Nucleophilic Reactivity of 4-Functionalized Cycloheptatrienones

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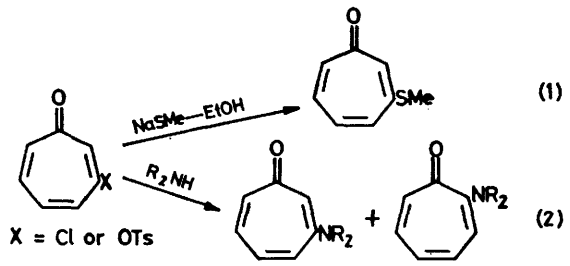
Replacement of either halogens or the tosyloxy-group from the troponoidal γ-carbon by dimethylamine occurs without rearrangement. Iodine and bromine are replaced in dimethyl sulphoxide as solvent much faster (the more so the higher is the amine concentration) than either the tosyloxy-group or chlorine, whereas the methoxy-group resists replacement. The relatively high reactivity of the iodo-compound is due to a lack of activation enthalpy–activation entropy compensation.

CYCLOHEPTATRIENONES carrying a mobile substituent, such as a halogen, at the α-carbon react in a basic medium *via* two principal pathways. That is, they undergo either nucleophilic substitution at the α-carbon [1] or ring contraction to benzenoids by expulsion of C(1),[2] C(6),[2] or, albeit in rare instances, of the α-carbon itself.[3]

The above substitution reactions can either take place *via* nucleophilic attack just at the carbon which is vacated by the mobile group,[1a,b] or can involve a rearrangement, proceeding *via* nucleophilic attack at C(7).[1c] Both processes have been carefully studied kinetically.[1]

Less is known about the chemistry in basic media of cycloheptatrienones carrying a mobile substituent at C(3). So far, no clean ring contraction process has been detected, strong bases, such as alkoxides or hydroxide, leading instead to resinification.[4]

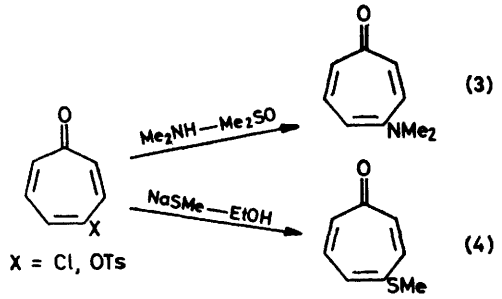
However, clean substitution at C(3) was observed for 3-chloro- and 3-tosyloxy-tropone with alkylmercaptides as nucleophiles [5] [Scheme 1, equation (1)], whilst with amines as nucleophiles substitution at C(2) was found to compete with substitution at C(3), the former process being favoured in non-polar solvents [6] [Scheme 1, equation (2)].



SCHEME 1

Although substitution at C(3) could not be investigated in detail because 3-substituted cycloheptatrienones proved difficult to synthesize, only 3-methoxy-, 3-chloro-, and 3-tosyloxy-tropone having been accessible, we arrived at an important conclusion concerning the reactivity of the β-carbon. Thus, for tosyloxy as a leaving-group, the troponoidal β-carbon proved to be more reactive than either the α- or the γ-carbons towards nucleophilic reagents such as amines and alkylmercaptides.[5]

Even less is known about the nucleophilic reactivity of cycloheptatrienones carrying a mobile group at the γ-carbon. No ring-contraction process has been discovered so far, whilst it is only known that both 4-chloro- and 4-tosyloxy-tropone undergo clean substitution at the γ-carbon by either dimethylamine [Scheme 2, equation (3)] or sodium methyl sulphide [Scheme 2, equation (4)], the γ-carbon being about as reactive as the α-carbon.[5]



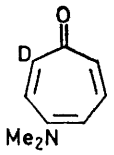
SCHEME 2

This work was devoted towards a better understanding of the nucleophilic reactivity of cycloheptatrienones carrying a mobile group at the γ-carbon. This was done by extending the above observations, as regards reactions with an amine, to 4-bromo-, 4-iodo-, and 4-methoxy-tropone and comparing the results with those for the corresponding reactions of α-substituted cycloheptatrienones.

