showed the major peaks of the tetrabromide along with strong peaks at 1650 and 1760 cm^{-1}, consistent with the assignment 1′-(1,2-dibromo-2-methoxy-3-ketocyclobutyl)-2′-methoxy-3′-ketocyclobutene (X). The material was very unstable, quickly lost hydrogen bromide on standing, and reacted with moisture to give water-soluble, yellow tars.

2,2′-Diketo-3,3,3′,3′-tetrafluorobicyclobutylidene (XI).—Concentrated sulfuric acid (60 ml) was placed in a beaker and 37 g (0.127 mole) of 2,2,2′,2′-tetramethoxy-3,3,3′,3′-tetrafluorobicyclobutylidene (III) was dissolved with stirring. To this was added 100 ml of methylene chloride and 100 ml of ice in portions. The mixture was shaken vigorously in a separatory funnel. The organic layer was removed and the acid layer was extracted with two additional 100-ml portions of methylene chloride. The extracts were combined and dried over anhydrous magnesium sulfate. The extracts were concentrated over a steam bath until yellow crystals began to deposit. It was then chilled overnight. Yellow crystals of diketone XI, mp 157–159°, were then filtered off. This amounted to 10.0 g (second crop, 1.5 g; total yield 47%). The infrared spectrum contained significant peaks at 1775, 1390, 1190, 1045, and 873 cm^{-1}, and lacked olefinic absorption as would be expected for a symmetrically tetrasubstituted olefin. Diketone XI was found to be very reactive to bases to give polymeric materials. In methylene chloride it reacted with triethylamine or with pyridine to give an intense purple solution.

Anal. Calcd for $C_8H_4F_4O_2$: C, 46.1; H, 1.93; F, 36.5. Found: C, 46.04; H, 2.18; F, 34.02.

This material slowly dissolves in water to form hydrates. In methanol it quite quckly forms a colorless hemiketal.

Registry No.—*cis* II, 10103-08-9; *trans* II, 10074-74-5; *cis* III, 10074-75-6; *trans* III, 10074-76-7; V, 10074-77-8; VIII, 10074-78-9; IX, 10074-79-0; X, 10074-80-3; XI, 10074-81-4.

Acknowledgment.—The authors wish to express their appreciation to the Minnesota Mining and Manufacturing Co., St. Paul, Minn., and the U. S. Army Natick Laboratories, Natick, Mass., under Scientific Project Officer Dr. Malcolm Henry, for their partial support of this work.

Heterocyclic Studies. XXIII. The Cleavage of 2,3-Dihydro-1,2-diazepin-4-ones with Base[1]

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Received September 23, 1966

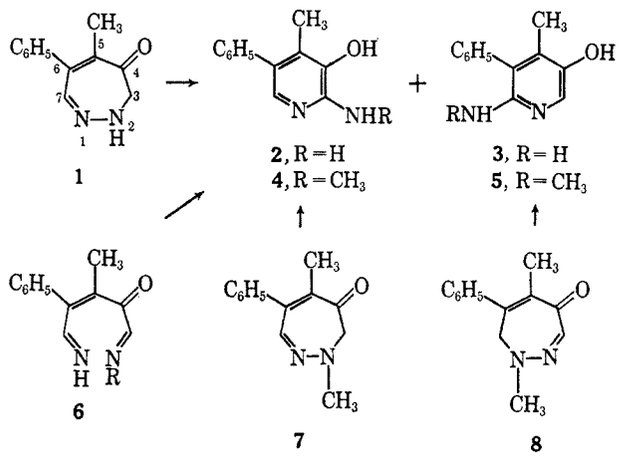
The rearrangement of dihydrodiazepinones **1** and **7** to α-aminopyridines by a cleavage–cyclization pathway has been found not to be subject to general base catalysis; the rate shows first-order dependence on hydroxide ion. These findings preclude a simple β elimination of the enolate, and a mechanism based on the initial formation of a carbinolamine intermediate is suggested. With the 1-acyl-7-methoxydiazepinone (**11**), on the other hand, enolization is the rate-controlling process. The cleavage of an α-hydrazinocarbonyl system to the α-ketoaldimine has been demonstrated with phenacylhydrazine, and the possible generality of this reaction is discussed.

