Nucleophilic Substitution with Rearrangement on Troponoids. The Reaction of 2-(1-Azoniabicyclo[2.2.2]oct-1-yl[3,5,7-$^2H_3$]-cyclohepta-2,4,6-trien-1-one Iodide with Piperidine Leading to 2-Piperidino[4,6-$^2H_2$]cycloheptа-2,4,6-trien-1-one *via* 7,2 Addition–Elimination[1]

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Abstract: Piperidine (either neat or in dimethyl sulfoxide) reacts with 2-(1-azoniabicyclo[2.2.2]oct-1-yl)cyclohepta-2,4,6-trien-1-one iodide (**1a**) to give 2-piperidinocyclohepta-2,4,6-trien-1-one (**2a**), while products of either ring opening of the bicyclic skeleton or of rearrangement to benzenoid compounds are not observed. Deuterium labeling experiments show that this is not a straightforward displacement of quinuclidine, piperidine becoming bound to C_7 (title reaction). This is confirmed by the fact that (i) when [1-^{2}H]piperidine is substituted for piperidine in the latter reaction, the position left free by the quinuclidine nitrogen in the troponoid ring is taken by deuterium and (ii) there is no uptake of deuterium by **2a** from [1-^{2}H]piperidine. Both the title reaction and its analog with nondeuterated materials occur in three distinct stages which, under certain conditions, are separately observable. Stage I and stage II reactions can be followed by a uv stopped-flow apparatus while stage III reaction can usually be followed by ordinary uv techniques. Stage I reaction is interpreted as the attack by piperidine at one (or at any one) of the C_3–C_6 ring carbons to give a spectrally observable intermediate which lies in a side equilibrium. Competitive attack on **1** at the C_7 ring carbon gives a second spectrally observable intermediate (stage II reaction) which, by protonation at C_2 followed by rate-limiting 7,2-base elimination (which gives rise to a strong primary kinetic deuterium isotope effect) (stage III reaction), gives the observed end product **2**. This mechanism is supported by the results of a detailed kinetic study in dimethyl sulfoxide and by the observation[1b] that on running the reaction in water the intermediate of stage I reaction is trapped to give *m*-hydroxybenzaldehyde. The driving force for attack by piperidine at unsubstituted troponoid ring positions must be activation by the $-^+NR_3$ group which also provides a good leaving group for the 7,2-base elimination step. Many unexplained results in literature fit this picture.

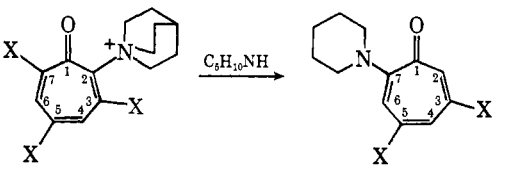
Interest in troponoids (cyclohepta-2,4,6-trien-1-one and its derivatives)[4] is very active as shown by a wealth of studies concerning their synthesis,[5a] biogenesis,[5b] physical properties and semiempirical calculations,[5c] and reactivity. From early research concerned with the latter problems[4] an unusually complex behavior of troponoids toward various reagents has emerged and whole areas, such as that of the reactions with nucleophilic reagents, received very little general clarification.

This state of affairs has stimulated our research in this field.[1a,b] We have been able so far to define, for 2-X-cyclohepta-2,4,6-trien-1-ones, conditions and mechanisms leading to either direct replacement of a ring substituent (X) with good anionic (or neutral) stability,[6] to nucleophilic attack on a side chain[7] or to nucleophilic attack at an unsubstituted ring position inducing rearrangement to *m*-hydroxybenzaldehydes.[1b]

We report here the discovery and a detailed study of a nucleophilic substitution with rearrangement on a 2-X-substituted troponoid (replacement of hydrogen at C_7 with expulsion of X from, and protonation at, C_2). The results of this study bear far reaching implications for the chemistry of troponoids.

Results and Discussion

Nature of the Reaction Products. We have observed that 2-(1-azoniabicyclo[2.2.2]oct-1-yl)cyclohepta-2,4,6-trien-1-one iodide (**1a**) reacts with piperidine (neat or in dimethyl sulfoxide (DMSO)) at room temperature to give 2-piperidinocyclohepta-2,4,6-trien-1-one (**2a**) in



1 **a** (X = H) **b** (X = D) **2**

high yield. Contrary to the case of either a tertiary amine, like quinuclidine, or of iodide ion as nucleophiles, which are known to attack **1a** exclusively at the α carbon of the bicyclic skeleton,[7] no trace of products

(1) (a) "The Reactivity of Pseudoaromatic Compounds. VI," presented in a lecture at the University of Leiden, the Netherlands, Nov 4, 1971. (b) Part V, G. Biggi, F. Del Cima, and F. Pietra, *Chem. Commun.*, 1627 (1971); (c) financial support from Consiglio Nazionale delle Ricerche, Roma, is acknowledged.

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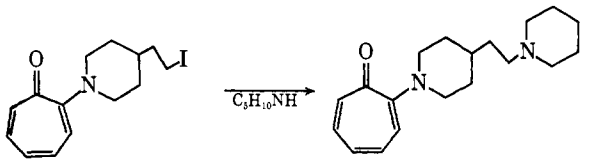
(4) For general reviews (a) P. L. Pauson, *Chem. Rev.*, **55**, 9 (1955); (b) T. Nozoe, "Non-Benzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience, New York, N. Y., 1959; (c) D. Lloyd, "Carbocyclic Non-Benzenoid Aromatic Compounds," Elsevier, Amsterdam, 1966.

(5) Recent representative references only are reported here: (a) A. R. Katritzky, and Y. Takeuchi, *J. Amer. Chem. Soc.*, **92**, 4134 (1970); (b) A. I. Scott, H. Guilford, and E. Lee, *ibid.*, **93**, 3534 (1971); (c) D. J. Bertelli and T. G. Andrews, *ibid.*, **91**, 5280 (1969); M. J. S. Dewar and N. Trinajstic, *Croat. Chem. Acta*, **42**, 1 (1970).

(6) (a) F. Pietra, M. Giocasta, and F. Del Cima, *Tetrahedron Lett.*, 5097 (1969); (b) F. Pietra and F. Del Cima, *J. Chem. Soc.* B, 2224 (1971).

