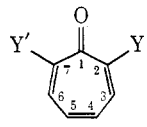
Base-Induced Ring Contractions of Cycloheptatrienones Carrying a Mobile α Substituent. Available Pathways and Competition with Substitution Reactions[1]

Gino Biggi,[2a,3] Arie J. de Hoog,[2b] Francesco Del Cima,[2a,4] and Francesco Pietra*[2a]

Contribution from the Department of Chemistry, University of Pisa, 56100 Pisa, Italy, and the Laboratories for Organic Chemistry, University of Leiden, Leiden, The Netherlands. *Received February 5, 1973*

Abstract: 2-Quinuclidiniotropone iodide with secondary amines in aqueous buffered solutions gives *m*-hydroxybenzaldehyde (–CHO originating from C(6)) and a small quantity of 2-piperidinotropone (C(7) substitution). With primary amines at high amine/cycloheptatrienone ratios substitution (at C(7)) predominates. With aqueous dilute alkali, benzoic acid is the only product, whereas with 6 *M* alkali a mixture of benzoic acid and salicylaldehyde (–COOH and –CHO deriving from C(1) and C(3), respectively) is obtained. With 2-chlorotropone and primary amines C(2) substitution predominates whereas with aqueous alkali the product distribution changes from a 40% salicylaldehyde (–CHO deriving from C(3))–60% benzoic acid mixture to solely benzoic acid to, finally, a 60% benzoic acid–40% tropolone mixture with increasing alkali concentration. All these observations are rationalized in terms of reversibly interconnected pathways and utilized in a simple synthesis of tropolone ethers.

Base-induced ring contractions of cycloheptatrienones carrying α substituents which are stable as anions (**1**) have long aroused considerable interest as a



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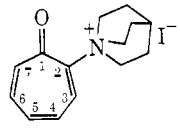

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method of locating, through resulting arenes of known structures, substituents on the cycloheptatrienone nucleus.[5] Most commonly, alkali hydroxides or alkoxides have been used as bases to give benzoic acid or esters, the exocyclic carbon being formed at the expense of C(1).[6,7]

Other competing base-induced rearrangements, initiated by conjugate attack, have also been found. Thus, it has been reported that while 2-chloro-, 2-bromo-, or 2-iodotropone give benzoic acid in quantitative yield on treatment with 20% aqueous sodium hydroxide, salicylaldehyde is formed, by extrusion of C(3), in more dilute alkali.[8]

Two basic questions, related to these problems, originated from recent studies on compound **2**. Thus, which set of factors determines rearrangements to compete favorably with substitutions and which one leads to the specific extrusion of a certain carbon atom, rather than another, in the course of the ring-contraction reactions? In fact, it was observed that, while in very dilute aqueous sodium hydroxide **2** gives only benzoic acid, in aqueous piperidine, at the same pH value, the major product is *m*-hydroxybenzaldehyde, accompanied by little 2-piperidinotropone.[9] Moreover, in dimethyl sulfoxide **2** reacts with piperidine to give **2**-piperidinetropone in quantitative yield by piperidine attack at C(7).[10] This work answers in a general way these two questions.

Results and Discussion

Identification of the Reaction Products. Product distribution for the reactions of 2-(1-azoniabicyclo[2.2.2]oct-1-yl)cyclohepta-2,4,6-trien-1-one iodide (**6a**, Y = quinuclidinio), 2-chlorotropone (**6a**, Y = Cl), or their 3,5,7-trideuterio analogs **6b** (Y = quinuclidinio or Cl) with ammonia, amines, sodium hydroxide, or potassium methoxide are listed in Table I. Pathways to either substitution products (**3** and **5**) or products of rearrangement to arenes (**4**, **12**, and **13**) are shown in Scheme I and will be subsequently discussed.

Labeling **6b** at the cycloheptatrienone nucleus with deuterium allows determining either the site of substitution (C(7), to give **3b**-type products, or C(2), to give **5b**-type products) or the carbon emerging from the ring (C(1) to give benzoic acid or benzamides (**4**), C(6) to give *m*-hydroxybenzaldehyde (**12**), or, finally, C(3) to give salicylaldehyde (**13**)).

Product identification and structural elucidation need some comment. Most of the products (**3** and **5**) are either commercial (tropolone) or were available from previous works (2-piperidino[3,5,7-$^2H_3$]tropone,[11] 2-(α-methylpiperidino)tropone,[1b], 2-diethylaminotropone,[1b] 2-*n*-butylamino[3,5,7-$^2H_3$]tropone,[1b] 2-amino-[3,5,7-$^2H_3$]tropone,[1b] and 2-methoxy[3,5,7-$^2H_3$]tropone[11]). The only new cases are 2-methylamino[3,5,7-$^2H_3$]tropone (**5b**, N = methylamino) and 2-methyl-

(1) (a) "The Reactivity of Pseudoaromatic Compounds. XI." (b) Part X: G. Biggi, F. Del Cima, and F. Pietra, *J. Amer. Chem. Soc.*, **95**, 7101 (1973). (c) Work in Pisa has been supported by Consiglio Nazionale delle Ricerche, Roma. We thank Mr. C. Erkelens, Leiden, for running the 100-MHz nmr spectra and for doing ^2H-decoupling experiments and the N.O.Z.W.O. for the possibility of running the 220-MHz nmr spectra.