In an earlier paper we reported the formation of the α-aminopyridines (**2** and **3**) in approximately equal amounts by alkaline treatment of the dihydrodiazepinone (**1**).[2] The methyldiazepinones (**7** and **8**[3]) similarly give rise to the methylaminopyridines **4** and **5**, respectively; in the latter reactions a single product was obtained. It was suggested that these ring contractions occur by a β elimination of the enolate anions, with formation of an acyclic intermediate, *e.g.*, **6**, which then cyclizes to the observed pyridines (see Scheme I).

This pathway provides a consistent explanation for all of the reactions, in particular the duality of products in the case of the unsubstituted ketone (**1**). Precedent for an elimination–cyclization sequence of this type is lacking, however, and no mechanistic details of the process are revealed by the product data. Direct evidence for the cleavage of an α-hydrazino ketone to an α-ketoaldimine is reported later in this paper. Although the opportunity has not previously arisen to generate a diimine such as **6**, the subsequent cyclization to **2**, **3**, and **4** follows a pattern well known in pyridine chemistry. We now present some kinetic results on these diazepinone rearrangements which require an important refinement of the previously suggested β-elimination step.

It was shown in earlier work[2] that the diazepinone (**1**) in 2 *N* NaOD solution undergoes deuterium exchange rapidly at C-3 and more slowly at C-7, and that the rearrangement to **2** and **3** is much slower than the exchange. These nmr studies have been repeated using DMSO solution and limited amounts of base, and have been extended to the 2-methyldiazepinone (**7**). In a 0.7 *M* DMSO solution of **1** containing 20% D_2O and 0.2 *N* in NaOD, the exchange at C-3 was 50% complete in about 5 hr, and at C-7 in about 18 hr. Under these conditions, pyridine formation was undetectable after 48 hr. Plots of the extent of D exchange as a function of time clearly indicate that the exchange reaction observes a simple first-order rate law as long as an excess of D_2O is present.

SCHEME I



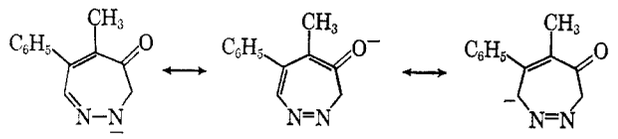
(1) Part XXII: J. A. Moore, R. W. Medeiros, and R. L. Williams, *J. Org. Chem.*, **31**, 52 (1966).

(2) J. A. Moore and E. C. Zoll, *ibid.*, **29**, 2124 (1964).

(3) J. A. Moore and W. J. Theuer, *ibid.*, **30**, 1887 (1965).

With the 2-methyldiazepinone (**7**), the rearrangement to the methylaminopyridine (**4**) was so rapid in 0.7 *M* DMSO–D_2O solution 0.1 *N* in NaOD that the relative rates of deuterium exchange and rearrangement could not be estimated by nmr. The rearrangement to **4**, which consumes 1 equiv of base, can be carried out essentially as a titration. With a 0.7 *M* DMSO solution of **7** which was 0.016 *N* in NaOD, it was possible to observe about 25% deuterium exchange before the base was consumed. As expected, there was no incorporation of deuterium at C-6 in pyridine **4**, since exchange at C-7 in **7** cannot occur.

The large difference in the rates of enolization and rearrangement of **1** and **7** is ascribed to the competing equilibrium in the case of **1** with the anion **9** which is responsible for the deuterium exchange at C-7 in **1**.



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It is reasonable to assume, however, that the rearrangements of **1** and of **7** and related 2-substituted derivatives occur by the same mechanism. To gain insight into the mechanism and examine the validity of the proposed cleavage–cyclization process, rate studies have been carried out with **7** and, to a limited extent, with **1**.

