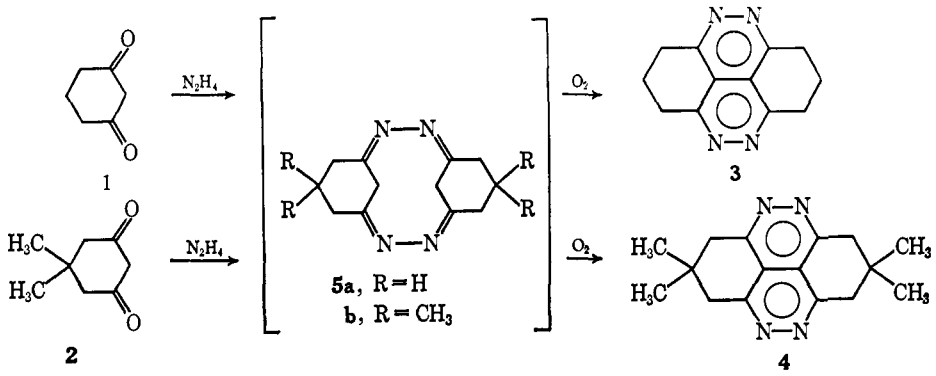
Abstract: The condensation of 5,5-dimethyl-1,3-cyclohexanedione with hydrazine to afford 2,2,7,7-tetramethyl-1,2,3,6,7,8-hexahydrocinnolino[5,4,3-*cde*]cinnoline was shown to proceed through an unstable diazine intermediate, 6,6,13,13-tetramethyl-2,3,9,10-tetraazatricyclo[9.3.1.1^{4,8}]hexadeca-1,3,8,10-tetracene. The mechanism of this reaction was investigated with respect to the conditions and steric requirements for the unusual oxidation reaction of the diazine intermediate. This oxidation occurs with atmospheric oxygen relatively easily, probably due to the steric crowding on the internal methylene groups of the intermediate. This method of cinnolinocinnoline formation was studied utilizing other six-membered cyclic β-diketones, as well as five- and seven-membered cyclic β-diketones. The five-membered compounds do not form the pyridazino[4,5-*d*]pyridazine derivatives with hydrazine; instead only hydrazone formation was observed. However, the condensation of 2,2′-biindan-1,1′3,3′-tetrone with hydrazine gave diindeno[1,2-*c*:2′,1′-*e*]pyridazine-11,12-dihydrazone. The seven-membered compounds did not form pyridazino[4,5-*d*]pyridazine derivatives with hydrazine and no identifiable products were isolated.

The reactions of 1,3-cyclohexanedione (**1**) and 5,5-dimethyl-1,3-cyclohexanedione (**2**) with hydrazine hydrate have been shown to afford 1,2,3,6,7,8-hexahydrocinnolino[5,4,3-*cde*]cinnoline (**3**) and 2,2,7,7-tetramethyl-1,2,3,6,7,8-hexahydrocinnolino[5,4,3-*cde*]cinnoline (**4**), respectively.[2] The formation of **3** and **4** was proposed to proceed through the unstable intermediates, 2,3,9,10-tetraazatricyclo[9.3.1.1^{4,8}]hexadeca-1,3,8,10-tetracene (**5a**) and 6,6,13,13-tetramethyl-2,3,9,-10-tetraazatricyclo[9.3.1.1^{4,8}]hexadeca-1,3,8,10-tetracene (**5b**), respectively, which then oxidized in the presence of air to the aromatic products. An oxidation of this nature occurs in several [2.2]metacyclophane derivatives, affording products containing the pyrene nucleus.[3-8] The observation of the inter-

(1) This research was supported by National Institutes of Health Grant No. A1-CA06302-01.

(2) J. K. Stille and R. Ertz, *J. Amer. Chem. Soc.*, **86**, 661 (1964).

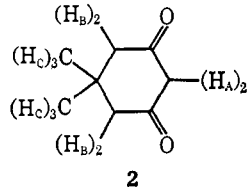
(3) B. H. Smith, "Bridged Aromatic Compounds," Academic Press, New York, N. Y., 1964, p 259.



mediates **5a** and **5b** and the conditions for their conversion to **3** and **4**, as well as the steric requirements necessary for the formation of **5a** and **5b**, were investigated to elucidate the mechanism of this unusual oxidation.

Results and Discussion

An attempt was made to isolate the pure diazine intermediate by carrying out the condensation of 5,5-dimethyl-1,3-cyclohexanedione (**2**) with hydrazine hydrate in an inert atmosphere. The intermediate **5b** was isolated by removing the solvent and any volatile products at reduced pressure. The compound isolated was a bright orange, semicrystalline glass which was soluble in a variety of organic solvents. The nuclear magnetic resonance (nmr) spectrum of this material showed that it contained some residual **2** and hydrazine.[9] The spectrum of **5b** was relatively simple, exhibiting a sharp singlet (six protons) at 1.19 ppm and a sharp singlet (four protons) at 2.41 ppm in methanol. The signals were assigned to the methyl groups (H_C) and methylene groups (H_B) of **5b**. The methylene group (H_A) which was located between the azine linkages could not be observed in the presence of hydrazine, and although **5b** could be purified enough to obtain a clean spectrum by prolonged storage at reduced pressure (10^{-4} mm), the last traces of residual hydrazine were impossible to remove. Purification of **5b** was hindered by its facile oxidation to the aromatic product **4**.



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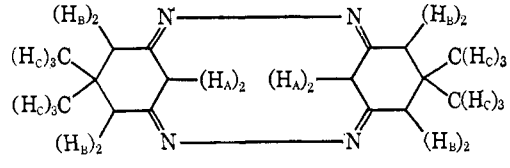
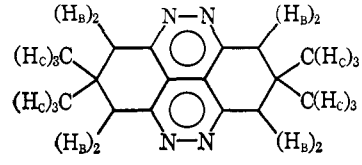


5b

Spectra of the starting material, **2**, the crude intermediate, **5b**, and the product, **4**, were observed in methanol, dimethyl-d_6 sulfoxide (DMSO), and chloroform-d_1 (Table I).