(2) (a) Department of Chemistry, Pisa; (b) Laboratories for Organic Chemistry, Leiden.

(3) Postdoctoral Fellow.

(4) Undergraduate.

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Table I. Reactions of 2-Y-Cycloheptatrienones (3,5,7-Trideuterated (**6b**) when not otherwise stated) with Various Reactants (N) in Various Solvents at Room Temperature[a]

Y[b]	N[b]	Solvent	Product distribution, %[c] 3b	4b	5b	12b	13b
$^+NR_3$	Piperidine	DMSO[d]	100				
$^+NR_3$ (2×10^{-3} *M*)	Piperidine (2×10^{-2} *M*)	H_2O[e]	6			82	
$^+NR_3$ (5×10^{-5} *M*)	Piperidine (2×10^{-2} *M*)	H_2O[e]				85	
$^+NR_3$	[1-^{2}H]Piperidine	D_2O	6	40[f]		40[g]	
$^+NR_3$	2-Methylpiperidine	DMSO[h]	90				
$^+NR_3$[i]	2-Methylpiperidine	H_2O[e]				56[j]	
$^+NR_3$	Et_2NH	DMSO[h]	85				
$^+NR_3$[i]	Et_2NH	H_2O[e]				60[j]	
$^+NR_3$	*n*-$BuNH_2$	DMSO[h]	99				
$^+NR_3$ (5×10^{-3} *M*)	*n*-$BuNH_2$ (6×10^{-2} *M*)	H_2O[e]	52	35		8	
$^+NR_3$ (5×10^{-5} *M*)	*n*-$BuNH_2$ (3×10^{-2} *M*)	H_2O[e]	85				
$^+NR_3$	$MeNH_2$	H_2O[e]	42	40		10	
$^+NR_3$	NH_3	H_2O[e]	75	25			
$^+NR_3$[i]	Quinuclidine or Me_3N	H_2O[e]		High			
$^+NR_3$	KOMe (0.7 *M*)	10:1 DMSO–MeOH	55		45		
$^+NR_3$[i]	NaOH (3×10^{-3} *M*)	H_2O		92[j]			
$^+NR_3$	NaOH (5.8 *M*)	H_2O		70			25
Cl[k]	NaOH (1 *M*)	H_2O		50			40
Cl[i,k,l]	NaOH (6.2 *M*)	H_2O		100			
Cl[i]	NaOH (10 *M*)	H_2O		50	40[j]		
Cl	KOMe (0.4 *M*)	5:1 DMSO–MeOH			85		
Cl[i]	KOMe (0.4 *M*)	MeOH			83[j,m]		
Cl	$MeNH_2$	H_2O			82		

[a] All reactions reported here, except those with very dilute ammonia or sodium hydroxide, which require 1–2 hr to go to completion, are complete in a few minutes. [b] $^+NR_3$ = quinuclidinium; reagent concentrations are indicated only when their change may strongly affect product distributions. [c] Yields are based on starting **6** and, when available, refer to spectroscopically or chromatographically determined yields. [d] From ref 10. [e] Buffered with amine hydrochloride. [f] N = OD. [g] Further deuterated at C(4). [h] From ref 1b. [i] Nonlabeled with deuterium (**6a**). [j] X = H. [k] Carried out under heterogeneous conditions of suspended chlorotropone. [l] From ref 8. [m] As a mixture constituted of 85% 2-methoxytropone and 10% tropolone.

amino[4,6-$^2H_2$]tropone (**3b**, N = methylamino). Structural assignment of these compounds is unequivocal on the basis of uv and ^{1}H-nmr spectral data (Experimental Section) following the line of a previous discussion[1b] for corresponding pairs of compounds made with different amines.

The structural assignment of [2,4,6-$^2H_3$]benzoic acid (**4b**, N = OH) is supported by both the mass spectrum (Experimental Section) which clearly shows the presence of three nuclear deuteriums and the ^{1}H-nmr spectrum which shows a singlet at δ 7.53 ppm, which sharpens on deuterium decoupling, as expected for the two meta hydrogens. Indeed, **4b** was the expected product.[6]