Experimental Section

Kinetic Measurements.—The kinetic study of the rearrangement involved observations of the rate of change of the optical density of a water solution of the substrate containing a minute amount of methanol as well as pure methanol solutions at 408 mμ with a Zeiss spectrophotometer.

The temperature of the reaction mixture was kept constant with a cell block employing water as the heat-transfer medium. A thermostated water bath regulated the temperature of the cell block. Initially, temperatures were recorded with a thermometer; later, however, increased precision was obtained with the use of a copper–constantan thermocouple used in conjunction with a high-quality potentiometer. All pH readings were obtained at 25° regardless of the temperature of the reaction itself.

The procedure of a typical run follows. The reaction mixture (minus substrate) was placed in the cell which was then installed in the thermostated cell block of the spectrophotometer. Approximately 30 min was required for the reaction mixture to come to constant temperature. At this time 30 μl of a methanol solution of the substrate was injected from a syringe through the silicone rubber stopple sealing the silica cell. The cell was vigorously shaken briefly and replaced in the cell block, and optical density readings were then begun.

Since the substrate can undergo a photorearrangement,[4] a control run of substrate without base was also carried out. The rate of rearrangement of this uncatalyzed substrate was essentially 0, indicating no influence at the light-energy levels present in the spectrophotometer on the rate of the base-catalyzed reaction.

The phosphate buffer was prepared by dissolving 1.905 g of $Na_3PO_4 \cdot 10H_2O$ and 1.317 g of anhydrous Na_2HOP_4 in 100 ml of distilled water. The pH of the resulting buffer was 11.3 (measured at 25°).

The carbonate buffer was prepared in the following manner. Solution A was prepared by dissolving 0.211 g of $NaHCO_3$ in 50 ml of distilled water. Solution B was prepared by dissolving 0.206 g of NaOH in 50 ml of distilled water. The buffer of pH 11.1 was then prepared by mixing 22.7 ml of solution B plus all of solution A.

(4) W. J. Theuer and J. A. Moore, *Chem. Commun.*, 468 (1965).

The methanolic KOH was prepared by dissolving 26.494 g of KOH in 200 ml of Fischer spectroscopic quality methanol. The exact concentration (1.95 *N*) of base was determined by titration in the usual way. The aqueous solutions of barium hydroxide were prepared by dissolving $Ba(OH)_2$ in hot water, allowing the water to cool in a CO_2-free atmosphere, and then filtering the solution rapidly. The diazepinone substrates were prepared for reaction by weighing out 3.6 mg and dissolving in 3.0 ml of methanol.

Cleavage of α-Hydrazinoacetophenone.—A solution of 2.0 g of α-hydrazinoacetophenone,[5] mp 83° dec, and 2.0 g of *o*-phenylenediamine in 300 ml of methanol was allowed to stand overnight and was then concentrated and diluted with water. The resulting precipitate was recrystallized from aqueous ethanol to give a total of 1.4 g (51%) of pale tan crystals of 3-phenylquinoxaline, mp 76° (lit.[6] mp 78°).

Kinetic Results

The response of rate to buffer concentration was tested in a series of experiments at nearly constant pH using two different buffer types, carbonate and phosphate. A summary of the data obtained in such runs is presented in Table I. Therein it is evident that the rearrangement rate is completely unaffected by either the nature of the buffer base or its concentration.

Catalysis of the rearrangement by hydroxide and/or methoxide ion was established through a series of runs whose results are summarized in Table II.