RESULTS

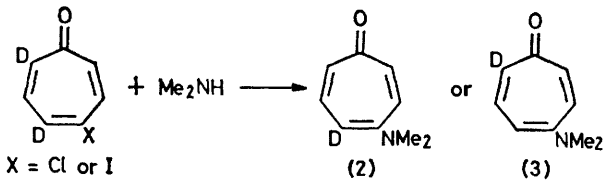
The principal experimental observations can be summarized as follows.

(*a*) As already known for 4-chloro- and 4-tosyloxy-tropone,[5] the reactions of 4-bromo- or 4-iodo-tropone with dimethylamine in either dried dimethyl sulphoxide or methanol give 4-dimethylaminotropone in practically quantitative yield. Ring labelling at both C(5) and C(7) of 4-chloro-, 4-iodo-, and 4-tosyloxy-tropone with deuterium showed that the dimethylamino-group takes the position vacated by the halogen atom. The basis of this conclusion is as follows. The ^{1}H n.m.r. data in the Experimental section show that one of the two deuterium atoms was lost during the process. Structure (1), derived from a hypothetical attack of the amine at C(5) on the substrate, can be immediately ruled out. In fact, (1), owing to three adjacent protons, could not have given the observed AB



(1)

system. Of the two remaining structures, (2) and (3) (Scheme 3), comparison with the ^1H n.m.r. spectrum of 4-dimethylaminotropone [5] in C_6D_6 allowed us to choose (2) as the correct structure. In fact, the latter spectrum consists of a doublet at δ 7.1, J = 13.6 Hz for H(2), a multiplet at 6.72 for H(6) and H(7), a doublet at 6.42, J = 13.6 and 2.8 Hz, for H(3), a multiplet at 5.40 for H(5) and a singlet at 2.30 for the dimethylamino-group. This assignment is clearly supported by (i) irradiation at 5.40 whereby the double doublet at 6.42 becomes a doublet with



SCHEME 3

J = 13.6, while the multiplet at 6.72 becomes a singlet; (ii) irradiation at 2.30 whereby a clear N.O.E. shows up at δ 5.40. On this basis, clearly the deuteriated analogue must have structure (2), the deuterium at C(5) accounting for the lack of a resonance at δ 5.4.

(*b*) Kinetic data for halogen substitution from 4-bromo- or 4-iodotropone by dimethylamine in dimethyl sulphoxide (DMSO) (Table 1) fit equation (11). Surprisingly, the

$$k = \text{Rate}/[\text{troponoid}][Me_2NH] = k_2 + k_3[Me_2NH] \quad (11)$$

TABLE 1

Kinetic data for substitution of bromine or iodine from 2-bromo-[a] 2-iodo-,[a] or 2-methoxy-tropone, or their 4-isomers,[a] by dimethylamine in DMSO

Group replaced	Me_2NH M × 10^3	Observed rate coefficient k_{obsd} × 10^2/mol^{-1} l s^{-1} at: 25 °C	31 °C	45 °C
2-Br	47.2	1.48		4.02
	58.0			4.00
	88.7	1.50		
4-Br	0.60	31.0		
	0.87	36.0		
	1.36	40.0		
	1.75	44.0		
	2.75	60.0	70.0	
	4.00	75.0	87.0	
	5.30			122
	5.35	95.0	108	
	5.82	100		
	6.50			140
	7.70			160
	10.0	150		
2-I	47.2	10.1		16.3
	58.0			16.6
	88.7	11.0		
4-I	0.50	235		
	0.60	240		
	0.75	255		275
	0.85	260		
	1.25	310		
	1.40	328		370
	1.90	400		
	2.70	495		550
	2.90	530		
	4.00	660		750
2-OMe	260	*b*		0.0124
4-OMe	Unchanged after several days at 25°			

[a] Initial concentrations ranging from 4 × 10^{-5} to 8 × 10^{-5}M; [b] No reaction after 3 h.