4

An nmr study of the reaction path was carried out to verify the formation of the proposed diazine intermediate. The condensation of **2** with hydrazine hydrate to afford **5b** was chosen because the reaction

Table I. The Chemical Shifts of **2**, **5b**, and **4** as a Function of Solvent

Compd	Solvent	Chemical shift[a] H_A	H_B	H_C
2	CH_3OH	(5.51)[c]	2.39	1.21
	DMSO-d_6	5.27	2.13	0.98
	$CDCl_3$	5.49	2.27	1.05
5b	CH_3OH	*b*	2.41	1.19
	DMSO-d_6	*b*	2.17	0.95
	$CDCl_3$	*b*	2.27	1.06
4	CH_3OH		(3.39)[c]	1.30
	DMSO-d_6		3.15	1.08
	$CDCl_3$		3.12	1.08

[a] All chemical shifts are in parts per million (ppm) downfield from TMS. [b] Addition of hydrazine hydrate immediately obscures this signal. [c] This signal was not observed because of the solvent. This is the predicted chemical shift, based on the DMSO-d_6 spectrum.

proceeded at a favorable rate and the spectra of the reactant, intermediate, and product, all containing the *gem*-dimethyl group, were less complicated than the unsubstituted analogs. Equimolar portions of 5,5-dimethyl-1,3-cyclohexanedione (**2**) and hydrazine hydrate in degassed methanol were placed in a nmr tube, and the spectrum was observed periodically over 24 hr, during which time the formation of **5b** was observed. Then oxygen was bubbled through the solution and the formation of **4**, concurrent with the disappearance of **5b**, was observed.

As the condensation proceeded in the absence of oxygen, the H_B proton signal of **2** began to decrease in intensity and the H_B proton signal of **5b** appeared and increased in intensity. The H_C proton signals of **2** and **5b** have the same chemical shift, and no change in this peak was observed. The H_A methylene groups of

(4) V. Boekelheide and J. B. Phillips, *J. Amer. Chem. Soc.*, **89**, 1695 (1967).
(5) H. R. Blattman, D. Meuche, E. Heilbronner, R. J. Molyneaux, and V. Boekelheide, *ibid.*, **87**, 130 (1965).
(6) J. Phillips, R. J. Molyeax, E. Strum, and V. Boekelheide, *ibid.*, **89**, 1704 (1967).
(7) V. Boekelheide and T. Miyasaka, *ibid.*, **89**, 1709 (1967).
(8) H. Blaschke and V. Boekelheide, *ibid.*, **89**, 2747 (1967).
(9) All spectra were recorded on a Varian Associates HA-100 spectrometer.

Table II. The Chemical Shifts[a] of 2, 5b, and 4, as a Function of Time during the Reaction

Time,[g] hr	2		5b		4	
	H_B	H_C	H_B	H_C	H_B	H_C
0	2.13 (2)[b]	1.21 (3)				
2.5	2.13 (1.75)	1.21 (3)[c]	2.41 (0.25)	1.21 (3)[c]		
24.0[d]	2.13 (0.9)	1.21 (3)[c]	2.41 (1.1)	1.21 (3)[c]		
24.5	2.13 (0.9)	1.21 (2.3)[c]	2.53 (0.25)	1.21 (2.3)[c]		1.30 (0.7)
25.5[e]	2.13 (0.9)	1.21 (1.6)[c]	2.66 (0.1)	1.21 (1.6)[c]		1.30 (1.4)

[a] All chemical shifts are in parts per million (ppm) downfield from TMS. [b] Relative intensity of the signal. [c] The chemical shifts of the H_C protons of 2 and 5b are the same and this relative intensity is the sum of both signals. [d] Oxygen was passed through the sample for 5 min immediately after this spectrum was taken. [e] Oxygen was passed through the sample for 5 min immediately before this spectrum was taken. [f] Solvent obscures observation of this signal. [g] After mixing.

both 2 and 5b are not observed because they exchange with the hydrazine hydrate protons under the reaction conditions. After a period of *ca.* 8 hr, the H_B proton signal of 5b ceased to increase in intensity and little further change was observed over an additional 12-hr period. Some decomposition occurred during this time, as evidenced by the appearance of a weak proton signal upfield from the H_C proton signal.

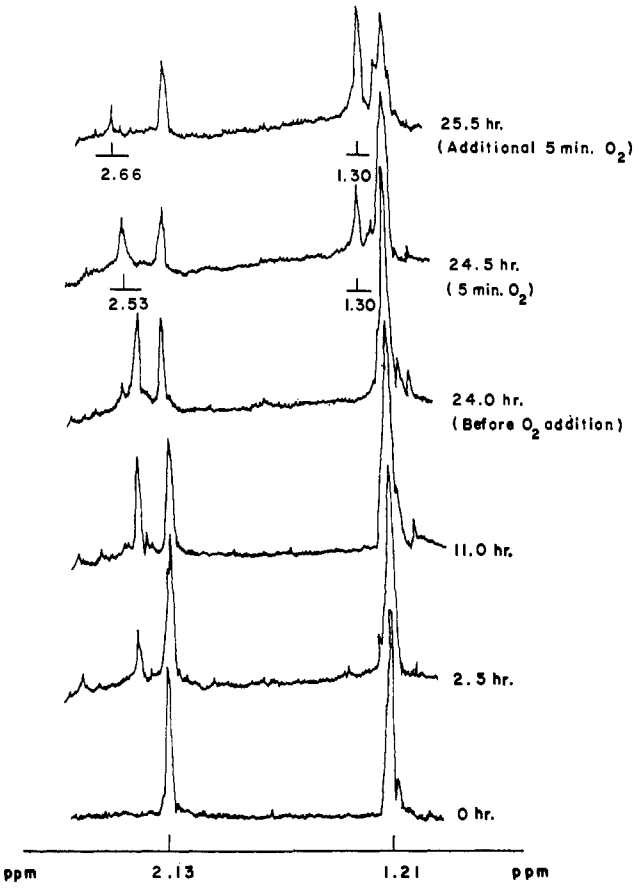


Figure 1. Nmr time study analysis of the formation of 4 *via* the diazine intermediate 5b.

When oxygen was passed through the sample for 5 min, the H_B and H_C proton signals of 5b began to diminish in intensity and the H_C proton signal of 4, which could be distinguished from the H_C proton signal of 2 and 5b, appeared and began to increase in intensity. The solvent obscured the H_B proton signal of 4. The sample was observed for 1 hr after the oxygen treatment and no change occurred during this time. When oxygen was passed through the sample for an additional 5 min, the intensity of the H_C proton signal of 4 increased with the concurrent decrease in the intensity of the H_B and H_C proton signals of 5b. During the oxygen treatment, the H_B signal of 5b was observed to shift slightly downfield. The nmr spectra appears in Figure 1 and a tabulation of the observed chemical shifts during the course of this reaction appears in Table II.

These results are in agreement with the proposed reaction path (2 → 5b → 4) and indicate that when the reaction is run in solution, the air-oxidation step is controlled by the availability of oxygen. Since oxidation only occurs when oxygen was passed through the sample, it appears that the rate of oxidation is controlled by the diffusion of oxygen through the condensed phase. The distinct singlet signals and the absence of any major extraneous signals supported the presence of only one intermediate, 5b.