TABLE I

RATE OF REARRANGMENT OF 2-METHYLDIAZEPINONE **7** AS A FUNCTION OF BUFFER CONCENTRATION AT pH 11.2 ± 0.1 AND 30.0 ± 0.1°

Buffer	Buffer concn, mole/l.	$k \times 10^4$, min^{-1}
Na_2HPO_4–Na_3PO_4	0.08	6.6
Na_2HPO_4–Na_3PO_4	0.03	6.6
Na_2HPO_4–Na_3PO_4	0.01	6.6
NaOH–$NaHCO_3$–Na_2CO_3	0.07	6.6
NaOH–$NaHCO_3$–Na_2CO_3	0.04	6.6

TABLE II

RATE OF REARRANGEMENT OF **7** IN METHANOLIC KOH AS A FUNCTION OF BASE CONCENTRATION AT 20.0 ± 0.1°

Base concn, moles/l.	$k \times 10^4$, min^{-1}
0.20	8.2
0.39	20
1.06	58
1.46	78
1.95	120

The plot of these data in Figure 1 establishes that velocity = k_2[base][diazepinone] since the observed rate constant is seen to be a linear function of base concentration. This deduction is supported by the corresponding data obtained in aqueous solutions of hydroxide ion, as given in Table III. The plot of these data in Figure 2, establishing unit linearity of pH and $-\log k$, indicates that the same rate law prevails in both water and methanol solutions, regardless of the presence of added neutral electrolyte.

The possible occurrence of a kinetic isotope effect in the α-deuterated diazepinone was tested in the experimental series whose results are listed in Table IV. It is seen that, within experimental error, the deuterated

(5) M. Busch and W. Foerst, *J. Prakt. Chem.*, **119**, 287 (1928).
(6) O. Fischer and F. Romer, *Ber.*, **41**, 2350 (1908).

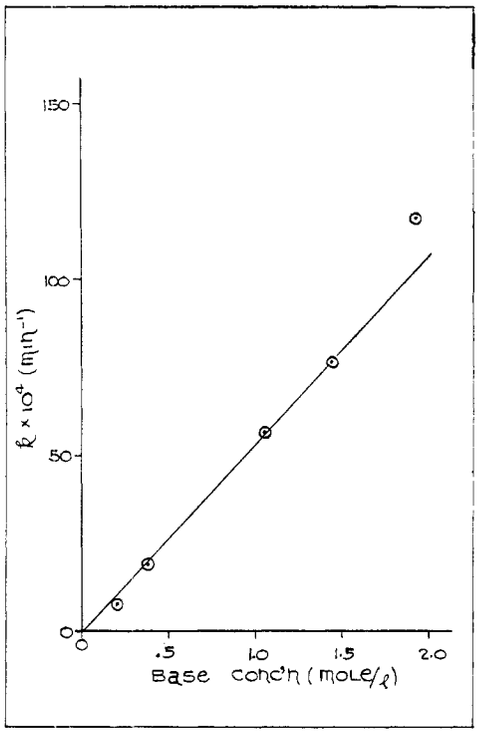


Figure 1.—Plot of $k \times 10^4$ (min^{-1}) *vs.* base concentration (moles/l.).

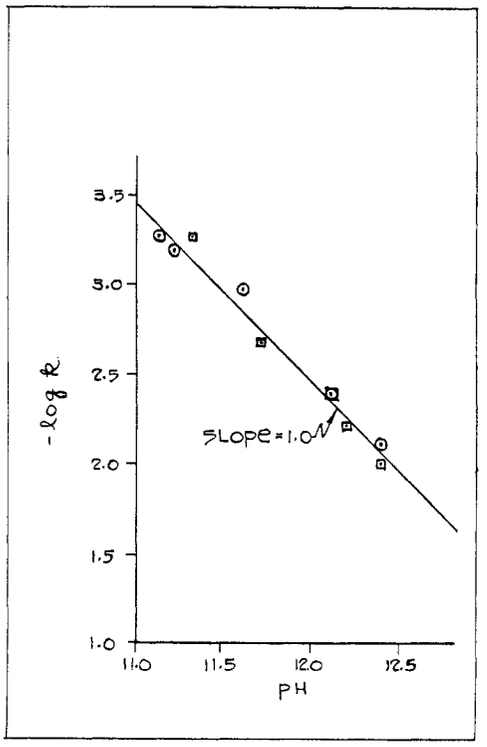


Figure 2.—Plot of $-\log k$ *vs.* pH: ⊙, variable ionic strength; ⊡, constant ionic strength = 0.19.