(7) (a) F. Pietra and F. Del Cima, *Chem. Commun.*, 297 (1970); (b) F. Pietra, G. Biggi, and F. Del Cima, *J. Chem. Soc. C*, 3626 (1971).

of the opening of the quinuclidinium ring is observed in this case. This was proved by synthesizing 2-(4-β-piperidinoethylpiperidino)cyclohepta-2,4,6-trien-1-one (**4**) (which was obtained together with its hydroiodide) from 2-(4-β-iodoethyl)piperidinocyclohepta-2,4,6-trien-1-one (**3**)[7] and piperidine. It is in fact easy



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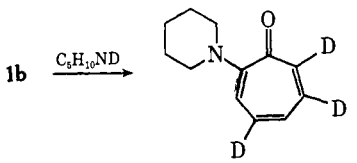
by tlc to detect **4** in the presence of **2a**.

However, the reaction of **1a** with piperidine is not a straightforward displacement of quinuclidine. This was proved by labeling the troponoid ring with deuterium. Thus, 2-(1-azoniabicyclo[2.2.2]oct-1-yl)[3,5,7-$^2H_3$]cyclophepta-2,4,6-trien-1-one iodide (**1b**) reacts with either piperidine in DMSO or with neat piperidine to give a high yield of a product to which we assign the structure **2b**.

This structural assignment is based on both uv and ^1H nmr spectral data. The uv spectrum (see Experimental Section), being identical with that of **2a**,[6] indicates that substitution may have occurred at either C_2 or C_7 on **1**. The products of substitution at C_3–C_6 of **1**, although unknown, would certainly have quite a different uv absorption spectrum from that observed. For example, 2-aminocyclohepta-2,4,6-trien-1-one strongly absorbs at both 385 and 395 nm[8a] (like **2**) while the longest wavelength absorption band of 3-aminocyclohepta-2,4,6-trien-1-one occurs at a much shorter wavelength (312 nm).[8b]

The ^1H nmr spectrum unequivocally proves that substitution has occurred at C_7. This shows, in fact, besides the piperidine protons, two other signals at δ 7.05 (1 H) and 6.18 (2 H). The δ 7.05 signal is assigned to the C_2 proton on **2b** because of both its low field appearance (due to the adjacency to the "carbonyl" group) and its relative sharpness (due to the adjacency to deuterium and not to hydrogen). In agreement with this assignment the ^1H nmr spectrum of the product of the reaction of **1b** with [1-^2H]piperidine (**5**) shows



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only the δ 6.18 signal (2 H) in the aromatic region. Thus, under these conditions, a deuterium has taken the place vacated by quinuclidine on the troponoid ring.

That the uptake of deuterium by the troponoid ring occurred during the substitution reaction by [1-^2H]-piperidine and does not represent merely the result of the equilibration between [1-^2H]piperidine and the reaction products, is shown by the fact that, under the conditions used for the substitution reaction, there is no uptake of deuterium by 2-piperidinocyclohepta-2,4,6-trien-1-one from [1-^2H]piperidine.

(8) (a) Reference 4b, p 374; (b) S. Seto, H. Sugiyama, and H. Toda, *Chem. Commun.*, 562 (1968).

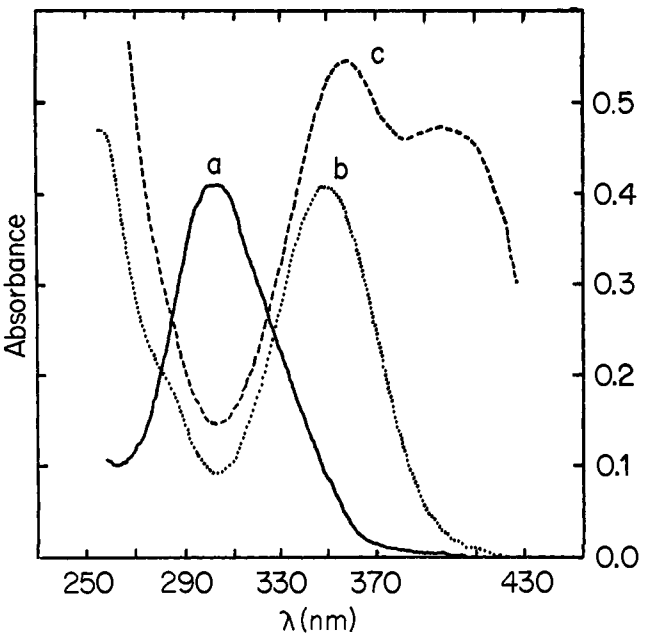
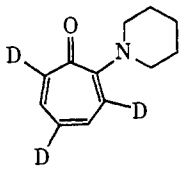


Figure 1. Spectra relevant to reaction of **1b** (6.7×10^{-5} *M*) with piperidine (0.14 *M*) in DMSO solution at room temperature (10-mm cuvette): (a) **1b** before addition of piperidine; (b) *ca.* 15 sec after addition of piperidine (spectrum of the second intermediate; see text); (c) 2-piperidino[4,6-$^2H_2$]cyclohepta-2,4,6-trien-1-one. Scanning rate 300 nm/min.

The structural assignment is further confirmed by the fact that the signal (δ 6.5)[6b] for the 4 and 6 protons of 2-piperidino[3,5,7-$^2H_3$]cyclohepta-2,4,6-trien-1-one (**6**), which would arise from substitution at C_2 on **1b**,



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is absent from the product of the reaction of **1b** with piperidine.

Clearly this is an example of a clean nucleophilic substitution with rearrangement at a troponoid ring. Also the possibility that **4** first forms from **1** and piperidine and then further reacts with piperidine to give **2** was ruled out. Such a reaction does not in fact occur under the experimental conditions used here to produce **2** from **1** and piperidine.

Spectral Detection of Reaction Intermediates. **2a** strongly absorbs near the visible region while **1a** only absorbs at much shorter wavelengths. It is therefore easy to follow the formation of **2a** in the reaction of **1a** with piperidine by uv spectrophotometry.

The initial experiments indicated that in DMSO at piperidine concentrations greater than 0.01 *M* the reaction is zero order with respect to piperidine. Since an SN1 type process cannot be conceived for these systems to rationalize the reaction observed, this suggested that the reaction could proceed through an adduct between piperidine and **1a** with formation of the adduct being complete in the concentration range of amine investigated.