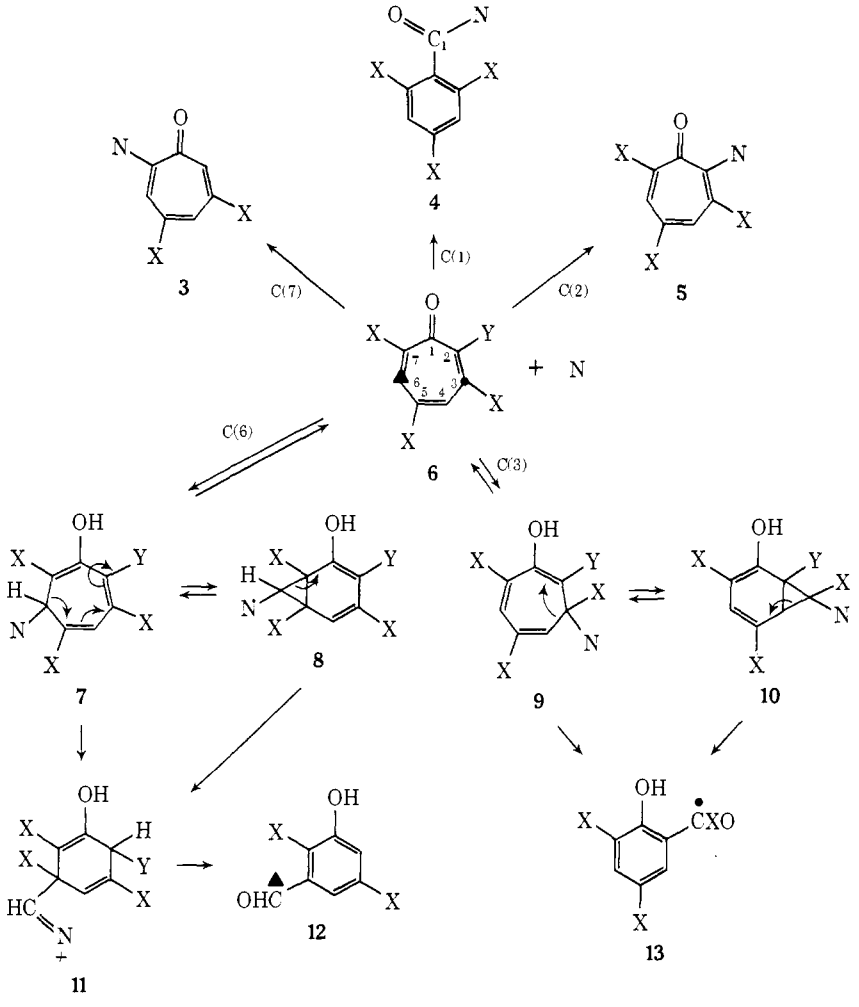
Structural assignment of 2-hydroxy[3,5-$^2H_2$]-α-deuteriobenzaldehyde (**13b**) is supported by ^{1}H-nmr spectral data. In fact, the multiplet at δ 7.46 ppm (see Experimental Section) on deuterium decoupling becomes a nice AB quartet, with J_{AB} = 1.6 Hz and $\Delta\delta_{AB}$ = 2.63 Hz, corresponding to two meta protons. Moreover, the chemical shift value, 7.46 ppm, is that expected[12] for the protons at C(5) and C(6) of a 2-hydroxybenzaldehyde. The only other route to an α-deuterated salicylaldehyde having two meta deuteriums would have required the expulsion of C(7) from **6b** (Y = quinuclidinio) to give 2-hydroxy[4,6-$^2H_2$]-α-deuteriobenzaldehyde. This structure can be ruled out because a multiplet centered at δ 7.0 ppm is expected for the C(3) and C(5) protons,[12] contrary to what has been found. We have also run the 100-MHz ^{1}H-nmr spectrum of salicylaldehyde in CCl_4 which confirms the presence of two multiplets centered at 7.45 and 6.94 ppm for the aromatic protons.

(12) W. Brügel, "Nuclear Magnetic Resonance Spectra and Chemical Structure," Vol. I, Academic Press, New York, N. Y., 1967, p 17.

Also the structural assignment of 3-hydroxy[2,5-$^2H_2$]benzaldehyde (**12b**) is based on ^{1}H-nmr spectra. The 100-MHz spectrum (Experimental Section) shows that a proton-bearing troponoidal carbon emerged from **6b** (Y = quinuclidinio) and that the *m*-hydroxybenzaldehyde nucleus is bideuterated. This is consistent with formation of the aldehyde carbon from either C(6) or C(4) of **6**. Therefore, the problem is reduced to that of distinguishing between **12b** (from attack at C(6)) and 3-hydroxy[4,6-$^2H_2$]-benzaldehyde (**14**) (from attack at C(4)). On deuterium decoupling both signals at δ 7.42 and 7.17 ppm become doublets with J = 1 Hz. This value is consistent with either meta coupling (**12b**) or para coupling (**14**) of the two nuclear protons.

The problem was unequivocally solved by a combination of the 100-MHz ^{1}H-nmr spectrum of the aldehydic product of the **6b** (Y = quinuclidinio) reaction with *N*-deuteriopiperidine in heavy water and the 220-MHz ^{1}H-nmr spectrum of 3-hydroxybenzaldehyde itself. The latter, in $(CD_3)_2CO$, revealed three multiplets centered at δ 7.16, 7.36, and 7.40 ppm which integrate for one, one, and two aromatic protons, respectively. The multiplet at 7.36 is by far the narrowest, having a total line width of 6 Hz only, which clearly allows it to be assigned to the proton at C(2) in the aldehyde. This rules out structure **14** but is consistent with structure **12b**. Moreover, the observation that, on carrying out the reaction in heavy water, the multiplet at 7.16 ppm disappears, clearly rules out structure **14** (expulsion of C(4) would have lead to deuterium incorporation at C(2), which coincides with the carbon vacated by Y in **6**) but is consistent with structure **12b** (expulsion of C(6) leads to deuterium incorporation at C(4) (Scheme I)). Computer calculations are consis-

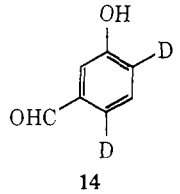
Scheme I



a, X = H

b, X = D

the nature of Y and N is specified in Table I



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tent with the protons ortho to the phenolic hydroxyl being shifted to higher field.

