Pseudoaromatic Compounds. Part XXII.[1] Reactions of 2-Functionalized Tropones with Sodium Toluene-*p*-thiolate

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Relative rates for replacement, without rearrangement, of the X group of some 2-X-tropones by sodium toluene-*p*-thiolate in dimethyl sulphoxide are in the order 82, 2.6, 3.5, 1.0, and *ca.* 29 000 for X = F, Cl, Br, I, and $N[CH_2CH_2]_3CHI^-$, respectively, whilst with X = OCH_3 slow demethylation occurs instead. The rate of replacement of the quinuclidinium group has been computed for the free reagents present in equilibrium with an adduct which lies off the reaction co-ordinate. These data give support to the idea that ready replacement of strongly bound X groups, such as fluorine or methoxy, of 2-X-tropones by primary or secondary amines is due to stabilisation of the transition state by proton bridging among the protonated nitrogen, the tropone carbonyl oxygen, and, for fluorine, the leaving-group.

DURING the course of studies aimed at finding appropriate methods for the regiospecific functionalization of the cycloheptatrienone nucleus, we have reported that primary or secondary amines cleanly replace, in an overall second-order process, halogeno- or methoxy-groups from the 2-position of the cycloheptatrienone nucleus.[2] No rearrangement was observed, the rate being nearly independent of both the nature of the leaving group and of the solvent because of an activation enthalpy–activation entropy compensation.[2] Only the fluoro-compound was found to escape the isokinetic relationship, being some 10^3-fold more reactive than the other compounds above.

It was proposed that the isokinetic relationship stems from a levelling stabilization of the transition state for the replacement process owing to proton bridging among the entering nitrogen, the tropone carbonyl oxygen and, for the fluoro-compound, the leaving-group.[2b]

Some support for this rationalization came from the observations that 2-fluorotropone is unique in resisting replacement by tertiary amines in such a non-assisting solvent as benzene [2b] and that 2-methoxytropone resists replacement of the methoxy-group by thiolates, forcing of the reaction conditions leading to demethylation instead.[3]

Because stabilization of transition states by such bridging interactions are not only of much interest in the area of pseudoaromatic compounds but they often have been suggested as the origin of the specificity of various reactions, typically including biological ones, we have tried to place the above ideas on firmer ground.[2b] Thus, we report here a kinetic investigation of the replacement of various 2-substituents on the cycloheptatrienone nucleus by a reagent, sodium toluene-*p*-thiolate, where the bridging phenomena are inconceivable.

RESULTS AND DISCUSSION

It is known from careful investigation with deuterium-labelled materials that both 2-quinuclidiniotropone

[1] Part XXI, B. Ricciarelli, G. Biggi, R. Cabrino, and F. Pietra, *Synthesis*, 1975, 189.

[2] (*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.

[3] G. Biggi, F. Del Cima, and F. Pietra, *Tetrahedron Letters*, 1973, 183.

iodide and 2-halogenotropones undergo exclusive replacement of the 2-group by thiolates in dimethyl sulphoxide (DMSO).[4] Also, because of the bathochromic effect of the *p*-tolylthio-group with respect to the halogeno-group on the 2-position of the cycloheptatrienone nucleus it was easy to follow by u.v. the formation of the sulphide. The relative rate data for these overall second-order processes are reported in the Table together with

Second-order rate coefficients and activation parameters for replacement of X from various 2-X-tropones by sodium toluene-*p*-thiolate (PPT) in dimethyl sulphoxide at 25°