In accordance with this suggestion, on mixing the deuterated reagent **1b** at room temperature with pip-

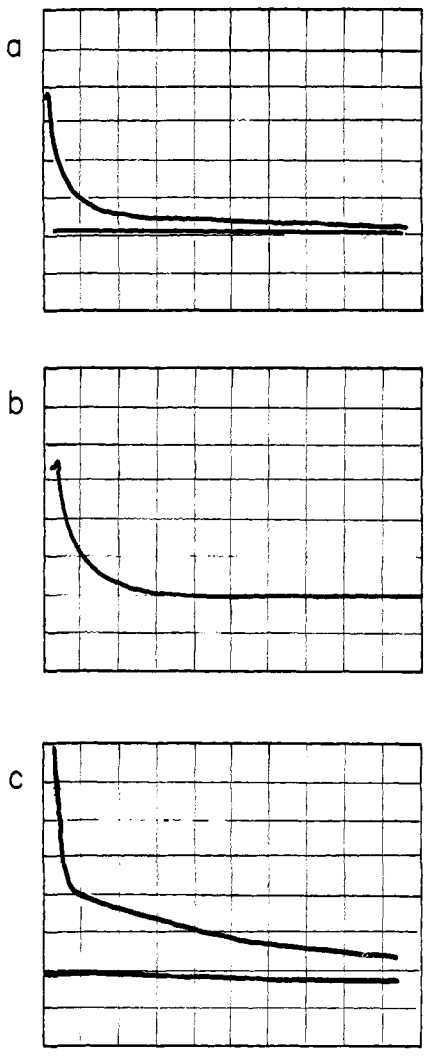


Figure 2. Representative oscilloscope traces of the reaction of **1b** (7.43×10^{-5} *M*) with piperidine in DMSO solution at room temperature (λ 370 nm): a, $[C_5H_{10}NH] = 0.1$ *M* (sweep time 50 msec/horizontal division; b, $[C_5H_{10}NH] = 5.1$ *M* + $[C_5H_{10}NH_2Cl] = 0.009$ *M* (sweep time same as a); c, concentrations same as a but sweep time 200 msec/horizontal division and ordinate scale expansion.

eridine in DMSO (at a concentration where the reaction is kinetically zero order with respect to piperidine), the spectrum of an intermediate is immediately observable by conventional uv absorption techniques while the absorption due to **1b** disappears. This intermediate decays at a measurable rate into **2b**. This is shown in Figure 1 where a, b, and c are the uv absorption spectra of **1b**, the intermediate, and **2b**, respectively.

In the corresponding reaction of the nondeuterated material (**1a**), decay of the intermediate into **2a** is too fast to allow its spectrum to be accurately recorded by conventional techniques.

When we went to a uv stopped-flow apparatus to investigate the kinetics of formation of the intermediate of Figure 1 we observed that on mixing the reagents under the above conditions the spectrum of an intermediate quite rapidly appears and then decays also at a high rate (the shortest half-life was *ca.* 20 msec) into that of Figure 1. This is illustrated in Figure 2a which shows the oscilloscope trace (λ 370 nm) for the reaction of **1b** with piperidine (0.1 *M*) in DMSO at room temperature (the ordinate gives the percentage of transmittance and the abscissa the sweep time). After a slight increase of transmittance due to the dead time of the apparatus (*ca.* 5 msec) a steep decrease of transmittance is observed due to the formation of the first intermediate, followed by a less steep decrease of transmittance due to the transition from the first to the second intermediate (that of Figure 1).

The increase of absorbance due to the transition from the first to the second intermediate is better appreciated in Figure 2c. Here the experiment of Figure 2a has been repeated with ordinate scale expansion and at a higher sweep time.

Addition of a fair amount of piperidinium chloride to the mixture of the experiment in Figure 2a accelerates the transition from the first to the second intermediate (while allowing only a lower concentration of the first intermediate to be formed owing to a mass effect on the equilibrium of formation of the intermediate from **1b**, as will be described in the following section) so that the two processes are no longer separately observable. This is shown in Figure 2b (decay of the second intermediate into 2-piperidinocyclohepta-2,4,6-trien-1-one is much slower and is not apparent in Figure 2b).

Stopped-flow experiments similar to those described above have been carried out at other wavelengths as well. The results show that the first intermediate has a uv absorption spectrum similar to that of the second intermediate (that of Figure 1, curve b). Absorption is, however, weaker for the first than for the second intermediate.

That the two successive spectral changes we have observed arise from two transient species which are intrinsic to the overall reaction we are studying and are not, even in part, an artifact due to, say, a trace of nondeuterated troponoid in our sample of **1b** or to the presence of trace water (giving a second nucleophile in the presence of piperidine) or to other impurities can be clearly demonstrated. The best arguments come from the kinetic study presented later. We can only say here that the pattern of the spectral changes described above for the reaction of **1b** is quite the same for the reaction of the nondeuterated material **1a** with piperidine in DMSO and that it remains unaltered on repeated careful purifications of both reagents and solvent used.

It is clear that neither transient intermediate we have observed can be a complex of the charge-transfer type. Rates of formation of species of the latter type can only be measured by temperature-jump or other techniques for very fast reactions.[9] Also mass effects, reported later, on the equilibria of formation of our transient intermediates point to the same conclusion. Clearly, covalent bond formation between the partners in the complex is involved.

The kind of spectra (uv) we have been able to obtain for the two intermediates involved in our reaction do not, of course, allow much detailed insight into their structures. They clearly point, however, to highly delocalized structures (more delocalized than those for the initial reactants **1a,b**). This piece of information will prove to be very useful later when inquiring about the likely structures for the two intermediates.

(9) R. Foster, "Organic Charge-Transfer Complexes," Academic Press, London, 1969, p 155; E. F. Caldin, D. O'Donnell, D. Smith, and J. E. Crooks, *Chem. Commun.*, 1358 (1971).