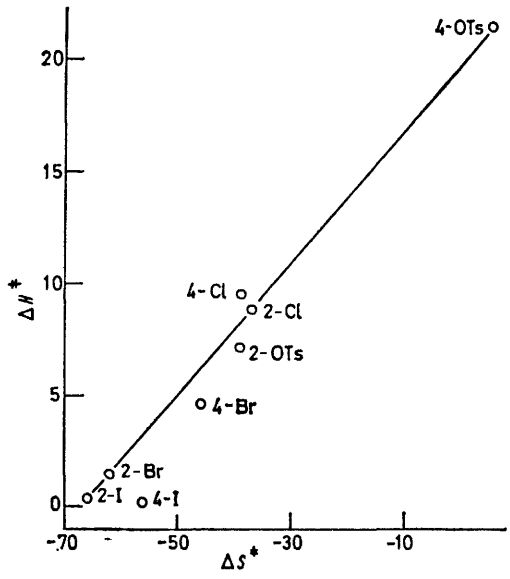
k_3/k_2 ratios are one order of magnitude larger than those for the corresponding reactions of 4-chloro- and 4-tosyloxy-tropone [5] (Table 2). Each value of the kinetic coefficients in Table 1 is the mean of several kinetic experiments, which gives confidence in the k_2 and k_3 data derived from equation (11).

(*c*) Added quinuclidine or triethylamine (10^{-2}M) failed to affect the kinetics of the reactions of dimethylamine with 4-iodotropone or 4-tosyloxytropone in DMSO.

(*d*) 4-Bromotropone and 4-iodotropone are more reactive towards dimethylamine in DMSO, as can be judged from k_2 rate coefficients (Table 2), than 4-chloro- and 4-tosyloxy-tropone by, respectively, one and two orders of magnitude.

(*e*) Addition of *m*-dinitrobenzene (1.4 × 10^{-3}M) to a solution of 4-iodotropone (4 × 10^{-5}M) and dimethylamine (1.4 × 10^{-3}M) in DMSO at room temperature had no noticeable kinetic effect.

(*f*) 4-Iodotropone failed to react with 10^{-3} M dimethylamine in benzene at room temperature in 24 h; the same occurred for 4-tosyloxytropone with 0.56M-dimethylamine in benzene.



Plot of activation enthalpy *vs.* activation entropy for the reactions of various α- or γ-functionalized tropones with dimethylamine in dimethylsulphoxide

(*g*) Like the reactions of 2-chloro- or 2-tosyloxy-tropone with dimethylamine in DMSO,[5] the corresponding reactions of 2-bromo- and 2-iodo-tropone in the same solvent are nicely first-order with respect to the amine (Tables 1 and 2).

(*h*) Activation data for reactions with dimethylamine in DMSO, calculated from the k_2 terms of equation (11), indicate that the similar reactivities of 4-tosyloxy-, 2-chloro-, 2-bromo-, and 2-iodo-tropone originate from a $\Delta H^{\ddagger} - \Delta S^{\ddagger}$ compensation (see Figure); in fact, $\Delta H^{\ddagger}$ decreases from the tosyloxy-compound to the iodo-compound, in the order shown above, by as much as 21 kcal mol^{-1}. Although data of the type shown in the Figure are, in general, subject to large experimental uncertainties, the relatively high reactivity of 4-iodotropone [point (*d*) above] genuinely arises from a lack of $\Delta H^{\ddagger} - \Delta S^{\ddagger}$ compensation and very likely this is also the case for the relatively high reactivity of the bromo-compound (see Figure).