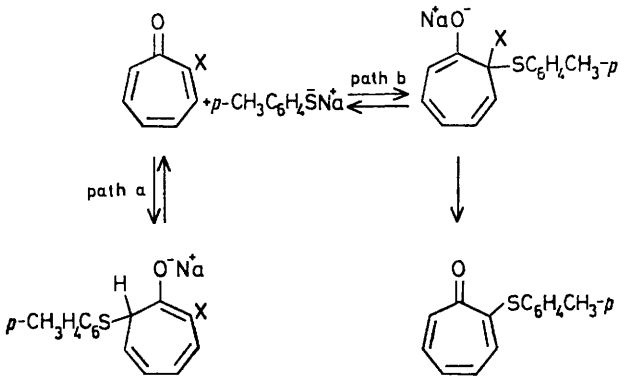
X	k/ mol^{-1} l s^{-1}	k_{rel}	$\Delta H^{\ddagger}$/ kcal mol^{-1}	$-\Delta S^{\ddagger}$/ cal mol^{-1} K^{-1}
F	2 800 [a]	82		
Cl	90 [b]	2.6	6.1	31
Br	119 [c]	3.5	3.6	39
I	34 [d]	1.0	8.7	24
$N(CH_2CH_2)_3CHI^-$	*ca.* 10^6 [e]	*ca.* 29 000		
OCH_3	Slow, demethylation occurs instead [f]			

[a] Stopped-flow measurement; initial concns.: 2-fluorotropone 6.2 × 10^{-5}M, PPT 4.01 × 10^{-4}M (average of two runs). [b] Interpolated datum; initial concns.: 2-chlorotropone 1.14 × 10^{-5}—1.15 × 10^{-4}M, PPT 3.76 × 10^{-4}—8.06 × 10^{-4}M, $k_{22°}$ = 84 mol^{-1} l s^{-1}, $k_{25.8°}$ = 102.5 mol^{-1} s^{-1} (averages of three runs). [c] Interpolated datum; initial concns.: 2-bromotropone 1.1 × 10^{-5}—5.8 × 10^{-5}M, PPT 3.76 × 10^{-4}—8.06 × 10^{-4}M, $k_{20.7°}$ = 108.5 mol^{-1} l s^{-1}, $k_{27.7°}$ = 125.5 mol^{-1} l s^{-1} (averages of three runs). [d] Interpolated datum; initial concns.: 2-iodotropone 1.25 × 10^{-5}—5.66 × 10^{-5}M, PPT 3.26 × 10^{-4}—4.91 × 10^{-4}M, $k_{22°}$ = 29.1 mol^{-1} l s^{-1}, $k_{29°}$ = 41.0 mol^{-1} l s^{-1} (averages of two runs). [e] For free reagents present in an equilibrium, having a constant K_{eq}, with an adduct which lies off the reaction coordinate; observed rates with initial concns.: 2-quinuclidiniotropone (CT) 5.07 × 10^{-5}M, PPT 2.01 × 10^{-4}M, k_{obs} 1.54 s^{-1}; CT 5.07 × 10^{-5}M, PPT 4.03 × 10^{-4}M, k_{obs} 2.72 s^{-1}; CT 5.07 × 10^{-5}M, PPT 8.06 × 10^{-4}M, k_{obs} 2.59 s^{-1}; K_{eq} = 18 400 mol^{-1} l (see text). [f] G. Biggi, F. Del Cima, and F. Pietra, *Tetrahedron Letters*, 1973, 183.

activation parameters, when available. The corresponding reaction of 2-quinuclidiniotropone iodide was easy to follow by u.v. for the same reason. In this case, however, the observed rate cannot be directly compared with those for the halogeno-compounds. In fact, whilst the halogeno-compounds react with the thiolate to give only 2-*p*-tolylthiotropone, 2-quinuclidinotropone iodide interacts reversibly with the thiolate at a rate which is too fast for stopped-flow techniques, to give an intermediate addition compound, presumably by thiolate attack at C-7 (Scheme 1, path a).* The slower ensuing formation of 2-*p*-tolylthiotropone must be attributed to interaction between the uncomplexed reagents (Scheme 1, path b).

The equilibrium constant, 18 400 l mol^{-1}, for the reversible formation of this adduct was evaluated, with the aid of a stopped-flow u.v. spectrometer, by taking the absorption, immediately after the mixing of the reagents at a wavelength, 380 nm, where only the adduct absorbs.[4] It was then easy to compute, through the observed rates reported in the Table (footnote *e*) the second-order rate coefficient, *ca.* 10^6 mol^{-1} l s^{-1}, for reaction between the uncomplexed reagents.