Table I. Reaction of **1a** or **1b** with Piperidine in DMSO at 25° (Data for Stage I and Stage II Reactions)

$[C_5H_{10}NH]$ $\times 10^2$ M	$[C_5H_{10}NH_2Cl]$ $\times 10^2$ M	$[(C_2H_5)_4NClO_4]$ $\times 10^2$ M	k_{1obsd}, sec^{-1}	k_1, M^{-1} sec^{-1}	$t_{1/2(II)}$, sec
		1a (Initial Concentration 8.01 $\times 10^{-5}$ M)[a]			
3.20			7.4	231	0.41
4.40	7.70				0.031[b]
6.20			14.1	234	0.60
8.80	5.70				0.029[b]
8.80	7.70				0.028[b]
10.0	0.088	1.08	19.5	195	0.15
10.0	0.194	1.08	19.7	197	0.090
20.0	0.088	1.08	40.0	200	0.25
20.0	0.194	1.08	40.6	203	0.15
		1b (Initial Concentration 7.43 $\times 10^{-5}$ M)[a]			
5.10	4.20				0.044[b]
5.10	8.40				0.024[b]
6.30			15.7	250	0.59
10.0		1.08	25.1	251	0.81
10.1	0.11	0.88	26.8	265	0.10
10.2	4.20				0.024[b]
10.2	8.40				0.023[b]
10.9	0.05	1.08	28.7	263	0.18
11.9		*c*	30.6	257	0.95
12.8			32.5	254	0.98
20.0		1.08	49.6	247	1.5
49.1		1.08	119	243	3.5

[a] Measurements at 370 nm. [b] Stage I and stage II reactions are not separately observable in these cases (see text); half-lives refer to the overall process leading from **1** to **9** (see Scheme I). [c] With added benzyltrimethylammonium chloride 1.05 $\times 10^{-2}$ M.

Therefore, the overall reaction occurs in three stages which, under appropriate conditions, are separately observable and have been studied in detail as reported below.

Stage I Reaction. This is the stage in which the intermediate spectroscopically first observed is formed. Kinetic data for this stage have been obtained by a uv stopped-flow apparatus from the steep portion of the oscilloscopic traces of the type in Figure 1a (working at a lower sweep time than used in this experiment).

A large excess of piperidine has always been used and either formation of the first intermediate or disappearance of **1** nicely fits a first-order plot. Rate coefficients for stage I reaction are indicated with the k_I symbol in Table I and it is seen that the kinetics are second order, first order with respect to both piperidine and the substrate.

The isotope effect, given as the ratio of the second-order rate coefficients for the light (**1a**) and for the deuterated substrate (**1b**), $k_{I(H)}/k_{I(D)}$, is small and inverse, *ca.* 0.9.

It is also seen that there is no large kinetic salt effect by either a neutral salt like tetraethylammonium perchlorate or a basic salt like benzyltrimethylammonium chloride.

Stage II Reaction. This is the stage in which transition from the first to the second observable intermediate occurs. Kinetic data have been obtained from the less steep portion of the oscilloscopic trace of the type in Figure 2c.

Change of absorbance with time can be nicely fitted into a first-order plot. However, as the uv spectra of the two intermediates are very similar to each other, we give (Table I) only half-lives ($t_{1/2(II)}$). In fact, under such circumstances, rigorous consistency can only be obtained among kinetic orders.

Data of Table I show that the rate of stage II reaction is depressed on increasing piperidine concentration while it is accelerated by added piperidinium chloride.

No kinetic effect is observed by either a neutral salt, like tetraethylammonium perchlorate, or a basic salt, like benzyltrimethylammonium chloride.

The deuterium kinetic isotope effect for reaction of the light (**1a**) and the deuterated substrate (**1b**) is very close to unity.

The oscilloscopic trace of Figure 2b clearly shows that in the presence of a fair amount of added piperidinium chloride, stage I and stage II reactions are no longer separately observable (this was discussed in detail in a previous section).

Working with an even greater concentration of added piperidinium chloride, the maximum attained value of the absorbance due to both intermediates, and then of their concentrations, is much lower than that observed in the absence of piperidinium chloride. Under these conditions a large fraction of **1** remains unchanged, as shown by its uv spectrum.

Stage III Reaction. In this stage the second spectroscopically observable intermediate decays into end reaction products. Stage III reaction is separately observable from the previous two (by measuring the increase of absorption of the end troponoid product at a wavelength (408 nm) where there is no appreciable absorption by other components of the reaction mixture) when a sufficiently high concentration of piperidine, greater than *ca.* 0.01 M, is employed.

In the absence of acidic catalysts the rates of stage III reaction are amenable to study by conventional techniques. Higher, acid-catalyzed rates were measured by a stopped-flow apparatus at the same wavelength.

A large excess of piperidine was always employed and formation of the end troponoid product (**2a** or **2b**) nicely fits a first-order plot.

From the kinetic data, which are collected in Table II, it is seen that stage III reaction is zero order with

Table II. Reaction of **1a** or **1b** with Piperidine in DMSO at 25°[a]

$[Substrate]_0 \times 10^5$ M	$[C_5H_{10}NH] \times 10^2$ M	$[C_5H_{10}NH_2Cl] \times 10^2$ M	$[(C_2H_5)_4NClO_4] \times 10^2$ M	$k_{111\ obsd} \times 10^3$ sec^{-1}
		1a[b]		
3.64	0.0236			0.025
3.64	0.0507			0.114
3.64	0.0761			0.246
3.64	0.250			2.70
6.85	0.235			2.31
3.64	0.250	0.01		2.37
3.64	0.250		c	2.55
5.10	0.980			10.0
12.80	1.19			11.0
2.74	1.27			10.7
8.01	4.40	7.70		79.1
8.01	8.80	5.80		173
8.01	8.80	7.70		182
8.10	9.80		1.08	10.0
8.10	9.80		c	9.50
8.01	10.0	0.097	1.08	23.1
8.01	10.0	0.194	1.08	40.7
8.01	20.0	0.097	1.08	23.8
8.01	20.0	0.194	1.08	38.5
5.10	29.7		1.08	10.5
		1b		
3.48	0.0231			0.0040
3.48	0.0522			0.017
3.48	0.0781			0.042
3.48	0.250			0.38
4.95	1.05		1.08	0.89
6.52	5.08		1.08	1.28
7.43	5.10	4.20		21.0
7.43	5.10	8.40		19.8
4.95	9.83	0.066	0.95	8.50
4.95	9.83	0.365	0.66	7.60
4.95	9.83	1.03		13.6
4.95	10.1		1.08	1.27
4.95	10.1		c	1.26
6.52	10.1			1.30
7.43	10.2	4.20		29.6
7.43	10.2	8.40		39.6
4.95	36.9	0.066	0.95	2.60
4.95	36.9	0.365	0.66	7.46
4.95	41.9	1.98		24.0

[a] Rates for overall reactions (at piperidine concentrations above *ca.* 1×10^{-2} M these identify with rates for stage III reaction). [b] Measurements at 408 nm. [c] With added benzyltrimethylammonium chloride 1.05×10^{-2} M.

respect to piperidine except at high (comparable with that of piperidine, for any single run) concentration of piperidinium salt.