(*i*) The rate of the reaction of 2-methoxytropone with dimethylamine in DMSO (to give, as can be judged from u.v. analysis of the reaction mixture, 4-dimethylaminotropone) is several orders of magnitude lower than those for the corresponding reactions of 2-halogenotropones in the same solvent (Tables 1 and 2).

(*j*) 4-Methoxytropone failed to react with dimethylamine in DMSO (Table 1).

(*k*) Kinetics for the reaction of either 2,4-dideuterio-5-chlorotropone or the non-deuteriated analogue with dimethylamine in dried methanol at 25 °C showed an isotope effect $k_H/k_D = 1.1$ on the observed rate coefficients.

In fact, because of the recent observations as to the loss of halide ions from electrochemically generated radical-anions of halogenotropones,[9] it is conceivable that nucleophilic substitution of 4-functionalized tropones occurs through the free-radical mechanism of Scheme 4.[10] Here an electron-rich species, such as the amine itself, is presumed to act as electron supplier.[11]

However, the free-radical mechanism of Scheme 4 can be ruled out for the reactions of dimethylamine with either 4-tosyloxy- or iodo-tropone. The evidence for the tosylate is that its radical-anion is known to decompose to give 4-hydroxytropone and toluene-*p*-sulphinate only.[12] As regards 4-iodotropone, lack of any detectable effect by a good electron acceptor like *m*-dinitrobenzene [11] [point (*e*) above] clearly speaks against the free-radical mechanism. Moreover, the dramatic rate drop from DMSO to benzene [point (*f*)

TABLE 2

Kinetic data at 25 °C, unless otherwise stated, for replacement of a 2- or 4-groups from cycloheptatrienones by dimethylamine in DMSO, computed by equation (11) from data of either Table 1 or the literature [a]

Group replaced	$10^2 k_2$ / mol^{-1} l s^{-1}	$10\,k_3$ / mol^{-2} l^2 s^{-1}	k_3/k_2 / mol^{-1} l	$\Delta H^{\ddagger}$ [b] / kcal mol^{-1}	$\Delta S^{\ddagger}$ [b] / cal mol^{-1} K^{-1}
2-Cl [a]	1.86	0	0	8.8	−37
2-Br	1.49	0	0	1.4	−62
2-I	1.05	0	0	0.3	−66
2-OTs [a]	10.9	0	0	7.1	−39
2-OCH$_3$	0.012 [c]				
4-Cl [a]	0.21	0.25	12	9.5	−39
4-Br	22.3	1 350	605	4.6	−46
4-I	160	12 500	780	0.1	−56
4-OTs [a]	0.76	7.24	95	21.4	3.6

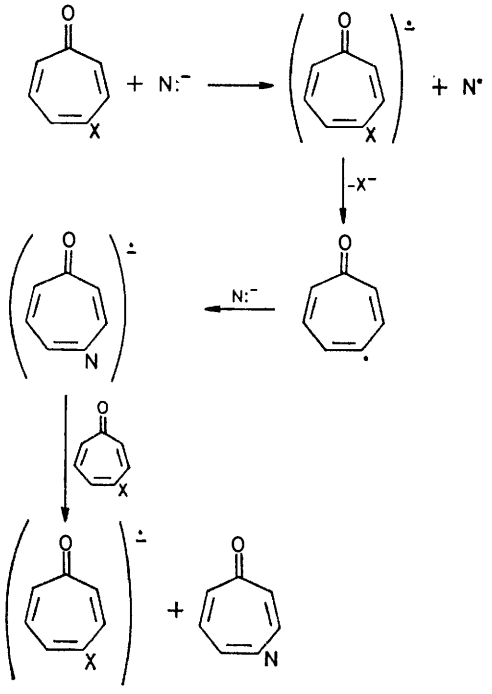
[a] Data from ref. 5. [b] Enthalpy and entropy of activation were computed from k_2 rate coefficients. [c] At 45 °C; really this represents the overall k term of equation (11) because the dependence of k on the dimethylamine concentration has not been investigated.