Reaction Pathways. It will become apparent that the causes for the occurrence of either substitution (to give **3** or **5**, Scheme I) or rearrangement (to give **4**, **12**, or **13**, Scheme I) can only be understood when it is realized that all these processes are intimately interconnected so that any change of either the nature of the carbonyl or the nucleophilic reactants, or their concentrations, as well as of the reaction medium, will reflect itself on the whole pattern shown in Scheme I. To this regard it must be noticed that also attacks at C(1)[6] or C(7)[1b] involve an initial reversible step so that single arrows in Scheme I refer to the overall process.

With this in mind let us begin to examine the process leading to *m*-hydroxybenzaldehyde (**12**), where C(6) emerges from **6**. This is the main reaction course taken when Y is a quaternary nitrogen, N a secondary amine, and the medium is water buffered with amine hydrochloride. Monitoring of the reaction of piperidine with deuterated cycloheptatrienone (**5b**) by uv absorption spectroscopy revealed that, immediately after the mixing of the reagents into a spectrophotometric cuvet to give a mixture of piperidine (0.7 *M*), piperidine hydrochloride (0.2 *M*), and **6b** (5×10^{-5} *M*), the absorption band of **6b** at 303 nm cannot be detected any more, while a new absorption band at 345 nm appears. The latter band changes completely, within 2 min, into that attributable to a mixture constituted mainly of **12b** and a little **3b** (N = piperidino). At lower (0.02 *M*) piperidine concentration the rate of disappearance of **6b** (by the 303-nm band) is the same as that of appearance of **12b** and **3** (N = piperidino). Thus, the situation immediately upon mixing of the reagents appears the same as that found for the same reaction in DMSO. In the latter case, however, the end product is exclusively **3b** (N = piperidino) and, moreover, the intermediate absorption at 345 nm is well detectable down to piperidine concentrations as low as 0.01 *M*. That association constants are lower in water than in DMSO is in line with our suggestion that we are dealing with the formation of intermediate σ-anionic complexes in these reactions.[10]

It is important to realize that we by no means imply that structure **7** (N = piperidino) should be attributed to the above observed intermediate. It seems reasonable to assume that, like in DMSO,[10] formation of **7** is too fast to be detected without the use of stopped-flow techniques, the above absorption band at 345 nm being rather attributable chiefly to the intermediate of piperidine attack at C(7) mixed with **7** in that amount which is allowed by the values of the equilibrium constants. Because it was found that the slow step in the formation of **3b** (N = piperidino) is the 1,3-elimination of HY from the C(2)-protonated intermediate, while protonation at C(2) occurs in a fast step,[10] driving of **7** toward **12** in water must be attributed to the higher protonating ability of the latter medium with respect to DMSO. In fact, in water higher percentages of **3** were obtained at higher piperidine concentrations, the base intervening in the slow 1,3-elimination step. By **8** or **10** (Scheme I) it is simply meant that norcaradiene species may be on the pathway, possibly as transition states, to products.

This picture accounts also for the prevalent formation of type-**3** products, even in water, from primary amines. Uv monitoring of the reaction of **6b** (Y = quinuclidinio) (5×10^{-5} *M*) with methylamine (0.16 *M*) and methylamine hydrochloride (0.04 *M*) in water revealed a transient absorption band at *ca.* 330 nm which disappeared completely within 4 min to give mainly **3b** (N = methylamino) (Table I). The same was observed with *n*-butylamine in the place of methylamine. It must be admitted that here **7** is not effectively driven toward **12** because of the lessened stabilization of the positive iminium salt nitrogen by a single alkyl group, compared to two alkyl groups with secondary amines.[13]

It must be noticed that in the above reactions with primary amines the detailed product composition depends on the amine/cycloheptatrienone ratio used. At high ratios (500) substitution predominates, while at lower ratios (10) much benzoic acid is also formed (Table I). Such behavior is attributable to less extensive formation of amine–cycloheptatrienone complexes, which in turn facilitates attack by hydroxide ion at C(1). Thus, the alkali has more chances to lead to the expulsion of C(1).

Formation of salicylaldehyde (**13**) now deserves consideration. Salicylaldehyde accompanies benzoic acid (where –CHO and –COOH derive from C(3) and C(1), respectively) when **6** (Y = quinuclidinio) is treated with concentrated aqueous alkali (Table I). With dilute alkali only benzoic acid was obtained. Such a dependence of the product distribution on the alkali concentration runs in the opposite direction to that found by Forbes, *et al.*,[8] for the reaction of 2-chlorotropone (**6a**, Y = Cl) with alkali, although even here (Table I, and Forbes, *et al.*[8]) C(3) is the carbon which emerges from the ring. Clearly, different mechanisms must be involved in the two cases.

Forbes, *et al.*,[8] rationalized the case of 2-chlorotropone in terms of a mechanism requiring C(2) protonation (this being the more disfavored the more concentrated the alkali is) in the route to salicylaldehyde but no protonation whatsoever in the route to benzoic acid. In our case C(2) protonation is not demanded even in the route to salicylaldehyde so that the mechanism in Scheme I may be proposed. Clearly, when Y = quinuclidinio the system benefits of a special driving force. This is the great activation (much greater than by chlorine) by the quaternary nitrogen which leads to loss of **6** by conjugate attacks of OH^- at sufficiently high concentration of OH^-.[1] This clarifies also why with protic amines in aqueous nonbuffered solutions substantial amounts of benzoic acid were observed (Table I).

