Nucleophilic Catalysis with Rearrangement. The Reactivity of Pseudo-aromatic Compounds. Part VII.[1] The 1-Azabicyclo[2,2,2]octane-catalysed Reaction of 2-Iodocyclohepta-2,4,6-trien-1-one with Piperidine †

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The reactions of either 2-chloro- or 2-iodo-cyclohepta-2,4,6-trien-1-one with piperidine give, in a variety of media, including benzene, 2-piperidinocyclohepta-2,4,6-trien-1-one in quantitative yield, no rearrangement being involved. An added tertiary amine, such as 1-azabicyclo[2,2,2]octane (quinuclidine), catalyses the reaction of the chloro-compound in benzene only to a negligible extent, while the reaction of the iodo-compound is appreciably catalysed. It can be excluded that this reflects base catalysis by quinuclidine since the same reactions are not catalysed by other bases such as piperidine or 2,4-dinitrophenolate (whereas they undergo efficient acid catalysis by compounds such as phenol). Rather, quinuclidine catalysis can be accounted for in terms of two consecutive nucleophilic displacements at the troponoid carbon atom which we have encountered in previous studies. The first, displacement of iodine by quinuclidine from 2-iodo-cyclohepta-2,4,6-trien-1-one to give the reactive intermediate 2-(1-azoniabicyclo[2,2,2]oct-1-yl)cyclohepta-2,4,6-trien-1-one iodide, is a substitution at the carbon occupied by iodine. The second, of quinuclidine by piperidine from the reactive intermediate, is a nucleophilic substitution with rearrangement [substitution at C(7)]. This mechanism, which could be termed 'nucleophilic catalysis with rearrangement' is proved by labelling experiments. Thus, in the case of 2-iodo[3,5,7-$^2H_3$]cyclohepta-2,4,6-trien-1-one, when quinuclidine is present, substitution by piperidine occurs at both C(2) and C(7) of the ring, substitution at C(7) occurring clearly *via* the reactive intermediate suggested above and substitution at C(2) occurring in a process in which quinuclidine does not take part.

In connection with our interest [1] in troponoids (cyclohepta-2,4,6-trien-1-one and its derivatives) [2] we have carried out a detailed investigation of the reactions of piperidine with some 2-X-cyclohepta-2,4,6-trien-1-ones (X = halogen or methoxy) which give 2-piperidinocyclohepta-2,4,6-trien-1-one by substitution at the position vacated by X.[3] Although these reactions in-

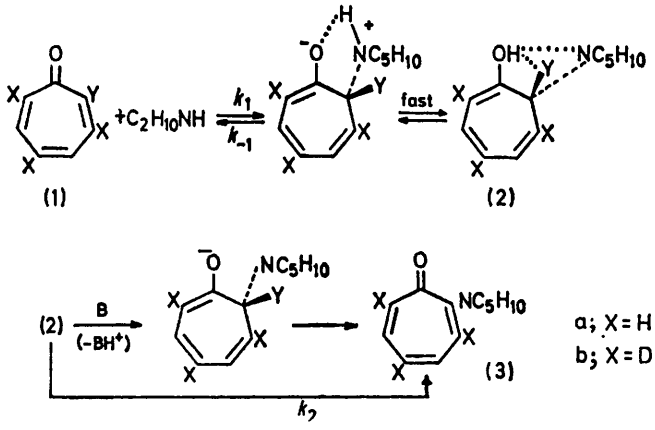
† The material in this paper was presented at a lecture in the University of Leiden, November 1971.

[1] Part VI, G. Biggi, F. Del Cima, and F. Pietra, *J. Amer. Chem. Soc.*, in the press.

[2] For general reviews see (*a*) P. L. Pauson, *Chem. Rev.*, 1955, **55**, 9; (*b*) T. Nozoe, in 'Non-benzenoid Aromatic Compounds,' ed. D. Ginsburg, Interscience, New York, 1959; D. Lloyd, 'Carbocyclic Non-benzenoid Aromatic Compounds,' Elsevier, Amsterdam, 1966.