The reaction is accelerated by added piperidinium chloride, whereas both a neutral salt, like tetraethylammonium perchlorate, and a basic salt, like benzyltrimethylammonium chloride, have no appreciable kinetic effect.

A large isotopic effect, given as the ratio of the observed rate coefficients ($time^{-1}$) for reaction of the light (**1a**) and the deuterated substrate (**1b**), is observed. Its magnitude, *ca.* 9, is independent of the conditions in which stage III reaction has been run.

At piperidine concentrations lower than 0.0025 M it is seen from Table II that second-order kinetics with respect to piperidine are obtained. Under these conditions the kinetic deuterium isotope effect drops to *ca.* 6.

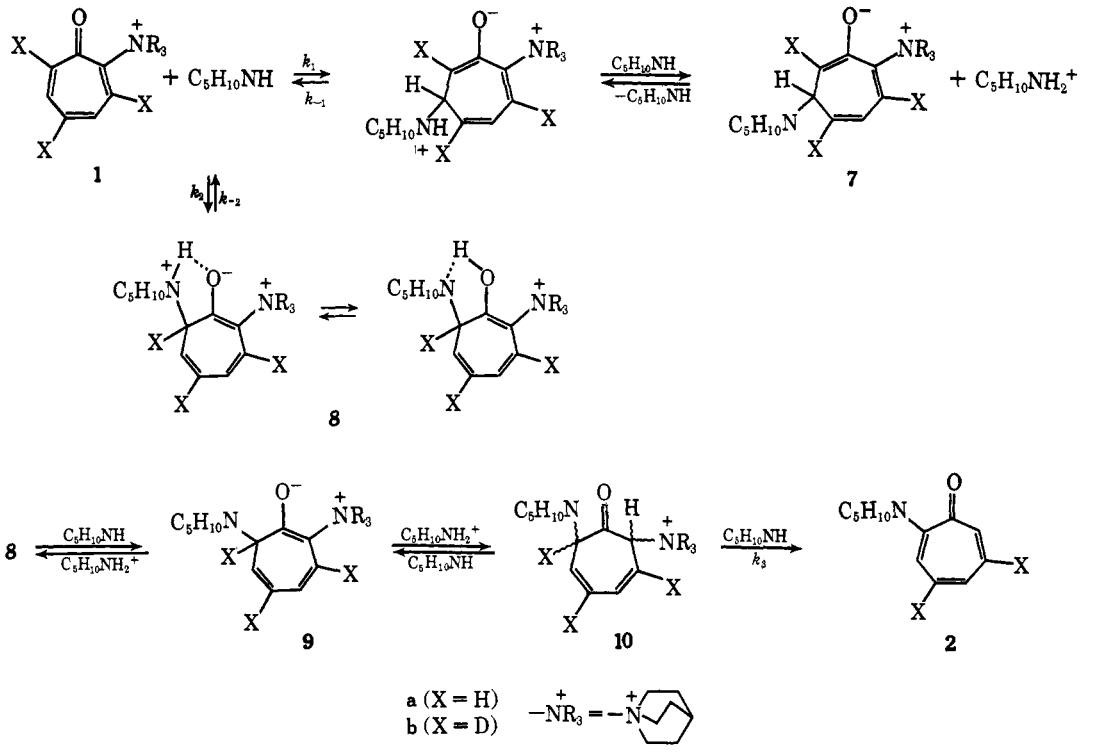
Mechanism. The primary question about the reaction mechanism is whether the two spectroscopically observable intermediates lie along the reaction pathway or rather are found in side equilibria.

First, it is not easy to write the structures (highly delocalized as suggested by their uv spectra) of two consecutive intermediates along the reaction pathway to the observed products.

Even more cogent was the observation of a negative kinetic order with respect to piperidine in the reaction of formation of the second intermediate (stage II reaction). This clearly demands that the first intermediate be in a side equilibrium involving more molecules of piperidine than in the rate determining transition state of stage II reaction.

This is the backbone of the mechanism for the reaction we have studied. The mechanism is presented in some detail in Scheme I where the first intermediate **7** is viewed as the conjugate base of the addition complex of attack of piperidine at C_6 of the troponoid ring of the substrate (stage I reaction). We have taken attack at C_6 as an example, although the same conclusions drawn here can be arrived at by postulating attack at any one of the C_3, C_4, or C_5 troponoid ring carbons as well. In any case the highly delocalized structures suggested for the two observable intermediates are compatible with their uv spectra. Available data do not allow a decision to be made about the exact position of attack to give the first intermediate. However, further pertinent comments about this point will be made later.

Scheme I



Competitively with attack at position C_3–C_6, attack at position C_7 of the troponoid ring of the substrate is envisaged (stage II reaction) as leading to the second intermediate, **9**, the slow step, k_2, involving a single molecule of piperidine.

Rapid deprotonation[10] from **8** to **9** is envisaged as an equilibrium which is wholly displaced toward the deprotonated species in the presence of excess piperidine, like in the corresponding step in stage I reaction.

Intermediate **9** may suffer protonation at either oxygen (or at nitrogen, which is equivalent) or at C_2. In the first case one goes back toward **1** while in the latter one the 3,5-cyclopentadienone derivative **10** is obtained.[11] No evidence concerning the question of the stereochemical relationship among substituents at 2 and 7 positions can be presented. Slow 7,2-base elimination from **10** then leads to the final product **2**.

The whole body of the kinetic data obtained here fits the rate expressions derivable from the proposed mechanism (Scheme I). Thus, the rate expression for stage I reaction in Scheme I is given by eq 1 which fits

$$\text{rate}_I = k_{I\text{obsd}}[\mathbf{1}]_0 = k_1[\mathbf{1}][C_5H_{10}NH] \qquad (1)$$

the simple second-order kinetics obtained for this stage reaction. This implies that deprotonation of the first adduct by a second molecule of amine to give **7** occurs in a fast step (which is well proved for strong acids as ammonium salts[10]).

As to the stage II reaction, letting $[\mathbf{1}]_0 = [\mathbf{1}] + [\mathbf{7}]$ and letting K_I be the equilibrium constant for stage I reaction, one derives eq 2. Equation 2 reduces to eq 3

$$k_{II\text{obsd}} = \frac{\text{rate}_{II}}{[\mathbf{1}]_0} = \frac{k_2[C_5H_{10}NH_2^+][C_5H_{10}NH]}{K_I[C_5H_{10}NH]^2 + [C_5H_{10}NH_2^+]} \qquad (2)$$

$$k_{II\text{obsd}} = k_2[C_5H_{10}NH_2^+]/K_I[C_5H_{10}NH] \qquad (3)$$

(in the special case $K_I[C_5H_{10}NH]^2 \gg [C_5H_{10}NH_2^+]$) which is fitted by our data.