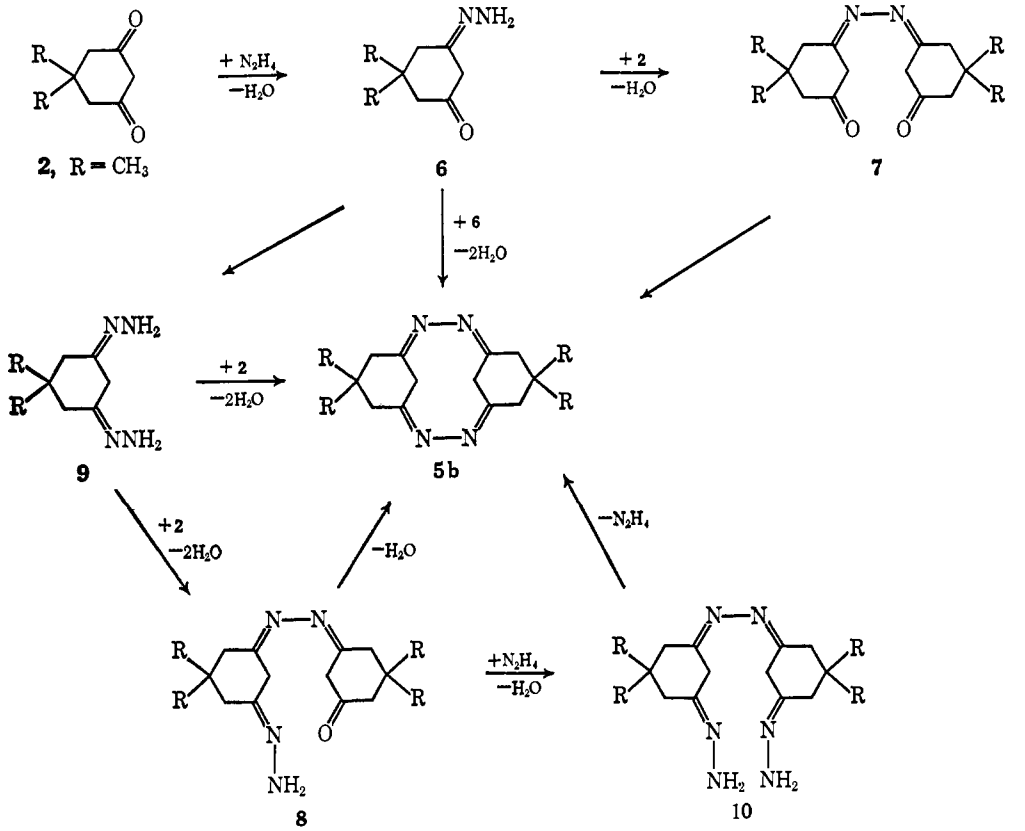
The intermediate diazine 5b could have been formed from 2 *via* any one of the several reaction paths indicated in Scheme I. None of these compounds except 5b could have been long lived or they would have been observed in the nmr study. Compounds 6–8 would not be expected to be long lived in a solution containing hydrazine, since they all contain a free ketone function. Compounds 9 and 10 could be stable but were not observed and therefore were either not present or were very short lived.

In the oxidation step, the conversion of 5b to 4 through a free-radical intermediate is a distinct possibility. Only when oxygen was admitted to the reaction mixture was the characteristic blood red color observed. Electron paramagnetic resonance (epr) spectra were recorded during the oxidation of 5b to 4, but no signal was observed in chloroform or ethanol. It is still possible that a free radical was involved in the oxidation, but it must have been too short lived or present in too low a concentration to permit observation.

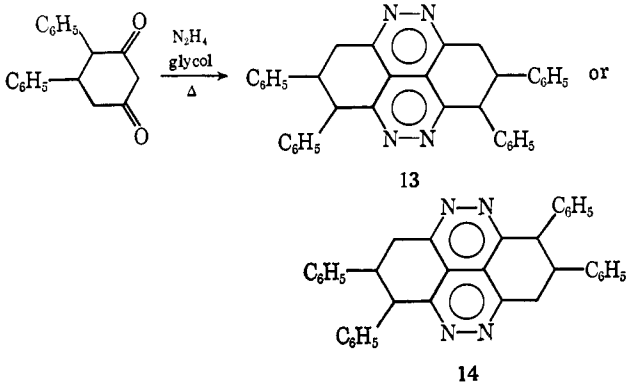
In order to test the generality of this unusual reaction and to evaluate the steric requirements attending the internal hydrogen crowding, several cyclic 1,3-diketones were subjected to the conditions of this reaction. The condensation of several six-membered cyclic β-diketones with hydrazine was investigated. Although the condensation was originally reported as occurring in ethanol at the reflux temperature,[2] the use of ethylene glycol at the reflux temperature generally led to higher yields, and in certain cases the condensation occurred only if refluxing ethylene glycol was employed.[10]

The reaction of 4,5-diphenyl-1,3-cyclohexanedione

Scheme I. Possible Reaction Pathways to the Diazine Intermediate **5b**

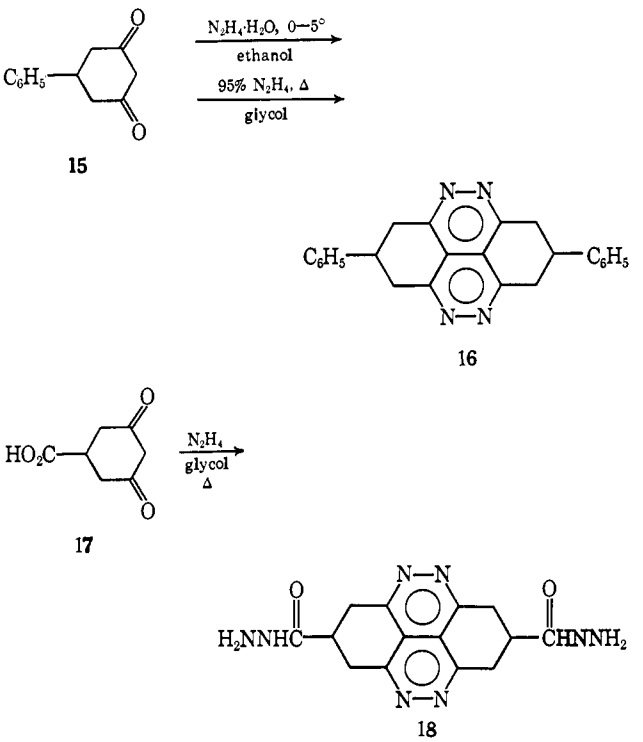


(12) with hydrazine in ethanol at 0° afforded an insoluble monohydrazone. When the condensation was carried out in refluxing ethylene glycol, the product was either 1,2,7,8- or 1,2,6,7-tetraphenyl-1,2,3,6,7,8-hexahydrocinnolino[5,4,3-*cde*]cinnoline (**13** or **14**). A definite structural assignment could not be made by the normal techniques (nmr) because of the insolubility of **13**–**14**. The condensation of 5-phenyl-1,3-cyclo-