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

volve the transfer of a proton at some stage during the reaction they do not undergo base catalysis. This is shown by the fact that the kinetic order with respect to piperidine is near unity in such a non-levelling solvent as benzene.[3] It was suggested that the 'carbonyl' oxygen atom exerts a powerful intramolecular catalysis of the removal of the ammonium proton from the addition intermediate formed between piperidine and 2-X-cyclohepta-2,4,6-trien-1-one (Scheme 1).[3b]



SCHEME 1

A parallel study of the influence of another added base, a tertiary amine such as 2-azabicyclo[2,2,2]octane (quinuclidine), gave puzzling results, only the reaction of 2-iodocyclohepta-2,4,6-trien-1-one with quinuclidine being appreciably accelerated. These observations, and their rationalisation and relevance for the problem of the reactivity of troponoids towards nucleophiles, are reported here.

RESULTS AND DISCUSSION

2-Chloro- (1a; Y = Cl) or 2-iodo-cyclohepta-2,4,6-trien-1-one (1a; Y = I) react with piperidine in benzene to give 2-piperidinocyclohepta-2,4,6-trien-1-one (3a) quantitatively.[3] Both reactions are only very mildly accelerated by piperidine, the kinetic order with respect to piperidine being only slightly greater than unity.[3] We were interested in the kinetic effect of another base in benzene and the highly basic tertiary amine relatively unhindered at nitrogen, quinuclidine, was the choice.

We found that even in the presence of a large amount of added quinuclidine the nature of the products of the above reactions in benzene is not altered. The rate data for the influence of added quinuclidine on these reactions in benzene are in Table 1. The reaction of 2-chlorocyclohepta-2,4,6-trien-1-one with piperidine in benzene is accelerated only negligibly by added quinuclidine. The corresponding reaction of 2-iodocyclohepta-2,4,6-trien-1-one is instead appreciably accelerated by quinuclidine. The rate data follow equation (1)

TABLE 1

Second-order rate coefficients (k = rate/[substrate][PIP]) for the formation of 2-piperidinocyclohepta-2,4,6-trien-1-one from the reactions of piperidine with 2-iodo- or 2-chloro-cyclohepta-2,4,6-trien-1-one in the presence of added quinuclidine in benzene at 25 °C

A 2-Iodocyclohepta-2,4,6-trien-1-one (initial concn. $4{\cdot}8 \times 10^{-5}$M); piperidine (initial concn. $6{\cdot}53 \times 10^{-2}$M)

[QUIN]/M		0·0786	0·157	0·471
10^4k/l mol^{-1} s^{-1}	5·76	28·7	55·6	147

B 2-Chlorocyclohepta-2,4,6-trien-1-one (initial concn. $5{\cdot}4 \times 10^{-5}$M); piperidine (initial concn. $4{\cdot}88 \times 10^{-2}$M)

[QUIN]/M		0·494
10^4k/l mol^{-1} s^{-1}	8·61	12·8

where PIP and QUIN stand for piperidine and quinuclidine, respectively. The values of the rate coefficients

$$k = \text{Rate}/[\text{substrate}][\text{PIP}] = k_0 + k_{\text{PIP}}[\text{PIP}] + k_{\text{QUIN}}[\text{QUIN}] \quad (1)$$

of equation (1) are in Table 2 (k_{PIP} values are from previous work,[3b] and k_{QUIN} is from a single experiment in the case of 2-chlorocyclohepta-2,4,6-trien-1-one).*

Could the acceleration by quinuclidine of the reaction

TABLE 2

Reactions of piperidine with 2-X-cyclohepta-2,4,6-trien-1-one (X = I or Cl) in the presence of added quinuclidine in benzene at 25 °C. Treatment of the data of Table 1 according to equation (1)

X	10^4k_0 / l mol^{-1} s^{-1}	10^4k_{PIP} / l^2 mol^{-2} s^{-1}	10^4k_{QUIN} / l^2 mol^{-2} s^{-1}
I	3·70	63·0	292
Cl	8·20	21·0	8·50

X	k_{PIP}/k_0 / l mol^{-1}	k_{QUIN}/k_0 / l mol^{-1}
I	17	79
Cl	2·5	1·0

of 2-iodocyclohepta-2,4,6-trien-1-one with piperidine reflect base catalysis? The mechanism (Scheme 1) we have suggested[3] leaves no room for catalysis by an external base and, in any case, base catalysis is not expected for the removal of a good leaving group like iodine in a reaction of this type.[4]