TABLE III

RATE OF REARRANGEMENT OF **7** IN AQUEOUS $Ba(OH)_2$ AT 20 ± 0.1°

At variable ionic strength		At constant ionic strength = 0.19	
pH	$-\log k$	pH	$-\log k$
11.1	3.31	11.3	3.31
11.2	3.24	11.7	2.71
11.6	3.01	12.1	2.41
12.1	2.41	12.2	2.23
12.4	2.11	12.4	2.01

substrate (**1a**) rearranges at the same rate as the (ordinary diazepinone (**1**) at various reaction conditions producing a fivefold rate change. This observation corroborates the results established earlier by nmr methods, namely that deuterium exchange occurs very much faster than rearrangement in hydroxylic media.

TABLE IV

RATES OF REARRANGEMENT OF **1** AND THE C-3 DEUTERATED ANALOG (**1a**) AS A FUNCTION OF $Ba(OH)_2$ CONCENTRATION IN AQUEOUS SOLUTIONS OF CONSTANT IONIC STRENGTH (0.32) AT 60 ± 0.1°

	$k \times 10^3$, min^{-1}	
pH	Substrate **1**	Substrate **1a**
11.6	4.2	4.5
11.9	21	22

The lack of general base catalysis in the rearrangement reaction, revealed by the rate data in Table I, indicates that proton transfer is not occurring along the path leading to or at the transition state. Moreover, the much greater rate of deuterium exchange as compared to the disappearance of **1** or **7** suggests strongly that ionization to enolate comprises an insignificant part of the activation energy requirement. The previous suggestion of rapid base-catalyzed ionization followed by rate-determining β elimination[3] is thus not consistent with these kinetic data. It would appear most probable that the role of hydroxide or methoxide in the critical complex depends upon the strong nucleophilic characteristic of these species.

An attractive interpretation of these results is that nucleophilic attack at some unsaturated center provides the driving force for subsequent rearrangement steps. That is to say, the event along the reaction coordinate in which the nucleophile is bonding to this center constitutes the major transition state of the reaction process. Thus phosphate ion, which is five powers of 10 less nucleophilic toward sp^2 carbon than hydroxide ion,[7] has no catalytic influence even at 100-fold greater concentrations. Furthermore, it may be stated with some confidence that the effective anionic nucleophiles (OH^-, OCH_3^-) investigated reacted exclusively with the neutral component of the substrate in equilibrium with its enolate anion dissociation product. We deduce this from the observed lack of rate influence by added neutral salt.

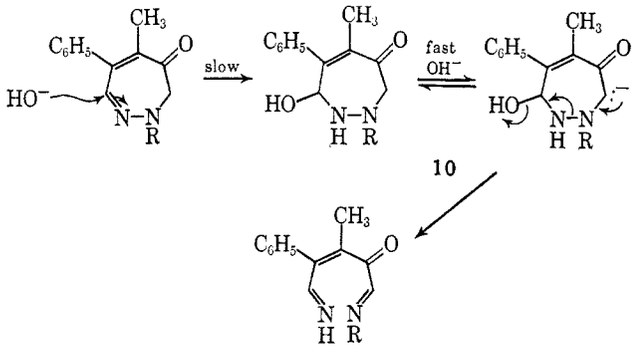
Discussion

In assigning a role to hydroxide ion, the effect of other nucleophiles on these ketones must be recalled. *A priori*, two centers, C-4 and C-7, can be considered most available for nucleophilic attack. Normal carbonyl addition reactions at C-4 are observed with sodium borohydride and semicarbazide, but the abnormal reaction of **1** and **7** with hydroxylamine[8] led to the conclusion that addition of hydroxylamine occurs at C-7. Facile attack of hydroxyl groups, both intramolecular and external, has been observed at C-7 in other reactions of this diazepine system.[1,9]

(7) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **82**, 1778 (1960).
(8) J. A. Moore and J. Binkert, *ibid.*, **81**, 6029 (1959).
(9) J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Wineholt, *J. Org. Chem.*, **31**, 34 (1966).