hexanedione (**15**) with hydrazine in ethanol at 0° or in ethylene glycol at the reflux temperature gave 2,7-diphenyl-1,2,3,6,7,8-hexahydrocinnolino[5,4,3-*cde*]cinnoline (**16**) in yields of 22 and 42%, respectively. When 3,5-diketocyclohexanecarboxylic acid (**17**) was allowed to react with 95% hydrazine in refluxing ethylene glycol, the product isolated was 2,7-dicarboxyhydrazido-1,2,3,6,7,8-hexahydrocinnolino[5,4,3-*cde*]cinnoline (**18**) in a 26% yield.

The condensation of tetrahydrothiapyran-3,5-dione 1,1-dioxide (**19**) with hydrazine hydrate gave a brittle

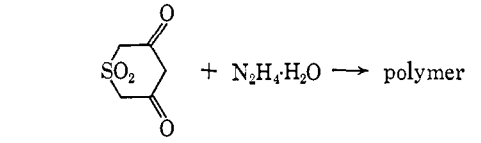


polymer as the only isolatable product. Barbituric acid (**20**) underwent ring cleavage with hydrazine and apparently gave N-carbamoylmalonamic acid hydrazide (**21**) in a manner analogous to that reported for the reaction of parabanic acid (**22**) with hydrazine.[11]

Substitution of methyl groups at the 2 position in 1,3-cyclohexanediones led to dihydrazone formation in

(10) We wish to thank Professor L. F. Fieser (private communication, Sept 30, 1966) for this suggestion.

(11) I. G. Farbenindustrie (K. Keller and W. Zereveck), German Patent 669,807 (Aug 7, 1939); *Chem. Abstr.*, **34**, 546 (1940).



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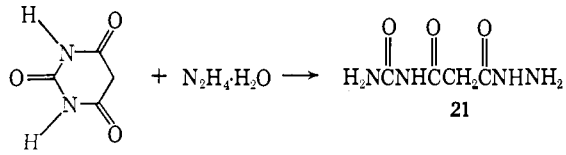
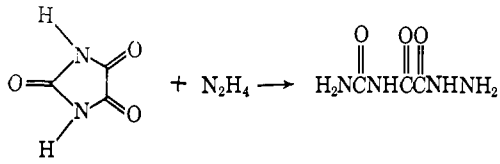
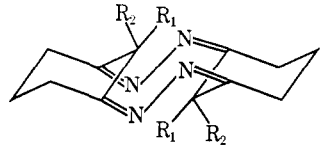


20 21

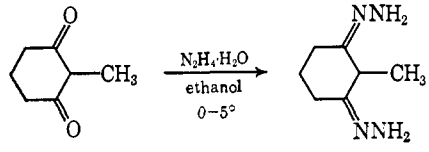


22

preference to macrocyclic ring formation. This was to be expected since a great deal of crowding would result in diazine (**23**) formation. When 2-methyl-1,3-cyclohexanedione (**24**) was condensed with hydrazine the isolated product was 2-methyl-1,3-cyclohexanedihydrazone (**25**). Similar hydrazone formation was reported for the condensation of 2,2,5,5-tetramethyl-



23, $R_1 = H$; $R_2 = CH_3$
or
$R_1 = R_2 = CH_3$



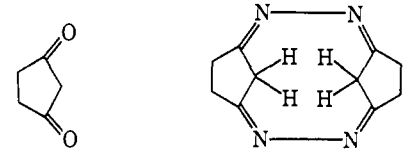
24 **25**

1,3-cyclohexanedione with hydrazine.[2] The reaction of 2,5,5-trimethyl-1,3-cyclohexanedione with hydrazine gave only an unidentified polymeric product.

On the theory that a mono- or dihydrazone was a possible intermediate in the formation of cinnolinocinnolines, 2-methyl-1,3-cyclohexanedione (**24**) and 2-methyl-1,3-cyclohexanedihydrazone (**25**) were allowed to react with one another in the absence of hydrazine. The only product isolated was polymeric in nature.

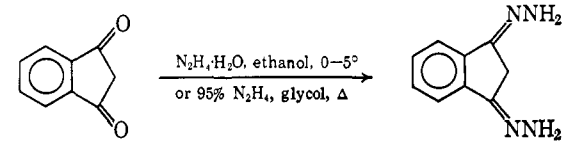
It can be concluded that the condensation of six-membered ring β-diketones with hydrazine to form cinnolinocinnoline derivatives is a general reaction for these compounds unless the 2 position of the diketone is substituted or if the ring is subject to cleavage, as with the heterocyclic compounds.

The ketone functions in 1,3-cyclopentanediones are apparently not oriented in space in as satisfactory a position for pyridazinopyridazine formation. In the keto form of the five-membered ring molecule (**26**) the angle between the two carbonyls presumably approaches 180° more closely than in the six-membered series, and this would tend to make ring closure to a pyridazinopyridazine an unlikely reaction path. Furthermore, in any intermediate diazine derivative such as **27**, crowding of the internal protons would be severe.



26 **27**

This was the apparent case with indan-1,3-dione (**28**) since condensation with hydrazine hydrate or 95% hydrazine in cold ethanol or hot ethylene glycol gave the identical product, indan-1,3-dihydrazone (**29**). The condensation of 2-cyclopentene-1,4-dione (**30**)



28 **29**

with hydrazine hydrate led only to an oily, polymeric product. Cyclopentane-1,3-dione (**26**) gave a solid material in a yield of less than 1%. This product was not characterized.

The ready availability of 2,2′-biindan-1,1′,3,3′-tetrone (**31**) provided a unique opportunity for the study of the condensation of five-membered ring β-diketones with hydrazine since this molecule already possessed the bridge between the two indan-1,3-dione systems. The results of the condensation of this compound with 95% hydrazine (Scheme II) pointed out the great difficulty involved in pyridazinopyridazine formation from cyclopentane-1,3-dione derivatives.