With the above discussion we do not intend to imply that with OH^- attack at C(3) is faster than attack at C(6) on **6** (Y = quinuclidinio). Rather, the reverse is likely to be true, as in the case of piperidine as the nucleophilic reactant. However, in the case of N = OH^-, intermediate **7** cannot proceed further because of the scarce protonating ability of the strongly alkaline medium used. This raises the interesting question of why C(6) is so strongly activated toward nucleophilic attack. We think it is so because C(6) is most favorably situated with respect to the two activating groups. In fact, C(6) is suitably placed for a most favorable 1,4-conjugate attack, while feeling electron attraction by the quaternary nitrogen along the other side of the ring. Clearly, this favorable situation is not shared by C(3), the two activating groups mutually disturbing each other to some extent in their influence on C(3).

However, this cannot be the whole story, and a secondary interaction mechanism may play a non-negligible role. Thus, with bulky amines it is likely that attack at C(6) is strongly preferred over attack at C(3) owing to steric repulsions at the latter site. With OH^- preference for attack at C(6) may be lessened somewhat because of electrostatic attraction between unlike charges and smaller steric repulsions for attack at C(3).

More interesting is that, according to predictions from the mechanisms in Scheme I, we observed that on raising the alkali concentration above the highest value (6.2 *M*) used by previous investigators,[8] substantial amounts of tropolone are generated at the expense of benzoic acid (Table I). The significance of this finding is, in our view, that on the raising of the alkali concentration the rate of C(1) extrusion reaches a limit due to either the rate-limiting opening of the cyclopropane ring of the intermediate norcaradiene species,[6] if this is really involved, or the rate-limiting expulsion of C(1) from its monocyclic seven-membered cycloheptatriene-like precursor,[6] thus substitution at C(2), for which no limiting factor is recognizable, has the chance to come into play.

This is quite an interesting observation because it suggests the possibility of a general synthesis of tropolone ethers by simple displacements of chlorine from easily accessible 2-chlorotropones and alkoxides, rather than along longer, indirect, routes which have limited generality.[14] Our hopes were substantiated for the case of 2-methoxytropone which was also obtained from 2-quinuclidiniotropone (Table I) (the occur-

(13) It is important to notice that, to save space, the present scheme is incomplete, not showing that attacks (reversible) of the nucleophilic reactant (N) at C(7),[10] and probably also at C(1),[6] involve accumulation of intermediates, at least with strongly activated **6**. In contrast, all available evidence[11] indicates that no accumulation of intermediates occurs along the pathway to **5** with these reagents. Therefore, of all reaction pathways in Scheme I, the last one is unique in being unable to provide intermediate species which can be diverted toward other directions.

(14) T. Nozoe, "Non-Benzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience, New York, N. Y., 1959.

rence of competing C(7) pathway here must be attributed to the availability of a protonating agent, methanol, in the medium). Preference for substitution over rearrangement to benzoic acid with potassium methoxide is probably a consequence of the stronger nucleophilicity of this reagent with respect to OH^-.[15] In fact, as the slow step for C(1) expulsion from **6** (see above) must be substantially independent of the nucleophilicity of the attacking reagent, a stronger nucleophile has more chances at its disposal than a weaker one to compete for substitution.

A further important point warrants notice. It is known that both 2-dialkylaminotropones and 2-methoxytropone resist alkaline rearrangement to arenes, being rather hydrolyzed to tropolone in alkali.[14] In light of the present discussion this must be attributed to lack of activation of the cycloheptatrienone nucleus (and thus, we emphasize, of C(1)) of these compounds toward nucleophilic attack. Thus, although sluggishly, the only position leading to a chemical reaction in these systems is that bearing a displaceable substituent. This is intimately related to the behavior of the same cycloheptatrienones as far as the problem[1b] of the competition for substitution at C(2) *vs.* C(7) is concerned.

Finally, it must be warned that, as will be detailed elsewhere,[16] with carbanionic species as nucleophilic reactants, the mechanisms of the present scheme should prove to be basically inadequate because of the expected irreversibility of the attacks on **6** by such species.

Experimental Section

Nmr spectra were recorded on Varian S 60T, Hitachi-Perkin-Elmer R10, and Jeol SP100 (equipped for ^{2}H-decoupling) spectrometers with TMS as internal standard. Uv spectra were recorded with a Unicam SP800 spectrophotometer. Melting points were measured with a Kofler hot-stage apparatus without correction. Dimethyl sulfoxide and methanol were distilled from calcium hydride or molecular sieves, respectively, under N_2. Deionized water was used. Potassium methoxide was prepared by adding potassium metal to dried methanol under N_2. Reactions with moisture exclusion were always carried out under N_2. All reactions were carried out at room temperature and product yields are based on starting **6**.