Stage III reaction shows a large kinetic deuterium isotope effect whose magnitude does not vary with changing the concentration of the reagents provided limiting conditions are maintained.[13] This indicates that the 7,2-base elimination step is rate limiting, extensive breaking of the C_7–H bond being involved in

(10) M. Eigen, *Angew. Chem.*, 75, 489 (1963).

(11) Intermediate **10** must only be able to absorb appreciable uv light of much shorter wavelength than any other of the troponoid structures shown in Scheme I. Only unsubstituted 3,5-cycloheptadien-1-one and its 2-alkyl derivatives have been reported.[12] These are stable compounds which display the character more of unconjugated than of conjugated dienes, strongly absorbing at *ca.* 210 nm and rather weakly at 290 nm.[12a] This behavior has been attributed to nonplanarity of the diene moiety in the more stable conformation.[12b]

Protonation of **9** at a ring position other than C_2 could be considered. Protonation at C_6 is the most interesting case as it would lead to a 2,4-cycloheptadien-1-one derivative which is expected to be more stable than the corresponding structure of type **10**. In this case, in fact, all trigonal carbons should be able to lie in the same plane as reported for methyl- or methoxyl-substituted 2,4-cycloheptadien-1-ones which strongly absorb at *ca.* 330 nm.[12b] While such a low wavelength value rules out a 2,4-cycloheptadien-1-one structure for the intermediates we have detected spectroscopically, let us consider the possibility that such a species be in equilibrium with **9**. While such a possibility cannot be rigorously ruled out in the presence of much added piperidinium salt, it can be discarded when no piperidinium salt has been added. Under the latter conditions, in fact, when the stage II reaction is completed no absorption at 330 nm appears.

(12) (a) J. Meinwald, S. L. Emerman, N. C. Yang, and G. Büchi, *J. Amer. Chem. Soc.*, 77, 4401 (1955); (b) O. L. Chapman, D. J. Pasto, and A. A. Griswold, *ibid.*, **84**, 1213 (1962).

(13) A lower value of the isotope effect at low (nonlimiting) piperidine concentrations indicates a fine balance among the various steps of the reaction under these conditions. The 1,3-base elimination step (k_3) is no longer alone rate controlling which leads to a smaller isotope effect. Such a state of affairs reflects also on other kinetic features. Thus, under these nonlimiting conditions, formation of type-**2** products no longer accurately fits a first-order plot. Curved, concave upwards, plots are rather obtained.

It is not easy to account for the lack of a strong secondary kinetic deuterium isotope effect on stage I and, particularly, stage II reactions. However, the complexity and the lack of general understanding of the factors determining secondary kinetic isotope effects entitles us not to be forced to give an explanation for this.

the transition state, under all conditions. Therefore, the rate for stage III reaction can be expressed by eq 4.

$$\text{rate}_{III} = d[\mathbf{2}]/dt = k_3[\mathbf{10}][C_5H_{10}NH] \quad (4)$$

Letting $[\mathbf{1}]_0 = [\mathbf{1}] + [\mathbf{7}] + [\mathbf{9}] + [\mathbf{10}]$, $K_{II} = [\mathbf{9}]\cdot[C_5H_{10}NH_2^+]/[\mathbf{1}][C_5H_{10}NH]^2$ as the equilibrium constant for stage II reaction, and $K_{III} = [\mathbf{10}][C_5H_{10}NH]/[\mathbf{9}]\cdot[C_5H_{10}NH_2^+]$ as the equilibrium constant for the interconversion of **9** and **10**, one obtains eq 5 from eq 4.

$$k_{III\,obsd} = \frac{\text{rate}_{III}}{[\mathbf{1}]_0} = \frac{k_3[C_5H_{10}NH]}{\dfrac{K_{III}(1 + K_{II}/K_I)[C_5H_{10}NH]}{[C_5H_{10}NH_2^+]} + \dfrac{K_{III}/K_{II}}{[C_5H_{10}NH]} + 1} \quad (5)$$

Equation 5 predicts, as found experimentally, that (i) at high piperidine concentrations and low acid ($C_5H_{10}NH_2^+$)[14] concentration the rate is first order with respect to the acid and (ii) at low piperidine concentrations the rate is second order with respect to piperidine.[15]

Conclusions

It must be emphasized that nucleophilic substitution on **1** has taken the course of a 7,2 addition (destroying the conjugation in the ring) followed by elimination because the unsubstituted ring positions of **1** (or at least some of them) are strongly activated toward nucleophilic attack. This is clearly shown by the fact that nucleophilic substitutions (without rearrangement) of X by piperidine from 2-X-cyclohepta-2,4,6-trien-1-ones in DMSO are much slower than the reaction of **1** with piperidine.[6b,16]

It can also be presumed that attack on **1** at C_2 by piperidine would otherwise not be particularly (or not at all) inhibited. For example, aza-activated nucleophilic aromatic substitution of $-^+N(CH_3)_3$ by OH^-, *via* the normal addition–elimination mechanism,[17] has been reported to be faster than replacement of chlorine.[18]

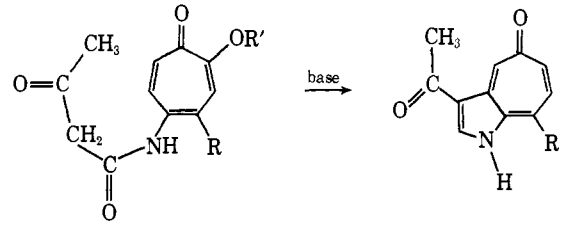
Activation by $-^+NR_3$ to attack at the unsubstituted ring positions of **1** recalls activation by $-^+N=$ to Michael additions on acridinium salts.[19]

Other evidence for the occurrence of attack on **1** by piperidine at ring positions other than C_7 was obtained by running the reaction of **1a** with piperidine in water. *m*-Hydroxybenzaldehyde was obtained, which demands attack by piperidine at any one of the C_3–C_6 ring positions.[1b] When the labeling experiments we are carrying out on this reaction[1b] are completed the exact position of attack by piperidine will be ascertained and this will throw more light even on the exact course of stage I reaction of the present work.

Another function performed by the $-^+NR_3$ group is that of providing a good leaving group for the 7,2-base elimination from **10**.