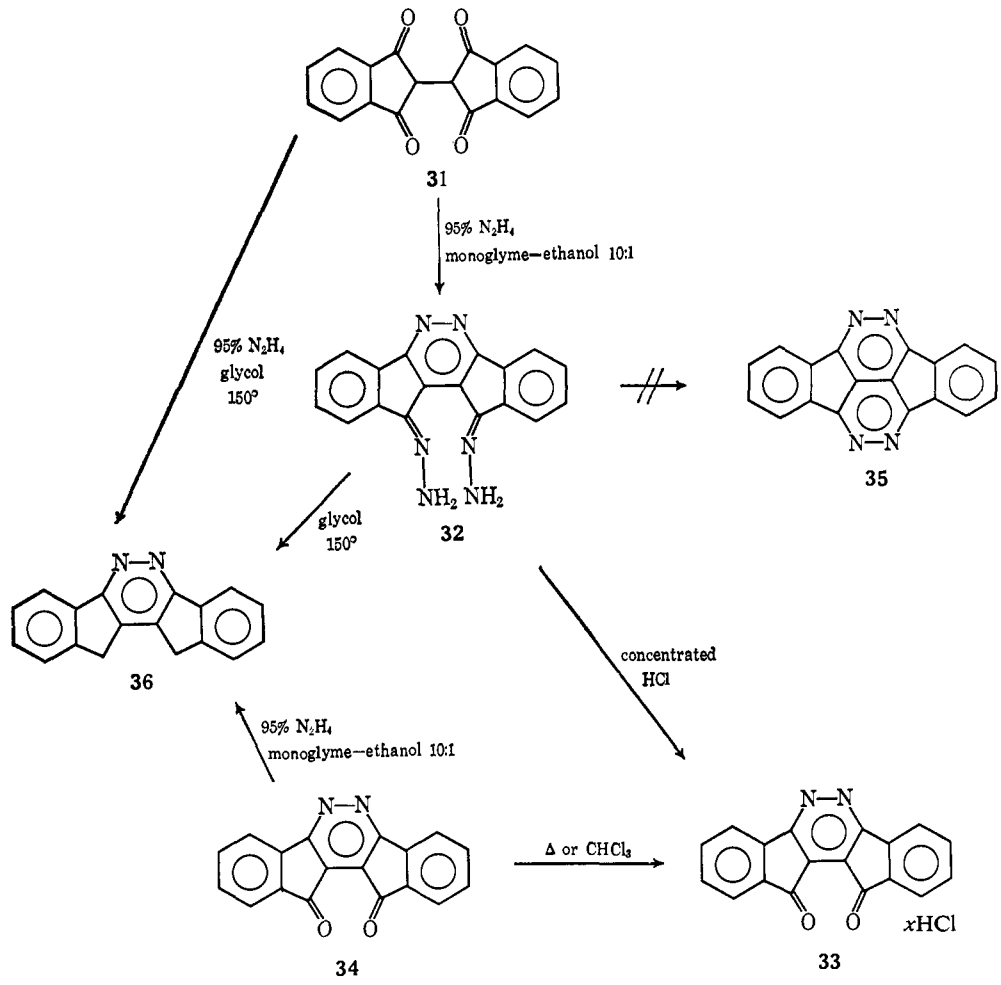
The condensation of **31** with 95% hydrazine was carried out in a 10:1 mixture of monoglyme and ethanol at reflux temperatures. This solvent system was necessary to ensure solubility of the ketone and miscibility of the hydrazine. The product of this condensation was diindeno[1,2-*c*:2′,1′-*e*]pyridazine-11,12-dihydrazone (**32**). Nitrobenzene at 110°, ethylene glycol at 80°, and methyl Cellosolve at 120° were also used as solvents for the condensation reaction and the same dihydrazone (**32**) resulted.

As further structure proof for compound **32**, its hydrolysis was carried out in concentrated hydrochloric acid to afford a hydrochloride salt of diindeno[1,2-*c*:2′,1′-*e*]pyridazine-11,12-dione (**33**). Recrystallization of this salt from chloroform gave the free diketone **34**; the hydrochloric acid present in **33** could also be driven off by heating it to 200°.

The condensation of **34** with 95% hydrazine in a 10:1 mixture of monoglyme and ethanol at the reflux temperature gave back the dihydrazone **32** in 30% yield. The dihydrazone was the only product isolated and was identical with the **32** prepared from **31**.

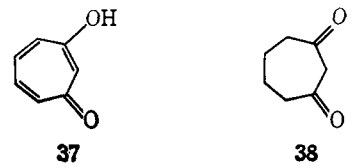
In an attempt to convert the dihydrazone **32** to the pyridazinopyridazine **35**, a solution of **32** in ethylene glycol was heated at 150° for 48 hr, but the result was the reduction of **32** (Wolff–Kishner) to afford diindeno-[1,2-*c*:2′,1′-*e*]pyridazine (**36**) in a 92% yield. The same product was isolated from the condensation of **31** with hydrazine in ethylene glycol at 150°. The typical

Scheme II. Reactions of 2,2′-Biindan-1,1′,3,3′-tetrone with Hydrazine



copper color of **32** appeared as the temperature was raised to 80° and, on continued heating to 150°, the reduction to **36** took place. When **34** was heated in ethylene glycol with hydrazine at 150°, the product isolated was **36**.

The condensation of two seven-membered cyclic β-diketones with hydrazine was attempted. The reaction of β-tropolone (**37**) with hydrazine gave a small amount of solid product that was unstable and decomposed rapidly in air. Cycloheptane-1,3-dione (**38**), upon condensation with hydrazine, afforded only an oily product which was not characterized. The seven-membered ring apparently did not meet the steric requirements necessary for pyridazinopyridazine formation.



37 **38**

Experimental Section

Condensation of 5,5-Dimethyl-1,3-cyclohexanedione (2) with Hydrazine Hydrate in an Inert Atmosphere. A solution of 1.0 g (0.0071 mol) of 5,5-dimethyl-1,3-cyclohexanedione (**2**) in 50 ml of absolute ethanol was placed in a flask equipped with a rubber septum and an inlet and outlet connection for nitrogen. The solution was swept with high purity dry nitrogen for 2 hr. At this time 1.4 g (1.4 ml, 0.028 mol) of hydrazine hydrate was added with a syringe through the septum. The solution was stirred an additional 6 hr and the continual sweeping of nitrogen slowly evaporated all of the ethanol. The remaining pasty solid was bright orange. The flask was sealed and transferred to a high efficiency vacuum line; the pasty solid was dried to a flaky orange crystalline solid. The flask was sealed and transferred to a drybox with a nitrogen atmosphere. Nmr samples of the solid in deuteriochloroform, dimethyl-d_6 sulfoxide, and methanol were prepared in the inert atmosphere. The results of the nmr study using a Varian Model HA-100 nmr spectrometer are tabulated in Table I.