The data in the Table show that the heavy halogen compounds react at very similar rates to one another. This is expected for a two-step substitution process (Scheme 1, path b) where small differences of bond



SCHEME 1

energies and solvation energies among different leaving groups can be levelled off.[5] However, the curiously low activation enthalpy for reaction of the bromo-compound is not easily rationalized.

Although fluorine is replaced at an enhanced rate with respect to the heavy halogens (Table), the enhancement is much smaller than that observed for reaction with primary or secondary amines.[2] A reasonable explanation is that because of the lack of assistance by a proton of the removal of fluorine, the greater energy of C(sp_2)–F bond than of C(sp_2)–heavy halogen bonds somewhat counterbalances the enhanced rate of formation of the tetrahedral intermediate of nucleophile attack at C(2) for the fluoro-compound.

The absence of methoxy-replacement (Table) can be explained along similar lines. Here not only there is no enhanced rate of formation of the tetrahedral intermediate of nucleophile attack at C(2), because the peculiar factors possessed by fluorine [2b] are lacking, but the high C(sp_2)–O bond energy cannot be compensated for by assistance to the removal of methoxide. The result is inertness, whilst under forcing conditions an easier path, with tropolonate as leaving-group, is found (Table).

The case of 2-quinuclidiniotropone iodide (Table) requires some comment. In fact, the much higher rate of substitution by toluene-*p*-thiolate by comparison with the chloro-compound (Table) might seem at first sight in contrast with the behaviour of the same troponoids toward hydroxide. In fact, whilst 2-chlorotropone with very concentrated alkali gives 40% of

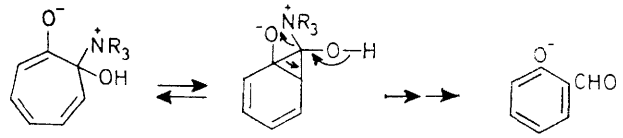
* The evidence for such an adduct rests on u.v. spectra which are similar to those obtained for authentic C(7) adducts.[4] However, the structure of the thiolate adduct could probably be unequivocally assigned by Fourier transform n.m.r. spectroscopy, as in the case of interaction of 2-chlorotropone with potassium methoxide (F. Pietra, *J.C.S. Chem. Comm.*, 1974, 544).

[4] G. Biggi, F. Del Cima, and F. Pietra, *J. Amer. Chem. Soc.*, 1973, **95**, 7101.

[5] F. Pietra, *Quart. Rev.*, 1969, **23**, 504.

tropolone,[6] 2-quinuclidiniotropone iodide only gives salicylaldehyde as the result of 1 : 1 hydroxide attacks at *C(3) and* C(2).[7]

Clearly, the intermediate of hydroxide attack at C(2) can collapse to the aldehyde by proton loss (Scheme 2),



SCHEME 2

a mechanism not available to a thiolate. However, comparison with the behaviour of 2-chlorotropone shows that quinuclidine is a poorer leaving group. The conclusion is that the dramatically enhanced rate of 2-quinuclidiniotropone iodide over 2-chlorotropone towards toluene-*p*-thiolate (Table) must be attributed to enhanced rate of formation of the tetrahedral intermediate of nucleophile attack at C(2) (Scheme 1) by the quaternary ammonium ion.

It is worth mentioning that whilst nitro-activated quaternary aromatic compounds are extremely difficult to prepare,[2b] aza-activated analogues are well known and react with nucleophiles, by replacement of the trialkylammonio-group, some 700—1 600 times faster than the corresponding chloro-compounds.[8] To the best of our knowledge it has not been reported if this figure represents a lower limit due to Meisenheimer adduct formation.

EXPERIMENTAL

U.v. spectra were taken with a Unicam SP 800 spectrometer and rapid reactions were measured with a Durrum stopped-flow apparatus. Starting compounds and products are from previous work.[2,4] DMSO was purified as before.[2,4]

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[6] G. Biggi, A. J. de Hoog, F. Del Cima, and F. Pietra, *J. Amer. Chem. Soc.*, 1973, **95**, 7108.

[7] G. Biggi, F. Del Cima, and F. Pietra, *Tetrahedron Letters*, 1974, 3537.

[8] G. B. Barlin and A. C. Young, *J.C.S. Perkin I*, 1972, 1269.