That these reactions do not undergo base catalysis is also shown by the rate effect of added phenol. Phenol is a powerful catalyst of the reaction of piperidine with 2-chlorocyclohepta-2,4,6-trien-1-one (Table 3). This is pure acid catalysis as shown by the fact that the rate data accurately fit equation (2) (as shown in the Figure)

$$F_{\text{D}} = (\text{Rate}/[\text{substrate}][\text{PIP}]_{\text{free}}) - k_0 - k_{\text{PIP}}[\text{PIP}]_{\text{free}} = k_{\text{PhOH}}[\text{PhOH}]_{\text{free}} \quad (2)$$

* The trend of the k_{PIP} term is qualitatively similar to that of the k_{QUIN} term. This can be appreciated from Table 2. However, only in the case of the k_{QUIN} term is the difference between the iodo- and the chloro-compound sufficiently wide to deserve the present comments.

[4] F. Pietra, *Quart. Rev.*, 1969, **23**, 504; W. P. Jenks and K. Salvesen, *Chem. Comm.*, 1970, 548.

where the substrate is 2-chlorocyclohepta-2,4,6-trien-1-one. The catalytic coefficient of phenol is 0·119 l^2 mol^{-2} s^{-1}. This analysis assumes that unassociated piperidine is the only active nucleophile and was carried out by use of the data of Table 3 and the association data reported for the reaction between phenol and piperidine.[5] Were the reaction between 2-chlorocyclohepta-2,4,6-trien-1-one and piperidine subject to catalysis by an external base, powerful acceleration by the salt formed between piperidine and phenol would have been expected.[5] This should result in a non-linear plot of F_D against free phenol concentration,[5] contrary to what was observed (Figure).

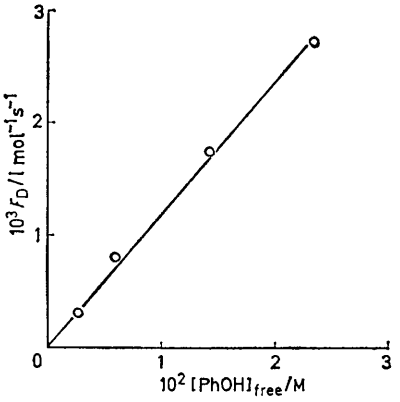
TABLE 3

First-order rate coefficient ($k/s^{-1} = 0·693/t_{\frac{1}{2}}$) for the reaction of 2-chlorocyclohepta-2,4,6-trien-1-one[a] with piperidine[b] in the presence of added phenol in benzene at 25 °C

10^3[PhOH]/M		5·21	10·4	20·9	31·3
$10^6k/s^{-1}$	8·97	9·70	10·8	11·1	11·1

[a] Initial concn. 6·58 × 10^{-5}M. [b] Initial concn. 1·10 × 10^{-2}M.

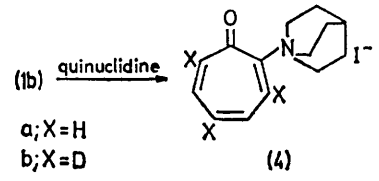
It is very likely that phenol helps the formation of the addition intermediate (k_1 step in Scheme 1) by becoming hydrogen bonded to the ' carbonyl ' oxygen of 2-chlorocyclohepta-2,4,6-trien-1-one. This is in keeping with the lack of catalysis by silver ions for the nucleophilic substitutions of 2-halogenocyclohepta-2,4,6-trien-1-ones.[6]



Plot of F_D = (rate/[substrate][PIP]$_{free}$ − k_0 − k_{PIP}[PIP]$_{free}$ = k_{PhOH}[PhOH]$_{free}$ for the reaction of 2-chlorocyclohepta-2,4,6-trien-1-one (substrate) with piperidine in benzene in the presence of phenol against free phenol concentration. Results computed from the data in Table 3 and from the association constant between phenol and piperidine [F. Pietra and D. Vitali, *J. Chem. Soc.* (*B*), 1968, 1318].