Reactions of Piperidine in Water. (a) With 2-(1-Azoniabicyclo[2.2.2]oct-yl)cyclohepta-2,4,6-trien-1-one Iodide[17] (6a, Y = quinuclidinio). An aqueous solution of piperidine (0.04 *M*, 0.1 mmol) and piperidine hydrochloride (0.02 *M*) (25 ml) was added to the equal volume of an aqueous solution of **6a** (Y = quinuclidinio) (0.004 *M*, 0.01 mmol). After *ca.* 12 min, as uv monitoring indicated that the reaction was practically complete, further piperidine was added and the mixture was benzene extracted. The benzene layer contained 2-piperidinotropone (**3a**)[13] (*ca.* 10% yield, as checked by tlc and measured by uv spectra). Large excess of piperidine is necessary to prevent the aldehyde going into the organic phase. The aqueous layer was neutralized and then extracted with methylene chloride. This was dried over magnesium sulfate and then evaporated under vacuum to leave a crystalline mass which was recrystallized from CCl_4 giving 0.01 g (82%) of *m*-hydroxybenzaldehyde (**12a**), mp 105–106° (lit.[18] mp 108°), 2,4-dinitrophenylhydrazone mp 259–260° (lit.[18] mp 259°). At lower concentration of **6a** (5×10^{-5} *M*) uv spectra showed *m*-hydroxybenzaldehyde (λ_{max}(0.05 *M* aqueous NaOH) 237, 267, and 357 nm (log ϵ 4.38, 3.79, and 3.41)) in *ca.* 85% yield and no product of substitution.

(b) With 2-(1-Azoniabicyclo[2.2.2]oct-1-yl)[3,5,7-$^2H_3$]cyclohepta-2,4,6-trien-1-one Iodide[17] (6b, Y = quinuclidinio). The reaction was carried out under the conditions described above for **6a** with a fourfold increase of the amount of materials. The benzene layer was dried over magnesium sulfate and then evaporated under vacuum to leave an oil which was sublimed and identified by ^{1}H-nmr spectroscopy as 2-piperidino[4,6-$^2H_2$]cyclohepta-2,4,6-trien-1-one (**3b**)[10] (6%). The methylene chloride extracts gave crystals, mp 103–104°, undepressed with *m*-hydroxybenzaldehyde, of 3-hydroxy-[2,5-$^2H_2$]benzaldehyde (**12b**) in 82% yield; δ (Jeol, $(CD_3)_2CO$) 9.95 (1 H, s), 9 very broad (1 H), 7.42 (1 H, multiplet), 7.16 ppm (1 H, multiplet); in addition a very small broad singlet was detected at 7.53 ppm which can be attributed to a trace of [2,4,6-$^2H_3$]benzoic acid (**4b**, N = OH) (see below).

Reaction of [1-^{2}H]Piperidine[19] with 2-(1-Azoniabicyclo[2.2.2]oct-1-yl)[3,5,7-$^2H_3$]cyclohepta-2,4,6-trien-1-one Iodide[17] (6b, Y = quinuclidinio) in Heavy Water. The reaction was carried out in a D_2O solution (25 ml) of **6b** (Y = quinuclidinio) (0.006 *M*) and amine (0.02 *M*) without the addition of the amine hydrochloride. The benzene extracts gave **3b**. The crystalline residue (0.015 g) from the methylene chloride extracts showed three nmr broad singlets at δ [Jeol, $(CD_3)_2CO$] 9.92, 7.53, and 7.42 ppm which integrated relatively as 1:2:1, respectively. This is consistent with a mixture (see text) of 3-hydroxy[2,4,5-$^2H_3$]benzaldehyde (**12b**, further deuterated at C(4); see text for ^{1}H-nmr data) in 40% yield and [2,4,6-$^2H_3$]benzoic acid (40% yield), identified by ^{1}H-nmr spectroscopy.

Reactions of Methylamine in Water. (a) With 2-(1-Azoniabicyclo[2.2.2]oct-1-yl)[3,5,7-$^2H_3$]cyclohepta-2,4,6-trien-1-one Iodide[17] (6b, Y = quinuclidinio). To 8 ml of a water solution of **6b** (Y = quinuclidinio) (0.11 g, 0.3 mmol) was added 3 ml of a water solution of methylamine (1.0 *M*, 3.0 mmol) and methylamine hydrochloride (0.5 *M*). After 4 hr the uv spectrum of the mixture was attributable to 2-methylaminotropone in 42% yield. Then the mixture was ether extracted; the ethereal layer was dried and then evaporated. The residue was chromatographed on a 1.5-mm thick silica gel layer, activated at 110°, with eluent 7:2:1 benzene–*n*-hexane–95% ethanol. The yellow band at R_f 0.65 was ether extracted. The ether was evaporated and the residue sublimed *in vacuo* to give 2-methylamino[4,6-$^2H_2$]tropone, mp 82–84° (2-methylaminotropone, mp 79–80°[20]), in 30% yield: δ (Varian, CCl_4) 7.3 br (1 H, which can be exchanged with D_2O), 7.0 (1 H, s), 6.6 (1 H, s), 6.4 (1 H, s), 3.1 ppm (3 H, d, J = 2.5 Hz). The aqueous layer, worked up as above (b), contained (nmr) 3-hydroxy[2,5-$^2H_2$]-benzaldehyde (**12b**) (10%) and [2,4,6-$^2H_3$]benzoic acid (see below) (**4b**, N = OH) (40%).