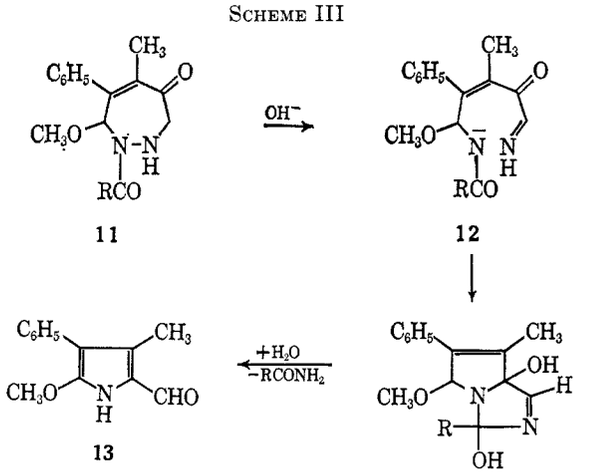
There seems to be no simple way in which addition of hydroxide ion at the C-4 carbonyl group of **1** or **7** could affect the transition state of the rearrangement. Addition at the C=N bond is readily understood, however, since no stabilization is available for the anion of intermediate **6**, which would arise in a simple β-elimination reaction of **1** or **7**. Prior formation of the carbinolamine (**10**) in the rate-determining step would provide a substrate in which cleavage of the N—N bond is a more favorable process; the elimination may be, in fact, a fragmentation leading directly to **6** (see Scheme II).

SCHEME II



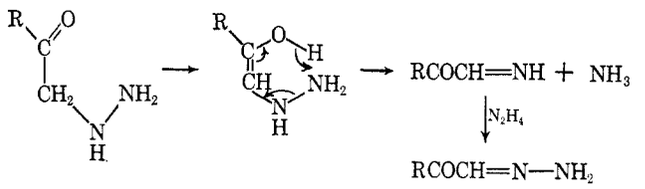
This interpretation of the rearrangements of the dihydrodiazepinones **1** and **7** requires further consideration of the related reaction of the 1-benzoyl-7-methoxytetrahydrodiazepinone **11**[9] in base. A similar acyclic intermediate (**12**) was proposed in this rearrangement, with subsequent steps leading to the methoxypyrrole aldehyde (**13**).[10] A different mechanism for the ring cleavage must obtain in this reaction, however, since the 7-methoxy group is not eliminated as in the carbinolamine (**10**). A crucial difference in the two cases, of course, is the presence of the amide carbonyl group in **11**, which can play an important role in stabilizing anion **12**; the reaction is formally analogous to the retro-Michael condensation (see Scheme III).

SCHEME III

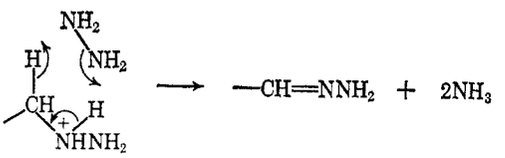


In this view the elimination might be facilitated to the point that enolization becomes the rate-controlling step, or occurs very close to the transition state along the reaction coordinate. To examine this point, the rearrangement of **11** was carried out with D_2O–NaOD under the conditions previously employed,[10] and no significant deuterium exchange was observed in the formyl group of the pyrrole (**13**). Since prior enolization at C-3 in diazepinone **11** would lead to deuterium incorporation at this center, this experiment indicates that the elimination step in **11** must be at least as rapid as enolization.