Nmr Studies of the Condensation of 5,5-Dimethyl-1,3-cyclohexanedione (2) with Hydrazine Hydrate. A solution of 0.10 g (0.00071 mol) of 5,5-dimethyl-1,3-cyclohexanedione (**2**) in 1 ml of absolute methanol was prepared in an nmr sample tube. The tube was transferred to a drybox with a nitrogen atmosphere. The nmr tube was flushed with nitrogen and 0.14 g (0.14 ml, 0.0028 mol) of hydrazine hydrate was added. The tube was sealed, and the nmr studies were carried out using a Varian Model HA-100 nmr spectrometer. These results are tabulated in Table II. Oxygen was bubbled through the solution periodically by submerging a capillary connected to an oxygen line into the nmr tube.

Epr Studies of the Condensation of 5,5-Dimethyl-1,3-cyclohexanedione (2) with Hydrazine Hydrate. I. Ethanol Solvent. A solution of 0.20 g (0.0014 mol) of 5,5-dimethyl-1,3-cyclohexanedione (**2**) in 2 ml of absolute ethanol was placed in the epr mixing cell. The cell was swept with nitrogen and 0.14 g (0.14 ml, 0.0028 mol) of hydrazine hydrate was added *via* a syringe to the opposite chamber of the mixing cell. The solutions were mixed and transferred to a drybox in a nitrogen atmosphere and allowed to stand overnight. The epr sample tube was filled and the cap to it was removed just prior to placing the sample in the spectrometer. The solution began to turn blood red at once. The sample cell suited for work with solvents of high dielectric constants was used. No signal was observed.

II. Chloroform Solvent. A solution of 0.20 g (0.0014 mol) of 5,5-dimethyl-1,3-cyclohexanedione (**2**) in 2 ml of chloroform was placed in a sample vial in a nitrogen atmosphere in a drybox. The sample vial was flushed with nitrogen and 0.14 g (0.14 ml, 0.0028

mol) of hydrazine hydrate was added. The sample was added to an epr sample tube and the tube was capped. The cap was removed immediately prior to placing the sample in the spectrometer. No signal was observed.

4,5-Diphenyl-3-ketocyclohexanehydrazone or 2,3-Diphenyl-5-ketocyclohexanehydrazone. To a solution of 3.8 g (3.7 ml, 0.076 mol) of hydrazine hydrate in 50 ml of absolute ethanol cooled to 0–5° in an ice bath, was added 5.0 g (0.019 mol) of 4,5-diphenyl-1,3-cyclohexanedione (**12**)[12,13] in 200 ml of absolute ethanol with stirring over a period of 30 min. The reaction mixture turned milky white during the addition and it was stirred an additional hour at 0–5°. The white solid was collected by filtration to give 3.4 g of crude product, mp 240° dec. The filtrate was placed in a refrigerator overnight and a second crop of 0.8 g of the same white solid precipitated for a total yield of 4.2 g (80%). The product was recrystallized from absolute methanol and gave a white solid, mp 273–275° dec.

Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.69; H, 6.47; N, 10.07. Found: C, 77.71; H, 6.50; N, 9.84.

1,2,7,8-Tetraphenyl-1,2,3,6,7,8-hexahydrocinnolino[5,4,3-*cde*]-cinnoline (13) or 1,2,6,7-Tetraphenyl-1,2,3,6,7,8-hexahydrocinnolino-[5,4,3-*cde*]cinnoline (14). A solution of 4.6 g (0.017 mol) of 4,5-diphenyl-1,3-cyclohexanedione (**12**)[12,13] and 7.3 g (7.4 ml, 0.21 mol) of 95% hydrazine in 50 ml of ethylene glycol was heated at the reflux temperature for 16 hr. On cooling, a dark orange solid deposited from solution and was collected by filtration to give 2.3 g (51%) of product, mp 198–201°, after one recrystallization from absolute ethanol.

Anal. Calcd for $C_{36}H_{28}N_4$: C, 83.92; H, 5.44; N, 10.85. Found: C, 83.87; H, 5.74; N, 10.31.

2,7-Diphenyl-1,2,3,6,7,8-hexahydrocinnolino[5,4,3-*cde*]cinnoline (16). I. Condensation in Ethanol with Hydrazine Hydrate. To a solution of 5.2 g (5.0 ml, 0.10 mol) of hydrazine hydrate in 50 ml of absolute ethanol cooled to 0–5° in an ice bath, was added a solution of 5.0 g (0.026 mol) of 5-phenyl-1,3-cyclohexanedione (**15**)[14,15] in 250 ml of absolute ethanol with stirring over a period of 3 hr. The solution was stirred an additional 2 hr at 0–5°. At this point the solution was clear yellow, the color of the diketone dissolved in ethanol. The solution, which was stored overnight in a refrigerator, turned dark orange with the appearance of a small amount of precipitate. The solution was filtered and the filtrate was clear red. The filtrate volume was concentrated to about 25 ml under reduced pressure. Allowing the solution to remain at room temperature resulted in the precipitation of a solid which was collected by filtration to give 1.0 g (22%) of a light pink material, mp 368–370° dec (darkens above 270°). The product was recrystallized from nitrobenzene.

II. Condensation in Ethylene Glycol with 95% Hydrazine. A suspension of 5.0 g (0.026 mol) of 5-phenyl-1,3-cyclohexanedione (**15**)[14,15] in 125 ml of ethylene glycol was heated at 100° until solution occurred. At this time 8.5 g (9.0 ml, 0.26 mol) of 95% hydrazine was added all at once. The clear yellow solution began to turn clear orange, and after heating for 30 min a light colored solid began to precipitate. The solution was heated at 110° for 12 hr. After cooling to 50° the solid was collected by filtration to give 2.0 g (42%) of product, mp 368–370° dec (darkens above 270°). The solid was recrystallized from nitrobenzene and gave mp 370–372° dec.

Anal. Calcd for $C_{24}H_{20}N_4$: C, 79.12; H, 5.49; N, 15.38. Found: C, 79.16; H, 5.72; N, 15.23.