(b) With 2-Chloro[3,5,7-$^2H_3$]tropone[11] (6b, Y = Cl). A solution of **6b** (Y = Cl) (0.12 g, 0.85 mmol) in 0.5 ml of methanol was added to 6 ml of an aqueous solution of methylamine (0.7 *M*, 4.2 mmol) and methylamine hydrochloride (0.16 *M*). The uv spectrum of the reaction mixture after 1 hr was that expected for formation of 2-methylaminitropone[20] in 82% yield. The mixture was then worked up as above in (a) to give 2-methylamino[3,5,7-$^2H_3$]tropone, mp 83–84°, in 40% yield: δ (Varian, CCl_4) 7.6 br (1 H, which can be exchanged with D_2O), 7.1 (2 H, br s), 3.1 ppm (3 H, d, J = 2.5 Hz); λ_{max} (95% ethanol) 337 and 405 nm (log ϵ 4.15 and 4.08). The aqueous layer was not worked up.

Reaction of *n*-Butylamine with 2-(1-Azoniabicyclo[2.2.2]oct-1-yl)-[3,5,7-$^2H_3$]cyclohepta-2,4,6-trien-1-one Iodide[17] (6b, Y = quinuclidinio) in Water. The reaction was carried out (and the mixture worked up as above (a) for the corresponding reaction of methylamine) with amine (6×10^{-2} *M*), amine hydrochloride (10^{-3} *M*), and **6b** (5×10^{-3} *M*). The spectroscopic (uv) yield of 2-*n*-butylaminotropone[1b] was 52%, that of *m*-hydroxybenzaldehyde *ca.* 8% and that of benzoic acid *ca.* 35%. 2-*n*-Butylamine[4,6-$^2H_2$]tropone[1b] (**3b**, N = *n*-butylamino) was isolated in 30% yield. The ^{1}H-nmr spectrum[1b] showed that it was not contamined by the product of substitution at C(2). At lower concentration of **6b** (5×10^{-5} *M*), under otherwise identical conditions, the yield of substitution product was 85%.

Reaction of Ammonia with 2-(1-Azoniabicyclo[2.2.2]oct-1-yl)-[3,5,7-$^2H_3$]cyclohepta-2,4,6-trien-1-one Iodide[17] (6b, Y = quinuclidinio) in Water. Aqueous 17 *M* ammonia (0.2 ml, 3.4 mmol) was

(15) Route C(6) (Scheme I) is precluded to an alkoxide for the same reasons adduced for OH^-. Route C(3) is also precluded to an alkoxide because of the lack of a removable proton at the C(3)-bound oxygen in **9** (or **10**).

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added to 8 ml of an aqueous solution of **6b** (Y = quinuclidinio) (0.11 g, 0.33 mmol) and ammonium chloride (0.25 g). After 4 hr the spectroscopic yield of 2-aminotropone[1b] was 75%. The mixture was thoroughly ether extracted, the ethereal layer dried and evaporated, and the residue distilled on a cold finger in a sublimation apparatus *in vacuo*. The ^{1}H-nmr spectrum of the distillate was analogous to that obtained from the reaction of ammonia with 2-chloro[3,5,7-$^2H_3$]tropone[1b] within 70 and 25% yields, respectively.

Reactions of 2-(1-Azoniabicyclo[2.2.2]oct-1-yl)cyclohepta-2,4,6-trien-1-one Iodide[17] (6a, Y = quinuclidinio) in Water. (a) With 2-Methylpiperidine. A 10^{-3} *M* aqueous solution of **6a** (Y = quinuclidinio) (0.3 ml) was added to 3 ml of a water solution of 0.3 *M* 2-methylpiperidine and 0.1 *M* 2-methylpiperidine hydrochloride. Monitoring by uv revealed the formation of *m*-hydroxybenzaldehyde in 56% yield and no 2-methylpiperidinotropone.[1b] The reaction is appreciably slower than the corresponding reaction of piperidine under similar conditions.

(b) With Diethylamine. The reaction was carried out and monitored as above in (a) with similar results. 60% of *m*-hydroxybenzaldehyde and no 2-diethylaminotropone[1b] were, in fact, obtained.

(c) With Quinuclidine or Trimethylamine. The reaction was carried out with the amine and its hydrochloride under the conditions described above in (a) for 2-methylpiperidine. The uv absorption of **6a** (Y = quinuclidinio)[17] disappeared within 0.5 hr while no other absorption was detectable in the spectral region from 270 to 500 nm. The reaction was then repeated with larger reagent amounts and carried out to completion. The mixture was then acidified and thoroughly extracted with methylene chloride. The organic layer was evaporated and the residue analyzed by tlc (silica gel; eluent 9:1 benzene–95% ethanol). Benzoic acid, R_f 0.35, was detected in nearly quantitative yield.

Reactions of Aqueous Sodium Hydroxide. (a) With 2-(1-Azoniabicyclo[2.2.2]oct-1-yl)[3,5,7-$^2H_3$]cyclohepta-2,4,6-trien-1-one Iodide[17] (6b, Y = quinuclidinio). To 0.37 g (1.1 mmol) of **6b** (Y = quinuclidinio), dissolved in water (15 ml), was added with stirring 50 ml of 7.5 *M* aqueous sodium hydroxide. After a few minutes the uv spectra indicated that the reaction was practically complete. Ethyl ether failed to extract any material from the reaction mixture which was then neutralized with concentrated hydrogen chloride. This mixture was extracted with methylene chloride. The organic layer was dried over magnesium sulfate and then most of the solvent was distilled off with a 10-cm column packed with glass Fenske helices. The residue was chromatographed on a 15-cm length silica gel column (internal diameter 8 mm), eluent CCl_4, to give 0.037 g (25%) of 2-hydroxy[3,5-$^2H_2$]-α-deuteriobenzaldehyde (**13b**): δ (Jeol, CCl_4) 10.92 (1 H, s), 7.46 ppm (2 H, multiplet); λ_{max} (0.1 *M* aqueous NaOH) 265, 376 nm (low ε 3.92, 3.79). Change of the solvent to 9:1 *n*-hexane–ether eluted 0.1 g (70%) of [2,4,6-$^2H_3$]-benzoic acid (**4b**, N = OH), ^{1}H-nmr spectrum as below in (c).