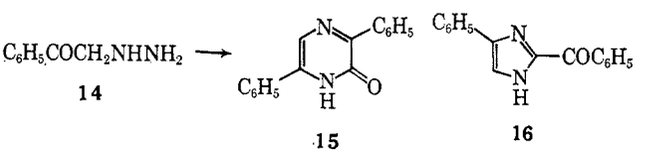
The central point in the foregoing discussion is the β elimination of an α-hydrazinocarbonyl system, but direct evidence for this initial step is not available from these rather complex rearrangements, nor is there a clear precedent for this type of cleavage in the literature. Two recent publications are pertinent in this connection, however. German workers have reported that the reaction of phenacyl bromides with excess hydrazine leads in high yields to the phenylglyoxal hydrazones.[11] The reaction was suggested to occur by a cyclic process involving enolization of the hydrazino ketone and initial formation of the phenylglyoxal imine. This mechanism would not, of course, be operable if the hydrazino ketone system were incorporated in a ring, as in diazepinones **1** and **7**. Another case is the



conversion of 6-halomethylpurines to hydrazones with excess hydrazine;[12] the products were considered to arise directly by oxidation of an intermediate α-hydrazinomethylpurine by hydrazine without the intermediacy of the aldimine.



In the original description of phenacylhydrazine (**14**),[5] which can be isolated from the controlled reaction of phenacyl bromide and hydrazine at low temperature, the decomposition of this α-hydrazino ketone to a dimeric product was reported. This compound was incorrectly formulated as pyrazinone **15** because of an error in the assignment of structures to two products which had earlier been obtained from the reaction of phenylglyoxal or dibromoacetophenone and ammonia.[13] It was subsequently established that the product, mp 197–200°, obtained in this condensation is 2-benzoyl-4(5)-phenylimidazole (**16**).[14] This imidazole



(10) R. L. Wineholt, E. Wyss, and J. A. Moore, *J. Org. Chem.*, **31**, 48 (1966).

(11) S. Hauptman, M. Kluge, K.-D. Seidig, and H. Wilde, *Angew. Chem. Intern. Ed. Engl.*, **4**, 688 (1965).

(12) A. Giner-Sorolla and A. Bendich, *J. Org. Chem.*, **31**, 4239 (1966).

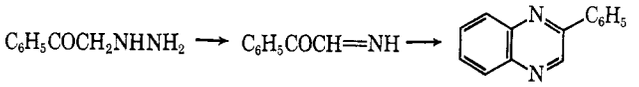
(13) A. Pinner, *Ber.*, **38**, 1531 (1905).

(14) J. J. Gallagher, G. T. Newbold, F. S. Spring, and J. C. Woods, *J. Chem. Soc.*, 910 (1949).

has also been obtained from the thermal decomposition of phenacyl azide *via* the nitrene and phenylglyoxal imine.[15] In discussing the formation of the dimeric product from **14**, Busch specifically rejected the possibility that imidazole **16** (in his view the pyrazine) arose from the hydrazino ketone by elimination to the aldimine, and invoked instead an initial dimerization to a tetrazocine followed by a double ring contraction.[5]

It was of interest to us to determine whether phenacylhydrazine, as a simple prototype of the diazepine systems, does in fact undergo elimination to phenylglyoxal imine, particularly in view of the diverse suggestions that have been made concerning this and related reactions. The base was obtained as described[5] and as previously observed, underwent rapid decomposition in methanol solution, with or without the addition of sodium methoxide.

The decomposition of **14** was also carried out in methanol solution in the presence of *o*-phenylenediamine. This reagent has been successfully used to trap phenylglyoxal imines formed in the pyrolysis of azides.[16] A product corresponding in melting point to 2-phenylquinoxaline (**17**) was isolated in 50% yield; the presence of the imidazole was detected by tlc. The yield was much lower when sodium methoxide was added.



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It is thus clear that decomposition of the α-hydrazino ketone gives rise to the imine by elimination of ammonia, and that excess hydrazine or strong base is not required in the case of a simple hydrazine. It seems quite possible that the other reactions mentioned above also occur by this process, and that this elimination will be found to be characteristic for compounds containing a hydrazinomethyl system attached to a negative group such as carbonyl or the α position of an azine. Similar reactions of hydroxylamino ketones[17] and α-chloromethylpyridines with hydroxylamines[18] have also recently been described.

Registry No.—**7**, 4084-21-3; **1**, 1706-26-9; α-hydrazinoacetophenone, 10137-56-1.