2,7-Dicarboxyhydrazido-1,2,3,6,7,8-hexahydrocinnolino[5,4,3-*cde*]cinnoline (18). A solution of 5.0 g (0.032 mol) of 3,5-diketocyclohexanecarboxylic acid (**17**)[16] and 11 g (11 ml, 0.32 mol) of 95% hydrazine in 300 ml of ethylene glycol was heated under reflux conditions for 24 hr. The solution was allowed to cool, and the solvent was concentrated by distillation to about 100 ml. An equal portion of ethanol was added to the solution. A red solid precipitated from the solution. The solid was collected by filtration and purified by solution in hot ethylene glycol and precipitation with ethanol to give 2.3 g (21%) of product which did not melt below 360°.

Anal. Calcd for $C_{14}H_{16}N_8O_2$: C, 51.21; H, 4.87; N, 34.14. Found: C, 51.39; H, 5.03; N, 33.90.

N-Carbamoylmalonamic Acid Hydrazide (21). To a solution of 9.3 g (9.0 ml, 0.19 mol) of hydrazine hydrate in a 1:1 mixture of absolute ethanol and tetrahydrofuran cooled to 0–5°, was added dropwise with stirring a solution of 5.2 g (0.045 mol) of barbituric acid (**20**) in 350 ml of tetrahydrofuran. The reaction mixture was maintained at 0–5° during the addition. Immediately upon beginning the addition of hydrazine a fluffy white solid precipitated. After the addition was complete the reaction mixture was stirred an additional 2 hr at 0–5°. The solid was collected by filtration to give a white product, mp 380° dec.

Anal. Calcd for $C_4H_8N_4O_3$: C, 30.00; H, 5.00; N, 35.00. Found: C, 29.83; H, 5.27; N, 33.90.

2-Methyl-1,3-cyclohexanedihydrazone (25). To a solution of 9.3 g (9.0 ml, 0.18 mol) of hydrazine hydrate in 50 ml of absolute ethanol cooled to 0–5° was added dropwise a solution of 5.6 g (0.044 mol) of 2-methyl-1,3-cyclohexanedione (**24**)[17] in 125 ml of absolute ethanol over a period of 1 hr. The reaction mixture was stirred an additional 3 hr at 0–5° and was stored in a refrigerator overnight. The reaction mixture was concentrated in volume to about 20 ml under reduced pressure at room temperature and a yellow-orange precipitate appeared. The flask was cooled and the product was collected by filtration. Recrystallization from absolute ethanol gave a yellow crystalline solid, mp 107–109° dec.

Anal. Calcd for $C_7H_{14}N_4$: C, 54.54; H, 9.09; N, 36.37. Found: C, 54.56; H, 8.85; N, 36.44.

The infrared spectrum showed a well-defined doublet at 3300 and 3400 cm^{-1} for the hydrazone $-NH_2$ groups and a sharp band at 1640 cm^{-1} attributed to the >C=N- function. The nmr spectrum at 60 Mc in deuterium oxide with tetramethylsilane as an external standard showed a doublet (J = 7 cps) centered at 1.21 ppm (CH_3–), a quartet (J = 7 cps) centered at 3.29 (–CH), a multiplet between 1.80 and 2.70 attributed to the methylene protons, and a singlet at 4.79 assigned to the hydrazone $-NH_2$ protons. The relative areas of the signals were 3:1:6:4, respectively.

Indan-1,3-dihydrazone (29). To a solution of 0.91 g (0.88 ml, 0.0181 mol) of hydrazine hydrate in 20 ml of absolute methanol cooled in an ice bath to 0–5°, was added a solution of 0.66 g (0.0045 mol) of indan-1,3-dione (**28**) in 60 ml of absolute methanol with stirring over a period of 1 hr. After the addition was complete the solution was stirred an additional hour at 0–5°. The volume of the methanol solution was concentrated to about 20 ml under reduced pressure. Immediately upon removing the flask from the rotary evaporator a crystalline solid came out of solution. The solution was allowed to cool and the solid was collected by filtration to give 0.35 g (44%) of crude dihydrazone. The product was recrystallized from absolute ethanol to yield yellow needle-like crystals, mp 181–182°.

Anal. Calcd for $C_9H_{10}N_4$: C, 62.06; H, 5.74; N, 32.20. Found: C, 61.67; H, 5.89; N, 32.05.

The nmr spectrum determined at 60 Mc in DMSO-d_6 showed a singlet at 3.07 ppm, a broad band centered at 6.20, and a complex multiplet centered at 7.30. The relative areas of the peaks were 1:2:2, respectively.

The infrared spectrum of the dihydrazone showed a typical doublet at 3275 and 3400 cm^{-1} for the $-NH_2$ absorption and a band at 1630 cm^{-1} attributed to the >C=N- function.

Diindeno[1,2-*c*:2′,1′-*e*]pyridazine-11,12-dihydrazone (32). A solution of 4.75 g (0.0164 mol) of 2,2′-biindan-1,1′,3,3′-tetrone (**31**) and 5.25 g (5.55 ml, 0.164 mol) of 95% hydrazine in 550 ml of a 10:1 mixture of monoglyme and ethanol was heated under reflux conditions overnight. Upon cooling the solution, 4.01 g of gold crystalline product precipitated and was collected by filtration. Concentration of the solvent volume gave an additional 0.36 g for a total of 4.37 g (85.0%), mp 195–200° dec.

Anal. Calcd for $C_{18}H_{12}N_6$: C, 69.23; H, 3.85; N, 26.92. Found: C, 69.00; H, 3.99; N, 26.32.

The infrared spectrum of the product showed a strong absorption in the $-NH_2$ region between 3350 and 3200 cm^{-1}. The >C=N- band appeared at 1600 cm^{-1} as a doublet. The indan aromatic C–H absorption appeared at 775 cm^{-1}.

The identical condensation was carried out in ethylene glycol at 80° and **32** was also obtained. When nitrobenzene at 110° or methyl Cellosolve at 120° were used as solvents, **32** was isolated in yields of 66 and 55%, respectively.

(12) H. E. Zimmerman and D. I. Schuster, *J. Amer. Chem. Soc.*, **84**, 4527 (1962).
(13) W. Borsche, *Ber.*, **42**, 4496 (1909).
(14) R. E. Papadakis, *J. Pharm. Sci.*, **51**, 85 (1962).
(15) R. L. Shriner and H. R. Todd, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 200.
(16) E. E. Van Tamelen and G. T. Hildahl, *J. Amer. Chem. Soc.*, **78**, 4410 (1956).
(17) A. B. Mekler, S. Ramachandian, S. Swaminathan, and M. S. Newman, *Org. Syn.*, **41**, 57 (1961).