(b) With 2-(1-Azoniabicyclo[2.2.2]oct-1-yl)cyclohepta-2,4,6-trien-1-one Iodide[17] (6a, Y = quinuclidinio). To 100 ml of a 2×10^{-3} *M* aqueous solution of **6a** (Y = quinuclidinio) was added, dropwise with stirring, 3 ml of 0.1 *M* aqueous sodium hydroxide. After 1 hr the uv spectrum showed that all the starting cycloheptatrienone disappeared while no absorption was detectable in the region of hydroxybenzaldehydes. The reaction mixture was concentrated, and then extracted with methylene chloride. The organic layer was dried and evaporated, the residue was dissolved in methanol, and ethereal diazomethane was added. Methyl benzoate was determined by glpc (92%).

(c) With 2-Chloro[3,5,7-$^2H_3$]tropone (6b, Y = Cl). The reaction was carried out with 1 *M* aqueous sodium hydroxide under the conditions (*i.e.*, with a heterogeneous mixture of suspended **6b**) used for 2-chlorotropone.[8] [2,4,6-$^2H_3$]Benzoic acid (**4b**, N = OH) [50% yield: mp (from C_6H_6) 120–121°; M^+ 125 (67); M^- − 17 (78), M^+ − 45 (100); δ (Jeol, $(CD_3)_2CO$) 7.53 ppm (2 H, s); (Jeol, CH_2Cl_2) 11.1 br (1 H), and 7.5 ppm (2 H, s)]; 2-hydroxy[3,5-$^2H_2$]deuteriobenzaldehyde (**13b**) [40% yield, nmr data as above in (a)].

(d) With 2-Chlorotropone. A 1 *M* methanolic solution of 2-chlorotropone (0.5 ml) was added to 10 ml of an aqueous 10 *M* sodium hydroxide solution. The mixture became immediately yellow and the uv spectrum matched exactly that of a solution of sodium tropolonate (40% yield). The mixture was acidified and thoroughly extracted with methylene chloride. The organic layer was dried and evaporated. The ir spectrum of the residue revealed, by comparison with those of those of mixtures prepared with authentic materials, benzoic acid and tropolone in 50 and 40% yields, respectively.

Reactions of Potassium Methoxide. (a) With 2-Chloro[3,5,7-$^2H_3$]tropone[11] (6b, Y = Cl). A 5.0 *M* solution (0.5 ml) of potassium methoxide in dried methanol was added, under N_2, to a solution of **6b** (Y = Cl) (0.10 g, 0.55 mmol) in dried DMSO (2.5 ml). After a few minutes the reaction mixture was rendered slightly alkaline with aqueous hydrogen chloride. Uv absorption spectra of this mixture revealed the presence of both tropolonate anion (10%) and 2-methoxytropone.[21] The mixture was ether extracted during 24 hr. The ether layer was dried and evaporated and the residue was chromatographed on a silica gel plate, eluent 9:1 benzene–ethanol. The material from the R_f 0.4 band (uv detection) was ether extracted, the solvent evaporated, and the residue distilled on a cold finger *in vacuo* (yield 85%): δ (Varian, $CDCl_3$) 7.22 (1 H, s), 7.06 (1 H, s), 3.92 (3 H, s), 1.4 ppm (H_2O). These data are consistent with 2-methoxy[3,5,7-$^2H_3$]tropone.[11] 2-Methoxytropone was also obtained in high yield (Table I) from 2-chlorotropone and potassium methoxide in methanol.

(b) With 2-(1-Azoniabicyclo[2.2.2]oct-1-yl)[3,5,7-$^2H_3$]cyclohepta-2,4,6-trien-1-one Iodide (6b, Y = quinuclidinio). A 7 *M* dried methanolic solution of sodium methoxide (0.2 ml, 1.4 mmol) was added to **6b** (Y = quinuclidinio) (0.12 g, 0.35 mmol) dissolved in 2 ml of dried DMSO. Work-up as above in (a) gave an oil whose ^{1}H-nmr spectrum (Jeol, CCl_4) shows five broad singlets at δ 7.1, 7.0, 6.9, and 6.7 ppm and singlets at δ 3.8 and 2.9 ppm. On deuterium decoupling the four signals at low field sharpen and, neglecting the 2.9-ppm signal which is due to water,[11] integration gives 0.45, 0.55, 0.45, 0.55, and 0.55, and three protons for the 7.1, 7.0, 6.9, 6.7, and 3.8 ppm signals. These are consistent with a mixture of 45% 2-methoxy[3,5,7-$^3H_2$]tropone[11] and 55% 2-methoxy[4,6-$^2H_2$]tropone.

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