(15) J. H. Boyer and D. Straw, *J. Am. Chem. Soc.*, **74**, 4506 (1952).
(16) J. H. Boyer and D. Straw, *ibid.*, **75**, 1642 (1953).
(17) S. C. Bell, R. J. McCaully, and S. J. Childress, *Tetrahedron Letters* 2889 (1965).
(18) H. Daniher, B. E. Hackley, and A. B. Ash, *J. Org. Chem.*, **31**, 2709 (1966).

Heterocyclic Studies. XXIV. The Formation and Reactions of the 1,6-Diazabicyclo[3.2.0]-3-hepten-2-one System[1]

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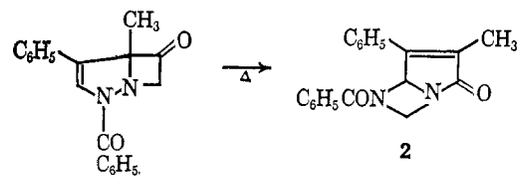
Received September 23, 1966

Compound **2**, the first example of the title system, is obtained by thermal isomerization of the bicyclic ketone (**1**). The reaction of **2** with alcohols or water leads to 1-alkoxymethyl-5-benzamido-3-pyrrolin-2-ones (**7**). Structure **7** was established by conversion to the 1-alkoxymethylmaleimide (**6**) and the pyrrolinones (**8** and **10**). A number of other derivatives of 5-benzamido-3-methyl-4-phenyl-3-pyrrolin-2-one are described. Isomerization of **2** with weak base gives the bicyclic oxadiazine (**14**). Synthetic efforts toward the 5-benzamidopyrrolinone (**8**) and the possible interconvertibility of succinimide and pyrrolinone tautomers are discussed.

Among the diverse transformations of the bicyclic ketone (**1**),[3] one of the more interesting reactions that has been encountered is the conversion of the compound, on heating in benzene or other inert solvents, to an isomer in 77% yield. In this paper we present evidence leading to the 1,6-diazabicyclo[3.2.0]heptenone structure (**2**) for the thermal isomerization product. The nature of this unusual rearrangement is discussed in the following paper.[4]



1 **2**

The main lines of evidence for the structure of the "thermal isomer" were developed from the products of a general acid catalyzed reaction with alcohols, water, or acetic acid to give addition products in excellent yield. These adducts, which will be shown to have structure **7**, had sharp infrared bands (data are for the methanol adduct) for CONH (ν^{CHCl_3} 3440 cm^{-1}, ν^{KBr} 3360 cm^{-1}) and two carbonyl groups (ν^{CHCl_3} 1680 and 1710 cm^{-1}, ν^{KBr} 1670 and 1700 cm^{-1}). The nmr spectra contained peaks for $CH_3C{=}$ (δ^{CDCl_3} = 1.98 ppm), nonequivalent CH_2 (δ_A = 4.70 ppm, δ_B = 4.98 ppm, J_{AB} = 10.5 cps) and a highly deshielded tertiary CH (δ = 7.0 ppm). The compounds were readily interconvertible, suggesting the functionality CON-CH_2OR, which is compatible with the nmr values. This grouping was characterized by mild chromic acid oxidation[5] of the hydroxy compound (A) to a formyl derivative (B, δ = 9.10 ppm) which was deformylated in acidic methanol to give methyl formate and a product (C), corresponding to the sequence shown.

(1) Supported in part by Grant DA-CML-18-108-61-G-24 from the Army Chemical Corps.
(2) National Science Foundation Cooperative Graduate Fellow, 1962–1963.
(3) J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Wineholt, *J. Org. Chem.*, **31**, 34 (1966).
(4) J. A. Moore, R. L. Wineholt, F. J. Marascia, R. W. Medeiros, and F. C. Creegan, *ibid.*, **32**, 1353 (1967).
(5) A similar chromic acid oxidation of a N-methylolamide has been reported by A. Einhorn, *Ann.*, **243**, 207 (1905).