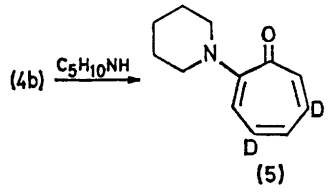
A general medium effect by quinuclidine is also an unsatisfactory rationalisation of the rate acceleration by quinuclidine of the reaction of 2-iodocyclohepta-2,4,6-trien-1-one with piperidine. Such an explanation would, in fact, demand an at least equally powerful rate acceleration of this reaction by piperidine, contrary to what was observed.

The clue to the correct answer comes from the observations that (i) quinuclidine reacts with compound (1b) to give 2-(1-azoniabicyclo[2,2,2]oct-1-yl)[3,5,7-$^2H_3$]cyclohepta-2,4,6-trien-1-one (4b), the position left free by iodine being taken by the quinuclidine nitrogen (Scheme 2)[7] and (ii) piperidine reacts with (4b) to give 2-piperidino-



SCHEME 2

[4,6-$^2H_2$]cyclohepta-2,4,6-trien-1-one (5b) in a nucleophilic substitution with rearrangement [substitution occurs at C(7) in (4b), Scheme 3].[1]



SCHEME 3

It might then be envisaged that quinuclidine, when present in excess, competes with piperidine for 2-iodocyclohepta-2,4,6-trien-1-one to give (4a) which is then rapidly transformed by piperidine into 2-piperidinocyclohepta-2,4,6-trien-1-one. The rate data to hand allow such a reaction path. In fact, in dimethyl sulphoxide the rate of reaction (i) is of the same order as the rate of the reaction of piperidine with 2-iodocyclohepta-2,4,6-trien-1-one.[7b] Moreover, both these reactions are much slower that reaction (ii).

That this is really the origin of the quinuclidine catalysis of the reaction of piperidine with 2-iodocyclohepta-2,4,6-trien-1-one was proved by the following experiment. 2-Iodo[3,5,7-$^2H_3$]cyclohepta-2,4,6-trien-1-one (1b) was allowed to react with piperidine in benzene in the presence of an excess (as in the kinetic experiments described above) of quinuclidine. An oil was recovered from the mixture which was proved by ^1H n.m.r. spectroscopy to consist of two products (5) [1] and (3b),[3] in accordance with the above expectation. The ^1H n.m.r. spectrum of the mixture of products from this reaction, freed from solvents and non-troponoid materials, shows, besides piperidine proton signals, three rather sharp signals at δ 7·05, 6·55, and 6·18 p.p.m. The peak areas for the signals at δ 7·05 and 6·18 p.p.m. are in the ratio 1 : 2.

[5] F. Pietra and D. Vitali, *J. Chem. Soc.* (*B*), 1968, 1318.
[6] W. Von E. Doering and C. F. Hiskey, *J. Amer. Chem. Soc.*, 1952, **74**, 5688.
[7] (*a*) F. Pietra and F. Del Cima, *Chem. Comm.*, 1970, 297; (*b*) F. Pietra, G. Biggi, and F. Del Cima, *J. Chem. Soc.* (*C*), 1971, 3626.

This is clearly interpretable as the superimposition of the spectra for (5) [the signals at δ 7·05 and 6·18 p.p.m. arise from the protons at C(7) and C(3) + C(5), respectively] [1] and for (3b) [the signal at δ 6·55 p.p.m. arises from the C(4) and C(6) protons].[3b] From the peak areas reported in the Experimental section, it is straightforwardly calculated that the mixture consists of 26% of (5) and 74% of (3b).

Thus, quinuclidine catalysis of the formation of 2-piperidinocyclohepta-2,4,6-trien-1-one from piperidine and 2-iodocyclohepta-2,4,6-trien-1-one can reasonably be accounted for in terms of a sequence of two nucleophilic displacements at the troponoid carbon atom, only the second one involving a rearrangement.