DISCUSSION

Ionic Mechanism.—We have recorded in the preceding section two peculiar findings, *i.e.* the high kinetic orders with respect to the reacting amine for both 4-iodo- and 4-bromo-tropone (*b*), and the low reactivity of 4-tosyloxytropone with respect to both 4-bromo- and 4-iodotropone by 30- and 200-folds, respectively (*d*).

Observation (*b*) has no precedent either for analogous reactions of isomeric α-functionalized tropones [1a] or for related ones of benzenoid substrates.[7] (To be sure to have to deal with an unusual observation, we have investigated the reaction of α-functionalized tropones with dimethylamine under identical conditions to those used for the γ-isomeric tropones. We have confirmed the unity order with respect to the reacting amine as can be seen from Table 2). The same is also true concerning observation (*d*). In fact, for α-functionalized tropones the tosylate is 10-fold more reactive than either the iodo- or the bromo-compound (Table 2), whilst in aromatic nucleophilic substitution tosylates are 100-fold more reactive than iodides.[8]

Because all the reactions taken for comparison with the reactions of 4-substituted substrates in the above paragraph are known to occur through the ionic addition–elimination mechanism,[1a,7a] the logical question arises whether such a mechanism applies also to the above reactions of 4-iodo- and 4-bromo-tropone or rather a different mechanism is operative, thus giving rise to the differences observed between the two groups of substrates.



SCHEME 4

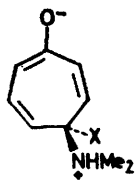
above] seems more in accordance with the addition–elimination mechanism,[1a] where charge can be created at the rate-limiting transition state, than with the mechanism shown in Scheme 4.

High Kinetic Orders in Amine.—Three recognized mechanisms might account for the high order with respect to dimethylamine in its reactions with either 4-iodo- or 4-bromo-tropone [point (*b*) above].

(1) ' A general medium effect by the amine.' This can be ruled out because of the polar nature of the solvent used (DMSO), the low concentrations of dimethylamine (Table 1), and the much less marked rate acceleration by dimethylamine of the closely related reactions of both 4-chloro- and 4-tosyloxytropone (Table 2).

(2) ' Addition of dimethylamine at the troponoidal C(5) followed by protonation at C(4) and elimination of either hydrogen bromide or hydrogen iodide by a second molecule of dimethylamine.' This is the mechanism which operates for attack at C(7) on certain 2-functionalized tropones.[1c] This mechanism is ruled out here both by the finding that substitution occurs without rearrangement [point (*a*) above] and by the lack of kinetic effect of added quinuclidine which could have replaced dimethylamine in the elimination step.

(3) ' Addition–elimination mechanism occurring through intermediate (4) which requires a second molecule of amine to collapse into products.' [1a,7] This mechanism is inconsistent with our findings that added tertiary amines, which, on the hypothesis above, could well replace dimethylamine as a catalyst, are devoid of kinetic effect on the reaction of the iodo-compound [point (*c*) above] and that dimethylamine accelerates the reaction of the chloro-compound less than that of the iodo-compound (Table 2). In fact, because it is well recognized that chloride is a poorer leaving-group than iodide, the reaction of the chloro-compound was expected to require amine catalysis to a larger extent than the reaction of the iodo-compound. To this must be added that amine catalysis in reactions of iodo- or bromo-compounds is unprecedented and catalytic phenomena in cases of facile breakdown of (4) into products could be



(4)

expected, if anything, in non-polar solvents, and not at all in DMSO.[1,7a]

Other mechanisms, such as elimination–addition *via* an aryne-like intermediate, are immediately ruled out both by the retention just at C(5), of a deuterium atom in the product and by the specificity of attack of the amine at C(5). This is also in accordance with the lack of a primary isotope effect [point (*m*) above].