Condensation of Diindeno[1,2-*c*:2′,1′-*e*]pyridazine-11,12-dione (34) with Hydrazine. Diindeno[1,2-*c*:2′,1′-*e*]pyridazine-11,12-dihydrazone (32). A mixture of 0.13 g (0.0045 mol) of **34** and 0.15 g (0.16 ml, 0.0045 mol) of 95% hydrazine in 30 ml of a 10:1 mixture of monoglyme and ethanol was stirred for 48 hr at room temperature and for 3 hr on a steam bath. The solution turned from dark green to orange. The reaction mixture was cooled and the solid was collected by filtration to give 0.040 g (30%) of **32**. The infrared spectrum was identical with the product **32** isolated from the condensation of **31** with hydrazine.

Diindeno[1,2-*c*:2′,1′-*e*]pyridazine-11,12-dione (34). A suspension of 0.20 g (0.00064 mol) of **32** in 100 ml of concentrated hydrochloric acid was heated on a steam bath for 2 hr. The solid remaining was removed by filtration while the solution was still hot and the filtrate was allowed to cool to give 0.050 g (27%) of a hydrochloride salt (**33**) of **34**. Recrystallization from chloroform removed the hydrogen chloride from the molecule and gave diketone **34**, mp 306–308°, as needle-like crystals. The hydrochloride salt (**33**) was also decomposed by heating a dry sample of it to about 200°. This was carried out in a capillary tube, and the hydrogen chloride was observed with wet litmus paper. The solid turned from a dark green to a light tan at 200° and continued heating gave mp 306–308°, that of the free diketone (**34**).

Anal. Calcd for $C_{18}H_8N_2O_2$: C, 76.06; H, 2.82; N, 9.86. Found: C, 75.76; H, 3.03; N, 10.20.

The infrared spectrum of **34** showed no >C=N- or $-NH_2$ absorption and did show a strong >C=O band at 1740 cm^{-1}.

Diindeno[1,2-*c*:2′,1′-*e*]pyridazine (36). I. Preparation from 32. A mixture of 4.0 g (0.013 mol) of **32** and 5.0 g (5.1 ml, 0.15 mol) of 95% hydrazine in 100 ml of ethylene glycol was heated at 170° overnight. The solution was filtered while hot, and the product was collected and washed several times with absolute ethanol to give 3.0 g (92%) of a dark purple, highly crystalline compound, mp 285° dec.

Anal. Calcd for $C_{18}H_{12}N_2$: C, 84.37; H, 4.68; N, 10.93. Found: C, 84.58; H, 4.53; N, 11.06.

The infrared spectrum showed no bands for >C=O, $-NH_2$, or -N=N- functions.

II. Preparation from 34. A mixture of 0.075 g (0.0021 mol) of **34** and 0.67 g (0.71 ml, 0.021 mol) of 95% hydrazine in 20 ml of ethylene glycol was heated at 150° for 2 days. The solution was allowed to cool, and the solid was collected by filtration to give 0.020 g (37%) of product, mp 285° dec.

The infrared spectrum was identical with that for the product when **32** was heated in hydrazine.

III. Preparation from 31. A mixture of 2.0 g (0.0070 mol) of **31** and 2.2 g (2.3 ml, 0.070 mol) of 95% hydrazine was heated at 80° for 6 hr, and the dihydrazone **32** precipitated as a copper colored crystalline solid. The solution was then heated at 150° overnight and **32** went into a solution to give a dark brown solution. The solution was allowed to cool and the product was isolated by filtration as a brown solid in a quantitative yield, mp 285° dec.

The infrared spectrum was identical with that for the product when **32** was heated in hydrazine.

The condensation of 2-cyclopentene-1,4-dione (**30**),[18] 1,3-cyclopentanedione (**26**),[19] β-tropolone (**37**),[20,21] or 1,3-cycloheptanedione (**38**)[22] with hydrazine under the normal reaction conditions afforded no identifiable products.

(18) G. H. Rasmussen, H. O. House, E. F. Zaweski, and C. H. DePuy, *Org. Syn.*, **42**, 36 (1962).
(19) C. H. DePuy and E. F. Zaweski, *J. Amer. Chem. Soc.*, **81**, 4920 (1959).
(20) J. Allan and R. Robinson, *J. Chem. Soc.*, 376 (1926).
(21) A. J. Birch, private communication, May 20, 1966.
(22) B. Eistert, F. Haupter, and K. Schank, *Ann.*, **665**, 55 (1963).

Reactions of Carbonyl Compounds with Difluoramine[1]

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Abstract: Ketones and aldehydes were found to react with difluoramine in sulfuric acid or oleum with replacement of carbonyl groups by two difluoramino groups. Carbonium ion precursors in the γ position cyclized to give α-(difluoramino)tetrahydrofurans. One such derivative, 2,5-bis(difluoramino)-2,5-dimethyltetrahydrofuran was treated further under more forcing conditions, to yield 2,2,5,5-tetrakis(difluoramino)hexane. Acetol gave 2,5-bis(difluoramino)-2,5-dimethyl-1,4-dioxane. Michael addition of difluoramine took place with α,β-unsaturated carbonyl compounds.

Difluoramine has been shown to react as a nucleophile in the presence of acids,[2,3] undergoing alkylation by carbonium ions. In the absence of catalysts, difluoramine was added reversibly to aldehydes and ketones to form α-difluoraminocarbinols.[4] Inasmuch as the difluoramino group is capable of supporting positive charge on neighboring atoms,[3] it appeared possible to prepare geminal bisdifluoramino compounds from carbonyl compounds in the presence of strong acids, with difluoraminocarbinols and difluoraminocarbonium ions as intermediates.

This result was achieved with the ketones shown in Table I. Simple ketones reacted readily with a mixture of concentrated sulfuric acid and refluxing difluoramine (bp −23°), although no reaction took place with sulfuric acid of less than 92% concentration. Electron-withdrawing substituents required more forcing conditions, such as a more acidic medium (oleum) or a higher reaction temperature (attained by using a closed reactor). The sequence leading to bis(difluoramino)alkanes was shown to be reversible; 2-octanone was recovered when 2,2-bis(difluoramino)octane was shaken with sulfuric acid for 1 hr at room temperature. Yields of bis(difluoramino)alkanes are therefore affected by any variables involved in the rates of the individual steps in the equilibria (Scheme I). In general, a high concentration of difluoramine, a solvent with a strong affinity for water, and a low solubility for the product are favor-

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(2) W. H. Graham and J. P. Freeman, *J. Am. Chem. Soc.*, **89**, 716 (1967).
(3) K. Baum, *J. Org. Chem.*, **32**, 3648 (1967).
(4) J. P. Freeman, W. H. Graham, and C. O. Parker, *J. Am. Chem. Soc.*, **90**, 121 (1968).