The above ideas may be used to explain some other results in literature. There is, for example, the case of the exclusive formation of 2-phenyl-4-cyanocyclohepta-2,4,6-trien-1-one in the reaction of 2-chloro-5-cyanocyclohepta-2,4,6-trien-1-one with phenylmagnesium bromide.[20] Here the C_7 in the substrate may be seen to be more activated, by the cyano group, than C_2 toward nucleophilic attack.

Even cyclizations of the type reported below[21] might



R = $(CH_3)_2CH-$
R′ = CH_3- or CH_3CO-

be interpreted along the same lines admitting that susceptibility to the Michael type of attack is also borne to some extent by troponoids not carrying strongly electron-attracting substituents (the case of R′ = CH_3). Intramolecular attack may be seen to be favored over intermolecular nucleophilic substitution of $-OR'$ by proximity effects.

It seems rather surprising that no products of substitution at C_2, without rearrangement, have been found for the reaction of 2-chloro-5-isopropylcyclohepta-2,4,6-trien-1-one with ammonia (neat or in ethanol) and for similar cases.[22] Here, exclusive formation of 4-isopropylbenzamide and of 2-amino-4-isopropylcyclohepta-2,4,6-trien-1-one have been reported.[22] It seems to be worthwhile to investigate accurately whether products of substitution at C_2 without rearrangement are really completely absent. In any case we would expect no rearrangement in the case of a strongly nucleophilic amine like piperidine in an inert solvent where we predict exclusive formation of 2-piperidino-5-isopropylcyclohepta-2,4,6-trien-1-one.

Current work in this area is also aimed at finding out what set of conditions will lead to reactions at the "carbonyl" carbon[1b] or at the side chain.[7]

Experimental Section

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. Uv spectra were recorded with a Cary 14 spectrophotometer and the kinetics were followed with a Beckmann DU spectrophotometer. Ir spectra were taken on a Perkin-Elmer 337 grating spectrophotometer. ^1H nmr spectra were run on a Jeol C-60AL spectrophotometer or on a Varian HA-100 spectrophotometer (10% solutions) with $SiMe_4$ as internal standard at 30°.

Reaction of 2-(1-Azoniabicyclo[2.2.2]oct-1-yl)cyclohepta-2,4,6-trien-1-one Iodide[7a] (1a) with Piperidine. A solution of piperidine (0.19 *M*) in dried dimethyl sulfoxide (0.3 ml, 0.059 mmol) was

(14) The data in Table II clearly show that catalysis (both in stage II and stage III reactions) by the salt used to produce piperidium ion (piperidinium chloride) is acid catalysis. Both a neutral salt, like tetraethylammonium perchlorate, and a basic salt, like benzyltrimethylammonium chloride, are in fact devoid of any kinetic effect on these reactions.

(15) Data in Table II for 1a (lines 4 and 6) show that addition of acid ($C_5H_{10}NH_2^+$) at low piperidine concentrations slightly but measurably depresses the rate. This may be attributed to diminished activity of piperidine owing to hydrogen-bonding interactions with the acid. Infrared evidence for the occurrence of the hydrogen-bonded complexes postulated here has been recently produced (R. Clements, F. N. Masri, and J. L. Wood, *Chem. Commun.*, 1530 (1971)).

(16) The comparison is straightforward as the rate of the latter type reactions is not affected by the nature of X for various X.[6]

(17) F. Pietra, *Quart. Rev., Chem. Soc.*, **23**, 504 (1969).

(18) G. B. Barlin and A. C. Young, *J. Chem. Soc. B*, 821, 1675 (1971).

(19) D. Dimroth and R. Crigee, *Chem. Ber.*, **90**, 2207 (1957).

(20) K. Kikuchi, *Bull. Chem. Soc. Jap.*, **40**, 355 (1967).

(21) S. Seto, K. Ogura, and H. Toda, *Bull. Chem. Res. Tohoku Univ.*, 17, 65 (1967); K. Ogura, H. Sasaki, and S. Seto, *Bull. Chem. Soc. Jap.*, **38**, 307 (1965).

(22) T. Nozoe, S. Seto, and T. Sato, *Proc. Japan Acad.*, **30**, 473 (1954).

slowly added to the equimolar amount of **1a** dissolved in 1.5 ml of dimethyl sulfoxide at room temperature. The reaction mixture immediately became green. After the mixture was allowed to stand for 1 night it was poured into water and extracted with ether. The ether layer was dried over magnesium sulfate and then evaporated to leave a yellow oil which showed a single spot on tlc (silica gel; eluent 9:1 benzene–95% ethanol) corresponding to 2-piperidinocyclohepta-2,4,6-trien-1-one[6] (R_f *ca.* 0.9) while 2-(4-β-piperidinoethylpiperidino)cyclohepta-2,4,6-trien-1-one (**4**) (R_f *ca.* 0.1) was not present in any detectable amount. Repeated sublimation of the yellow oil (50° (1 mm)) gave 2-piperidinocyclohepta-2,4,6-trien-1-one, mp 56–57° (9 mg, yield 80%). The same result was obtained when the reaction was carried out with a tenfold excess of piperidine.

Reaction of 2-(1-Azoniabicyclo[2.2.2]oct-1-yl[3,5,7-$^2H_3$]cyclohepta-2,4,6-trien-1-one Iodide[7b] (1b) with Piperidine. (a) In Dimethyl Sulfoxide. A solution of piperidine (0.0380 g, 0.45 mmol) in dried dimethyl sulfoxide was slowly added to the equimolar amount of **1b** dissolved in *ca.* 10 ml of dimethyl sulfoxide at room temperature. After the mixture was allowed to stand for 1 night, it was poured into water and extracted with ether. The ether layer was evaporated to leave a brown oil which was chromatographed on a silica gel column. A violet eluate containing only a negligible amount of solute was obtained first with benzene as eluent. The elution was then continued with 95:5 benzene–95% ethanol which eluted a yellow-orange broad band which was fractionally collected. All these fractions were mainly constituted (by tlc analysis) of a material showing the same R_f value as 2-piperidinocyclohepta-2,4,6-trien-1-one. The central fractions, which were the purest, were evaporated to leave a yellow oil which, after repeated sublimation (50° (1 mm)), gave a compound of mp 57° (yield 40% based on the molecular weight of 2-piperidinocyclohepta-2,4,6-trien-1-one); δ (Varian, C_6D_6) 7.17 (undeuterated solvent peak), 7.05 (1 H, s), 6.18 (2 H, s), 3.05 (4 H), 1.36 br (6 H). No signal was detectable at δ 6.5. At 60 MHz the peak of the solute at lowest field appeared only as a shoulder at high field of the solvent peak. In deuterated chloroform the signals in the aromatic region appeared as an extremely complex pattern. The uv spectrum was identical with that of 2-piperidinocyclohepta-2,4,6-trien-1-one.[6]