We must conclude that the origin of the high kinetic orders observed for the reactions of 4-iodo- and 4-bromo-compounds shown in Table 2 is obscure. To compare the reactivity of these compounds with the other ones in Table 2 we have, therefore, used the rate coefficients k_2 which were obtained by extrapolating the observed rate coefficients k to zero amine concentration according to equation (11) (*i.e.* we compare rate coefficients for mechanistically homogeneous reactions).

The ' Element Effect '.—The activation data in Table 2 indicate that the unusual ' element effect ',[8] on which we have commented at the beginning of this discussion, becomes the more ' normal ' (in the sense discussed above) the higher is the temperature at which the comparison is made. This makes difficult the comparison with the ' element effect ' for related reactions such as nucleophilic replacements at either the aromatic carbon,[8] or the vinylic carbon,[13] where both tosylates and iodides have been studied, but where activation data are lacking.

However, it is interesting that according to the plot in Figure 1 the 4-tosylate seems to have a normal behaviour, due to a $\Delta H^{\ddagger} - \Delta S^{\ddagger}$ compensation whilst the 4-iodo- and 4-bromo-compounds exhibit an enhanced reactivity. It is regrettable that theories are still insufficiently developed to allow the easy translation of extrathermodynamic relationships, such as those shown in Figure 1, into explicit mechanisms.

The last point concerns 2-methoxytropone. It is interesting that the near equality of rates for reactions of secondary amines in benzene with either 2-methoxytropone or 2-halogentropones [1a] is not maintained in DMSO as solvent [point (i) above]. This further confirms our ideas as to the origin of isokinetic relationships for reactions of α-functionalized tropones with amines in non-polar solvents.[1a,b]

Conclusions.—Although many important mechanistic questions remain unanswered, this work has shown that the leaving groups of choice for nucleophilic replacements at the troponoidal γ-carbon, without rearrangement, are either iodine or bromine. In these cases, for protic amines as reagents, there is great advantage in using high amine concentrations because the reaction rate increases with nearly the second power of the amine concentration.

In contrast, the tosyloxy-group, in spite of its reputation of very good leaving-group, is a relatively poor one for nueleophilic substitution at the troponoidal γ-carbon. Finally, replacement of the alkoxy-group from the troponoidal γ-carbon by nucleophiles is so difficult as to be of no use.

As regards the exchange at C(7) to give (1), all the above data point to an exchange after formation of the amino-product. This cannot in any way influence substitution on troponoids but, being interesting *per se*, should be further studied.

EXPERIMENTAL

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. U.v. spectra and kinetics were per-

formed with a Unicam SP 800 spectrometer. ^{1}H N.m.r. spectra were run on a JEOL PS 100 spectrometer, chemical shifts being given with respect to $SiMe_4$.

Chemicals.—DMSO was dried and handled as before.[5] Reagent grade dimethylamine was dried by passage over potassium hydroxide pellets.

Troponoids available from previous studies or re-prepared according to published procedures include 2-bromotropone,[1a] 2-iodotropone,[1a] 2-methoxytropone,[1a] 4-methoxytropone,[14,*] and 4-dimethylaminotropone.[5]

4-Bromotropone.—A solution of 4-chlorotropone [5] (0.036 g, 0.26 mmol) in 1 ml of glacial acetic acid saturated with hydrogen bromide was refluxed for 2 h. The mixture was then evaporated under reduced pressure; the residue was shaken with water–chloroform and the organic layer was dried ($MgSO_4$) and then evaporated under reduced pressure. The solid residue was chromatographed on a silica gel layer (eluant benzene–methanol 90 : 10) to afford crystals (0.016, 34%) of m.p. 110—111 °C (lit.,[15] 110 °C, where 4-bromotropone was obtained as a by-product in a very low yield).