The reaction of 2-chlorocyclohepta-2,4,6-trien-1-one with piperidine is not accelerated by quinuclidine because this troponoid compound reacts only sluggishly with quinuclidine in benzene.[7b]

These results rule out also a mechanism of nucleophilic catalysis [8] for the acceleration of the reaction of piperidine with 2-iodocyclohepta-2,4,6-trien-1-one by quinuclidine. Such a mechanism had to be considered because it is frequently involved when a good leaving group like iodine has to be replaced in the case of nucleophilic substitutions at the carbonyl carbon atom of carboxylic acid derivatives.[8]

By analogy the mechanism of catalysis by quinuclidine discovered here could be termed ' nucleophilic catalysis with rearrangement ' and could be proved to be a new general mode of catalysis for appropriate systems.

Incidentally, these results prove again [3] that troponoids, on close examination, show quite different behaviour from carboxylic acid derivatives. Therefore, the concept of vinylogy between these two classes of substance, useful at the time it was suggested when the properties of troponoids were still insufficiently known,[2] should be abandoned.

EXPERIMENTAL

M.p.s were taken on a Kofler hot-stage apparatus and are uncorrected. U.v. spectra were recorded with a Unicam SP 800 spectrophotometer and the kinetics were followed with a Beckman DU spectrophotometer. ^{1}H N.m.r. spectra were run on a JEOL C-604L spectrophotometer or on a Varian HA-100 spectrophotometer (10% solutions) with tetramethylsilane as internal standard at 30 °C.

Reaction of 2-Iodo- or 2-Chloro-cyclohepta-2,4,6-trien-1-one with Piperidine in Benzene in the Presence of Either Quinuclidine or Phenol.—The reactions were carried out under the conditions and with the methods described for the analogous reactions in the absence of addenda.[3b] A molar excess (*ca.* 10 : 1) of either quinuclidine or phenol over the troponoid substrate was used. 2-Piperidinocyclohepta-2,4,6-trien-1-one, m.p. 56—57 °C (lit.,[3b] 56—57 °C), was obtained in 90% yield.

Reaction of 2-Iodo[3,5,7-$^2H_3$]*cyclohepta-2,4,6-trien-1-one* (1b) *with Piperidine in the Presence of Quinuclidine.*—A solution of dry piperidine (0·148 g; 1·74 mmol) and quinuclidine (0·59 g; 5·29 mmol) in dry benzene (*ca.* 9 ml) was slowly added to a solution of (1b) (0·110 g, 0·466 mmol) in benzene (*ca.* 1 ml). The mixture immediately became deep yellow. After one day at room temperature a salt-like precipitate was obtained which was filtered off and the solution was then evaporated under vacuum. The yellow oily residue gave a main spot on t.l.c. corresponding to 2-piperidinocyclohepta-2,4,6-trien-1-one together with some very minor spots. This oil was chromatographed on a silica gel column, (eluant 95 : 5 benzene–95% ethanol) to eliminate the minor spots. The best fractions were evaporated and sublimed (50 °C at 1 mmHg) to give a yellow oil (0·045 g, yield 50% based on the molecular weight of 2-piperidinocyclohepta-2,4,6-trien-1-one) which showed a u.v. absorption spectrum identical with that of 2-piperidinocyclohepta-2,4,6-trien-1-one; [3b] δ (Varian, C_6D_6) 7·17 (non-deuteriated solvent peak), 7·05 (s, 0·26H), 6·5 (s, 1·48H), 6·18 (s, 0·52H), 3·05br (4H), and 1·36br (6H) p.p.m.

Kinetics.—Benzene,[5] phenol,[5] piperidine,[5] and 2-iodo-[3b] and 2-chloro-cyclohepta-2,4,6-trien-1-one [3b] were purified as described in the references. Quinuclidine was repeatedly sublimed.

The kinetics of the reactions of piperidine with either 2-chloro- or 2-iodo-tropone in benzene in the presence of added quinuclidine or phenol were followed as described in the absence of addenda.[3b] A quantitative yield of 2-piperidinocyclohepta-2,4,6-trien-1-one was always obtained. Accurately first-order kinetics, up to 90% reaction, were obtained in all cases with excess of piperidine.

Financial support by C.N.R., Roma, a postdoctoral Fellowship from the ' Scuola Normale Superiore ', Pisa (to G. B.), and undergraduate support (to F. D. C.) are acknowledged.

[1/2457 *Received*, 22*nd December*, 1971]

[8] V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc.* (*C*), 1968, 515.