(b) In Neat Piperidine. A suspension of **1b** (0.092 g, 0.27 mmol) in neat piperidine was left at room temperature for 5 days. Then, since some **1b** was still undissolved, the mixture was refluxed for 3 hr. A deep brown mixture was obtained. The excess piperidine was then distilled under vacuum. The residue was poured into water and extracted with benzene. The benzene layer was dried over magnesium sulfate and then evaporated and finally the oily residue was sublimed (50° (1 mm)) to give a compound of mp 57° (yield 60%, based on the molecular weight of 2-piperidinocyclohepta-2,4,6-trien-1-one), which showed the same spectral characteristics as the product described above from the reaction in dimethyl sulfoxide.

Reaction of 2-(1-Azoniabicyclo[2.2.2]octane)[3,5,7-$^2H_3$]cyclohepta-2,4,6-trien-1-one Iodide[7] (1b) with [1-^{2}H]Piperidine. A suspension of **1b** (0.103 g, 0.3 mmol) in an excess of [1-^{2}H]piperidine was heated in a sealed glass tube at 100° for 12 hr. Work up of the reaction mixture as in the last case above afforded a yellow oil (yield 60%, based on the molecular weight of 2-piperidinocyclohepta-2,4,6-trien-1-one) which had a uv absorption spectrum identical with that of 2-piperidinocyclohepta-2,4,6-trien-1-one; δ (Varian, C_6D_6) 7.17 (undeuterated solvent peak), 6.18 (2 H, s), 3.05 br (4 H), 1.36 br (6 H).

Treatment of 2-Piperidinocyclohepta-2,4,6-trien-1-one with [1-^{2}H]-Piperidine. A solution of 2-piperidinocyclohepta-2,4,6-trien-1-one (0.029 g, 0.154 mmol) in excess [1-^{2}H]piperidine was sealed into a glass tube and heated at 100° for 12 hr. Evaporation of the amine under vacuum and sublimation of the residue (50° (1 mm)) afforded 0.021 g (70% yield) of yellow crystals, mp 56–57°, which showed the same ^{1}H nmr spectrum as an authentic sample of 2-piperidinocyclohepta-2,4,6-trien-1-one.

Reaction of 2-(4-β-Iodoethylpiperidino)cyclohepta-2,4,6-trien-1-one[7] (3) with Piperidine. A solution of piperidine (0.06 g, 0.66 mmol) in 0.5 ml of dry benzene was added to a solution of **3** (0.088 g, 0.26 mmol) in 0.8 ml of dry benzene and then an additional 1.2 ml of benzene was added. After the solution was allowed to stand for 1 day at room temperature, it became yellow and crystals precipitated. After some days the mixture was evaporated and the residue was extracted with boiling light petroleum ether. This extract was cooled at −20° to give 0.024 g of yellow crystals which after recrystallization from light petroleum ether had mp 53–54° (*Anal.* Calcd for $C_{19}H_{28}N_2O$: C, 76.0; H, 9.4; N, 9.3. Found: C, 76.1; H, 9.5; N, 9.1); δ (Jeol, $CDCl_3$) 7.1–6.4 (5 H, complex pattern), 4.0 br (1 H), 3.8 br (1 H), 2.9–1.3 (21 H, series of broad signals); ν_{max} (liquid film) 3020 w, 2930–2750 s, 1620 w, 1575 s, 1500–1450 s, 1390 m, 1280 m, 985 and 970 m, 765 and 710 m; λ_{max} (95% ethanol) 253, 355, and 400 nm (log ε 4.18, 4.01, and 3.94). These data are consistent with 2-(4-β-piperidinoethylpiperidino)-cyclohepta-2,4,6-trien-1-one (**4**). The residue above from the extraction with petroleum ether was recrystallized from *ca.* 2 ml of boiling 95% ethanol. On cooling to room temperature, 0.042 g of yellow-brown crystals (very slightly soluble in acetone, water, or chloroform) of mp 224–225.5° precipitated. (*Anal.* Calcd for $C_{19}H_{29}N_2OI$: C, 53.3; H, 6.8; N, 6.5; I, 29.6. Found: C, 53.2; H, 7.0; N, 6.5; I, 29.8). The uv absorption spectrum was identical with that of **4**. This material was suspended in chloroform and then it was shaken with an aqueous solution of potassium carbonate. The crystals dissolved and the organic layer became yellow. The organic layer was evaporated to dryness and the residue was recrystallized from light petroleum ether to give 0.022 g of **4**. Therefore the above data are consistent with 2-(4-β-piperidinoethylpiperidino)cyclohepta-2,4,6-trien-1-one hydriodide.

Treatment of 2-(4-β-Piperidinoethylpiperidino)cyclohepta-2,4,6-trien-1-one[7] (4) with Piperidine. A solution of piperidine (0.2 *M*) in dimethyl sulfoxide (0.050 ml, 0.01 mmol) was added to a solution of **4** (0.0016 g, 0.0055 mmol) in 0.5 ml of dimethyl sulfoxide. After the solution was allowed to stand for 1 night at room temperature, no trace of 2-piperidinocyclohepta-2,4,6-trien-1-one was found (analysis by tlc).

Kinetics. Both dimethyl sulfoxide and piperidine were purified as before.[23] The kinetics of the overall reaction of **1a** with piperidine were followed in a spectrophotometric cuvette, placed in a thermostated cell compartment of a uv spectrophotometer, by measuring the increase of the absorbance at 408 nm of the 2-piperidinocyclohepta-2,4,6-trien-1-one formed. The Lambert–Beer law was strictly followed. The experimental infinity was that expected for the quantitative production of 2-piperidinocyclohepta-2,4,6-trien-1-one. Excellent first-order plots were obtained up to 90% reaction completion except at very low piperidine concentration as explained in the text.

Stage I and stage II reaction kinetics (as well as stage III reaction kinetics in the case of high, catalyzed rates) were followed by a Durrum stopped-flow apparatus as described in the text.

(23) F. Pietra and F. Del Cima, *J. Org. Chem.*, 33, 1411 (1968).