4-Iodotropone.—A solution of 4-chlorotropone [5] (0.045 2 g, 0.32 mmol) and potassium iodide (6 mmol) in acetic acid (6 ml) and water (20 ml) was refluxed for 5 h. The mixture was evaporated under reduced pressure and the residue was then dissolved in warm water and extracted with chloroform. The organic layer was dried ($MgSO_4$) and then evaporated under reduced pressure to give a solid residue which was chromatographed on silica gel (eluant benzene–methanol 90 : 10) and then sublimed to give 4-iodotropone (0.050 g, 67%), m.p. 117—119 °C (Found: C, 36.1; H, 2.17; I, 54.7. C_7H_5OI requires C, 36.2; H, 2.18; I, 54.5%), $\lambda_{max.}$ (EtOH) 320, 310, and 235 nm.

2,4-Dideuterio-5-hydroxytropone.—4-Hydroxytropone (0.5 g) was neutralized with aqueous 2M-sodium hydroxide. The mixture was evaporated under reduced pressure and the yellow crystalline residue was dried over phosphoric anhydride and then dissolved in 2 ml of 99.9% D_2O. The mixture was sealed in a Pyrex ampoule which was heated at 133 °C for 3 days and then acidified to pH 5 with hydrogen chloride to precipitate 2,3-dideuterio-5-hydroxytropone in 80% yield. ^{1}H N.m.r. spectrum of the sodium salt: $\delta(D_2O)$ 7.22br (1 H, attributable to the proton between the two deuterium atoms) and 7.10 (2 H, s).

2,4-Dideuterio-5-chlorotropone.—This compound was prepared from 2,4-dideuterio-5-hydroxytropone according to the directions given for the preparation of the non-deuteriated analogue; [16] it had m.p. 104—106 °C; $\delta(CCl_4)$ 7.1 (1 H, s), and 6.95 (2 H, s).

2,4-Dideuterio-5-iodotropone.—This compound was prepared from 2,4-dideuterio-5-chlorotropone according to the directions given above for the preparation of the non-deuteriated analogue; it had m.p. 123—125 °C; $\delta(CDCl_3)$ 7.5 and 6.6 (2 H, AB system, J = 13 Hz), and 6.6br (1 H, s).

* 4-Methoxytropone was a by-product in the preparation of 4-hydroxytropone, as indicated in the literature at ref. 6, or was prepared by methylation of 4-hydroxytropone.

2,4-Dideuterio-5-tosyloxytropone.—This compound was prepared from 2,4-dideuterio-5-hydroxytropone according to the directions given for the preparation of the non-deuteriated analogue; [14] it had m.p. 83—85 °C; $\delta(CDCl_3)$ 7.8 (2 H) and 7.4 (2 H) (AB system, J = 8.0 Hz), 7.0 (1 H, s), 6.9 (2 H, s), and 2.5 (3 H, s).

Reaction of 2,4-Dideuterio-5-iodotropone with Dimethylamine.—To a solution of 2,4-dideuterio-5-iodotropone (0.025 g) in methanol (1.5 ml) was added, at room temperature, dimethylamine (0.3 ml) which reacted immediately. Work-up as described before [5] led to pale yellow crystals (90%), m.p. 78 °C; $\delta(CDCl_3)$ 7.1 (2 H, s), 7.1 and 6.5 (2 H, AB system, J = 12 Hz), and 3.17 (6 H, s); $\delta(C_6D_6)$ 7.12 (1 H, d, J = 13.6 Hz), 6.72 (2 H, s), 6.45 (1 H, J = 13.6 Hz), and 2.30 (6 H, s).

Reaction of 2,4-Dideuterio-5-chlorotropone with Dimethylamine.—The reaction was run as above for the iodo-compound, but it took 1 h to go to completion. The same product, m.p. 78 °C, with an identical ^{1}H n.m.r. spectrum to that above, was isolated in 87% yield.

Reaction of 2,4-Dideuterio-5-tosyloxytropone with Dimethylamine.—The reaction was run as above for the chloro-compound to give the same product in similar yields and with the same ^{1}H n.m.r. spectrum.

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